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ORIGINAL ARTICLE

Shaping the curve from the microscopic transsphenoidal to the endoscopic endonasal approach for the sellar region

Dando forma a la curva desde el abordaje transesfenoidal microscópico al endonasal endoscópico para la región selar

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Abstract

Objective: *This study aimed to investigate the limitations, barriers, and complications in the early transition from the microscopic transsphenoidal approach (MTA) to the endonasal endoscopic approach (EEA) to the skull base in our institution.* **Methods:** *Technical challenges, as well as clinical features and complications, were compared between MTA, EEA, and mixed cases during the early surgical curve.* **Results:** *The period from the early learning curve was 1 year until the EEA protocol was used routinely. A total of 34 patients registered a resection using a transsphenoidal approach. Eighteen patients underwent EEA, 11 underwent MTA, and five underwent a mixed endonasal and microscopic approach. Non-significant differences were found in endocrine outcomes between the three groups. Patients with unchanged or improved visual function were higher in the EEA group (p = 0.147). Non-significant differences were found in terms of the extent of resection (EOR) between groups (p = 0.369). Only 1 (2.9%) patient in the whole series developed a post-operative CSF leaking that resolved with medical management, belonging to the EEA group (5.5%).* **Conclusions:** *The early phase of the learning curve did not affect our series significantly in terms of the EOR, endocrine status, and visual outcomes.*

Keywords: *Skull base. Endoscopic surgery. Pituitary gland. Middle-income country.*

Resumen

Objetivo: *Investigar las limitaciones, las barreras y las complicaciones en la transición del abordaje transesfenoidal microscópico (ATM) al abordaje endonasal endoscópico (AEE) para la base del cráneo en nuestra institución.* **Método:** *Se compararon las características clínicas y las complicaciones entre ATM, AEE y casos mixtos durante la curva quirúrgica temprana.* **Resultados:** *El periodo desde la curva de aprendizaje inicial fue de 1 año hasta que se utilizó el protocolo AEE de forma sistemática. Un total de 34 pacientes tuvieron una resección por vía transesfenoidal. A 18 pacientes se les realizó AEE, a 11 ATM y a 5 abordaje mixto endonasal y microscópico. Se encontraron diferencias no significativas en los resultados endocrinos entre los tres grupos. Los pacientes con función visual sin cambios o mejorada fueron más en el grupo AEE (p = 0.147). No se encontraron diferencias significativas respecto a la extensión de la resección (p = 0.369). Solo 1 (2.9%) paciente desarrolló una fístula de líquido cefalorraquídeo que se resolvió con manejo médico, perteneciente al grupo AEE (5.5%).*

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Conclusiones: *La fase inicial de la curva de aprendizaje no afectó significativamente a nuestra serie en términos de extensión de la resección, estado endocrino y resultados visuales.*

Palabras clave**:** *Base del cráneo. Cirugía endoscópica. Glándula pituitaria. País de medianos ingresos.*

Introduction

In 1907, Schloffer described the first case of a transsphenoidal approach for the resection of a pituitary tumor[1]. Initially, Harvey Cushing popularized this approach, modifying the original Schloffer's technique[2,3]. Regardless, its popularity decreased in the following decades, due to the limited light penetration in the narrow surgical corridor and Cushing's complete conversion to transcranial procedures[4]. Despite this trend, some surgeons including Norman Dott and many otolaryngologists continued to use the endonasal path, particularly in Europe. Afterward, Guiot introduced the fluoroscope for intraoperative guidance, which was further complemented with the surgical microscope by Hardy and Wisger[5], contributing to the rebirth of this approach during the 1960s[5,6]. Likewise, Guiot also registered the first transsphenoidal surgery with the use of an endoscope in 1962[1]. In the mid-1960s, Storz and Hopkins created the Storz-Hopkins endoscope, which contributed to the development of endoscopic technology, bringing optical improvements, better visualization, and improved illumination[7]. In the late 1970s Apuzzo et al.[8], in the USA, as well as Bushe and Halves[9], in Germany, started the description of combined microsurgical and endoscopic techniques for better visualization of skull base anatomical landmarks. Later on, Jho and Carrau described their one-nasal fossa technique without the use of a nasal speculum, achieving a purely endonasal endoscopic approach (EEA)[10,11]. Finally, during the late 1900s and early 2000s, former endoscopic schools started to arise, mainly in Italy and the USA, where several groups of neurosurgeons and otorhinolaryngologists started investigating the surgical features, advantages, and limitations of this approach[10-17].

Many features of EEA, including the imaging magnification, increased visualization of bone and neurovascular landmarks with different angles, without having to retract the brain, and decreasing manipulation of different neurovascular structures, have allowed a global trend to be toward performing purely endonasal endoscopic procedures for the treatment of many skull base lesions[14]. The wide access to endoscopes and instruments for endoscopic surgery has allowed the implementation of these procedures worldwide[18-21]. Other instruments including the neuronavigation system and intraoperative vascular micro-Doppler have empowered these approaches to allow surgeons to achieve a maximal safe resection of these lesions[18,22]. Trends moving forward to EEA have demonstrated the importance of the availability of adequate instruments and surgical experience to achieve satisfactory results. Unfortunately, many socioeconomic limitations slow down the capacity to develop education and perfection of these techniques in low- and middle-income countries (LMICs). This study aims to describe the learning curve and the experience of the transition between the traditional microscopic transsphenoidal approach (MTA) and the EEA for the resection of sellar lesions with suprasellar extension in a middle-income country center.

Materials and methods

Clinical features and study design

This is a cross-sectional study that reviews a prospective acquired case series that included patients surgically treated with endonasal transsphenoidal approaches at our institution between January 2018 and January 2019. Despite we have been using EEA for 6 years now, only a small group of cases were carefully selected based on detailing the dates of use of the MTA in our institution and the start of using the endoscope for the resection of sellar tumors up to the standardization of purely endoscopic resection of these lesions, as those cases going further in time (retrospectively with MTA and prospectively with EEA) will analyze different data like expertise and challenges of treating more complex cases over the tailored surgical curve. The analysis of this study is focused on the transition curve rather than comparing two different techniques. This analysis implies the selection of only a few cases. Patients scheduled for elective surgery and those who presented directly to the emergency department were included in the study. Patients over 18 years old with sellar lesions, with or without suprasellar extension that underwent endonasal

transsphenoidal surgery were selected. These patients were divided into three groups: the MTA group, the EEA group, and a group of patients where a combination of both techniques was used in the same procedure. Patients who received medical management for sellar or suprasellar lesions (e.g., prolactinomas that responded to medical treatment with cabergoline) or patients in whom transcranial approaches were performed, were excluded accordingly. Authorization by our Institutional Ethics Board as well as by our Institutional Review Board was obtained. This research was performed in accordance with the Declaration of Helsinki. Clinical data were retrospectively collected from medical records including visual outcomes, endocrine function, and complications. Non-parametric tests including two-tailed Student's t test, X^2 analysis, or Fisher's exact test were performed, as appropriate. Tests were considered significant with $p < 0.05$.

Pre-operative protocol

After the neurological assessment, including a visual field testing, a non-enhanced CT of the head/paranasal sinuses, as well as an enhanced MRI of the brain and the sella were performed. In addition, all patients had a preoperative evaluation by the otolaryngology, ophthalmology, and endocrinology teams. All patients were assessed preoperatively with computerized visual fields. The endocrine evaluation consisted of a complete pre- and post-operative work-up, including cortisol, adrenocorticotropic hormone, thyroid function tests (thyroid-stimulating hormone, total, and free T4, total and free T3, when available), growth hormone, insulin-like growth factor 1, prolactin, and gonadal function, including the follicle-stimulating hormone, luteinizing hormone, estradiol, or free and total testosterone according to gender. The diagnosis of diabetes insipidus (DI) was based preoperatively on the patient's symptoms and postoperatively on the patient's last follow-up if he/she was on 1-deamino-8-d-arginine vasopressin replacement. The interpretation of endocrine test results was based on the medical records of the endocrinologist. After finishing the hormonal assessment, and by the thyroid and corticotropic axes, the surgical treatment was further performed. The techniques used for the surgical procedure were either microscopic or endoscopic according to the experience and individual consideration of the neurosurgeon. All surgical procedures were performed by a senior neurosurgeon, a young neurosurgeon, and a senior otolaryngologist. The senior neurosurgeon had significant experience on MTA and the young neurosurgeon as well as the otolaryngologist were trained on EEA. Criteria to decide which approach would be performed were based on attending neurosurgeon's preference. The decision for conversion from EEA to MTA was based on intraoperative recommendation of the senior neurosurgeon if the perception of lack of stereoscopic view or the extent of resection (EOR) was considered not satisfactory.

Microscopic technique

An enhanced CT and/or an enhanced MRI of the head (depending on the pre-operative access to an MRI scanner) are always performed before the procedure. Patients surgically treated with MTA are draped in a usual fashion and operated under general anesthesia. The patient is positioned supine, and the head is slightly rotated and extended for the placement of the nasal speculum. The initial part of the approach is mainly performed by the otolaryngologist and is, in most cases, trans-septal without harvesting any flap. A posterior septostomy and sphenoidotomy are performed. The opening of the sella is done under direct visualization with the use of a chisel or diamond drill until a proper entry to the sella is achieved. Tumor resection is performed using the traditional technique of using different-sized ring curettes and micro pituitary rongeurs (Fig. 1). Resection is continued until the surgeon feels that a reasonable neurovascular decompression is achieved, and a maximal safe resection is completed. Depending on the intraoperative cerebrospinal fluid (CSF) leaking, closure is done with either autologous fat grafting, repositioning of a piece of septal bone/cartilage, and/or the use of fibrin sealant.

Endoscopic technique

The day before surgery an enhanced CT and/or an enhanced MRI of the head (according to the availability and access to the MRI scanner) is performed to use it for neuronavigation. The navigation system equipment used for each case varied according to the insurance company's approval (NDI Polaris system [NDI, Canada] or Fusion [Medtronic, USA]). In contrary to MTA, neuronavigation system was used according to the new availability of new equipment at our institution when this approach was introduced. A Mayfield skull clamp is used for fixation. The initial approach performed by the otolaryngologist consisted of the

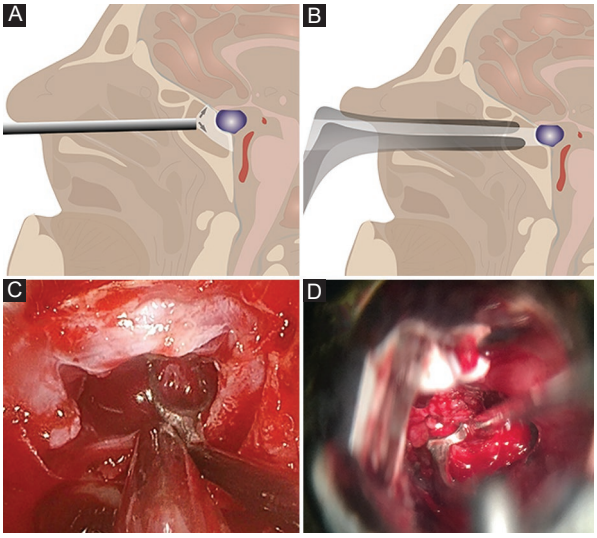

Figure 1. *Microscopic and endoscopic views of the sella.* **A:** *the illumination of the sella with an endoscope is illustrated. Inverted funnel-shaped lighting is observed.* **B:** *an illustration of a microscopic transsphenoidal approach using a nasal speculum is shown. A funnel-shaped illumination of the nasal cavity and sphenoid sinus is illustrated.* **C:** *an endoscopic and a* **D:** *microscopic view of a tumor resection using a ring curette and suction are demonstrated.* Copyright: Édgar G. Ordóñez-Rubiano.

lateralization of the superior and middle turbinate. The nasal septum is infiltrated and a pedicled nasoseptal flap is harvested. At this point of the procedure, the neurosurgeon starts drilling the sphenoidal septum until clear visualization of both opticocarotid recesses, the tuberculum sellae, and the floor of the sella is achieved. A diamond drill and Kerrison forceps are used for adequate bone removal. The dura is usually opened in a wide "X" shape fashion. Resection is performed using micropituitary rongeurs and ring curettes. After resection is done, Floseal or Surgiflo are used for hemostasis if needed. Then, the nasoseptal flap is rotated for adequate closure and covered with a fibrin sealant. Finally, verification of hemostasis in both nasal fossae up to the choana is done, performing a final closure with nasal packing with Surgicel, which is usually removed 2 days after the procedure.

Results

Demographic and clinical characteristics

Thirty-nine patients registered a resection using a transsphenoidal approach in the 1-year period selected for analysis. Five cases were excluded due to a history of a prior transcranial or endonasal resection. Eighteen patients underwent EEA, 11 MTA, and five mixed approaches using both techniques. The demographic and clinical data are presented in table 1. 32 (94.1%) patients had pituitary adenomas and 2 (5.9%) had sellar arachnoid cysts. Non-significant differences were found in terms of the EOR between groups ($p \geq 0.05$). The sellar arachnoid cysts were not included for this analysis. Both cysts underwent marsupialization and cystic volume decreased postoperatively. Only 1 (2.9%) patient in the whole series developed a persistent post-operative CSF leaking that resolved with medical management, belonging to the EEA group (5.5%). Regarding the endoscopic group, 1 (5.5%) patient developed postoperative epistaxis that was treated with anterior nasal packing, 1 (5.5%) patient developed a postoperative hematoma that required evacuation with transcranial drainage, and 1 (5.5%) patient developed a postoperative hematoma with subarachnoid and ventricular draining that resolved spontaneously. From the MTA group, 1 (9%) patient developed seizures due to post-operative cerebral edema and required anticonvulsants and corticoids for seizure control. All endoscopic cases presented crusts during the first 3 months of follow-up. Only one patient persisted after 6 months of follow-up. No patient presented loss of olfaction in this series. Despite trends in an increased length of stay in the endoscopic group given the presence of associated complications, these differences were not statistically significant. Illustrative endoscopic cases are presented in figure 2.

Endocrine and visual outcomes

When evaluating the post-operative endocrine outcomes regarding the anterior pituitary axis in the EEA group, 2 (11.1%) patients developed new-onset hypocortisolism, 2 (11.1%) patients presented with hypogonadism, and only 1 patient (5.5%) had new-onset DI. In the MTA group, 3 (27.3%) patients presented with new-onset hypocortisolism, 1 (9.1%) hypothyroidism, 1 (9.1%) hypogonadism, and 1 (9.1%) had a new-onset DI. No patients presented with a new endocrine deficit in the mixed approach group. Regarding visual outcome, in the endoscopic group, there were 16 (88.9%) patients who improved or had no changes in visual function, and only 2 (11.1%) had a visual function decline. In the MTA group, 8 (72.8%) patients improved or remained with no changes in their visual function, and 3 (27.3%) worsened their function, while in the mixed group, 4 patients (80%) improved or presented no

Table 1. Demographic and clinical information

Variable	MTA (n = 11)	EEA (n = 18)	Mixed (n = 5)	Total (n = 34)	p-value
Gender (no.)					0.099
Female	8 (72.7%)	9 (50%)	2 (40%)	19 (56%)	
Male	3 (27.3%)	9 (50%)	3 (60%)	15 (44%)	
Age (Mean ± ED)	52.3 ± 15.1	50.2 ± 10.1	40.6 ± 16.1		ns
Pathology (no.)					
Functional adenoma	1 (9.1%)	8 (44.4%)	3 (60%)	12 (35.3%)	0.016
Non-functional adenoma	9 (81.8%)	10 (55.6%)	1 (20%)	20 (58.8%)	ns
Other	1 (9.1%)	0	1 (20%)	2 (5.9%)	ns
Tumor volume in cc (Mean ± ED)	2.1 ± 1	9.6 ± 9.2	21.4 ± 27.9		
Extent of resection					ns
Gross total resection	6 (54.5%)	11 (61.1%)	3 (60%)	20 (58.8%)	
Subtotal resection	5 (45.5%)	7 (38.9%)	2 (40%)	14 (31.2%)	
Presenting symptom (no.) Visual disturbances	10 (90.9%)	11 (61.1%)	5 (100%)	26 (76.5%)	ns
Headache	6 (54.5%)	9 (50%)	3 (60%)	18 (52.9%)	
Seizures	0	0	1 (20%)	1 (2.9%)	
Vomit	1 (9.1%)	7 (38.9%)	0	8 (23.5%)	
Hypothalamic/Endocrine	6 (54.5%)	6 (33.3%)	4 (8%)	16 (47%)	ns
Memory loss	0	1 (5.6%)	0	1 (2.9%)	
Amenorrhea	1 (9.1%)	2 (11.1%)	0	3 (8.8%)	
Polyuria/Polydipsia	2 (18.2%)	0	0	2 (5.8%)	

ns: not significant.

changes in their visual function, and 1 patient (20%) worsened (Table 2). However, between approaches, no statistically significant differences were found in visual outcomes (p = 0.147).

Discussion

In our institution, traditional MTA had been used for almost four decades after the introduction of micro neurosurgery in Colombia[23,24]. Previously to the integration of the microscope to the surgical technique, the initial cases were performed using a sublabial approach. However, microscopic amplification exposure allowed to a magnified vision with lower rates of mucosal damage and a progressive transition was done between the two techniques in our institution in the 1980s. Many aspects including the generational change and the progressive socioeconomic development of the region, as well as the introduction of new technologies, have allowed the development of different skull base surgery techniques in Latin America[25,26]. This study describes the clinical, surgical, and endocrine features of the transition from the traditional MTA approach to the EEA. We included cases that were in a frame of time that was dependent of the caseload in the time of transition between both techniques. This may limit an adequate comparison between them in respect to the surgeon's experience based on the number of cases per year. Despite the use of MTA was the gold standard in our institution, there were many cases where the transcranial approach was still used. To allow all cases to be done endonasal, the respective approach transition was performed. We did not compare the results of both large series of patients operated with both techniques in the past 40 years, as this was not the goal of the study, and the analysis would focus only on comparing two different techniques for the same purpose. In the pure introduction of the endoscope (described as a mixed approach), a total of 5 (14.7%) patients required both the microscope and the

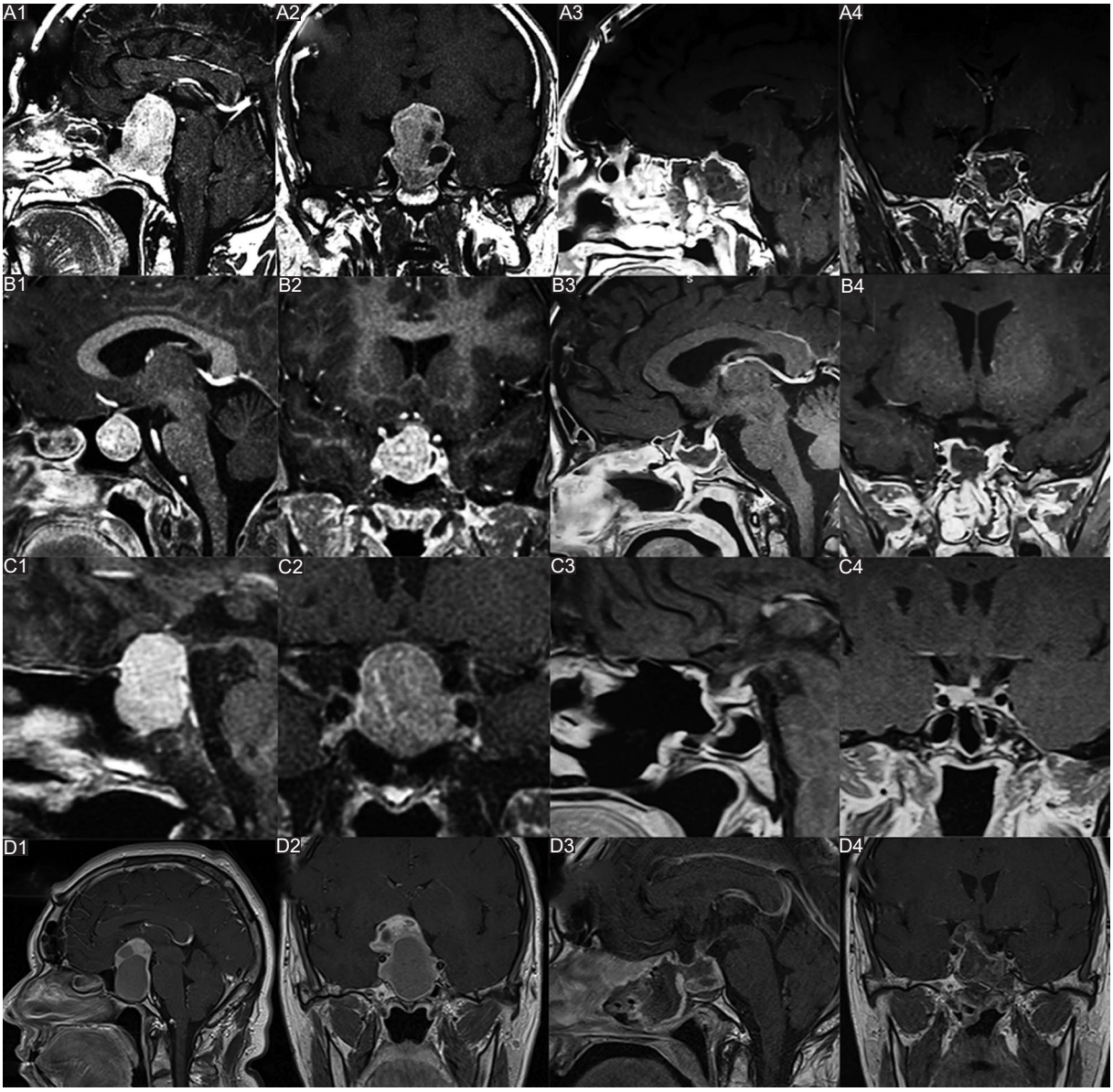

Figure 2. *Pre- and post-operative MRIs of endoscopic resection of pituitary adenomas.* **A:** *case 1: pre- and post-operative-enhanced MRIs demonstrating a near-total resection of a large macroadenoma with extension to the suprasellar space and distorting the floor of the third ventricle. Post-operative images demonstrate the preservation of the pituitary gland and the pituitary stalk.* **B:** *case 2: a rounded macroadenoma is shown. Immediate post-operative images demonstrate a satisfactory tumor resection with preservation of the gland and the stalk.* **C:** *case 3: a macroadenoma compressing the optic apparatus is observed.* **D:** *case 4: a mixed solid and cystic macroadenoma is illustrated. The suprasellar component of the tumor distortions the floor of third ventricle. Post-operative images demonstrate resection of the tumor with satisfactory decompression of the chiasm.*

endoscope for resection. This was a consequence of one or more of the following aspects: (1) the senior neurosurgeon was not satisfied with the EOR due to the lack of stereoscopic view of the endoscope or (2) because surgery time prolongation was imminent due to bleeding or technical difficulties with the endoscope such as the perception of poor lighting. In consequence, the final steps of resection were performed under the microscope. Despite one of the main advantages of the endoscopic technique is the magnified exposure and the better lighting, the perception of lighting was affected by the constant obscuration of the scope with clots in the mucosa of the septum and lateral boundaries of the surgical corridor. This leads to a constant need of cleaning of the endoscope, which may explain the uncomfortable perception of the

Table 2. Visual outcomes and surgical complications

Variable	MTA (n = 11)	EEA (n = 18)	Mixed (n = 5)	Total (n = 50)	p-value
Visual outcome					ns
Improved or nor changes	8 (72.8%)	16 (88.9%)	4 (80%)		
Deteriorated	3 (27.2%)	2 (11.1%)	1 (20%)		
Surgical complications					N/A
Hematoma	-	2 (11.1%)	-		
Nasal bleeding	-	1 (5.5%)	-		
Infection	-	-	-		
CSF leaking	1 (9.1%)	1 (5.5%)	-		
Mortality	-	-	-		
Others	-	1 (5.5%)	-		

ns: not significant; N/A: not applicable.

neurosurgeon, generating the preference to finish the procedure using the microscope. Contrary to the usual learning curve, where the surgeries became endoscopic-assisted, the conversion in our series was more in a microscopic-assisted fashion, as the rest of the procedures were done under the endoscope. This allowed for a better understanding of the complete technique and a faster adaption to the 2D view. To improve assimilation to the endoscopic view and manipulation of the instruments, different strategies were implemented. The activities included: (1) cadaveric drilling and (2) non-biological practice. For non-biological practice, the simulation stations for laparoscopic training were used. For example, some exercises such as using a grape wrapped with a glove were used to resemble the dissection and resection of a macroadenoma (Fig. 3). The cadaveric training was done with a donation of an endoscope and the use of complete cadavers, which were not amenable for injection but were useful for bony anatomy dissection. Unfortunately, the use of heads in Colombia, even for academic and scientific purposes, is prohibited as the law restricts the amputation of cadaveric specimens. Despite this, the biological (with complete cadavers) and non-biological simulation exercises are still used for resident training in our institution. All strategies aim to improve the familiarization of surgeons and residents with the endoscope.

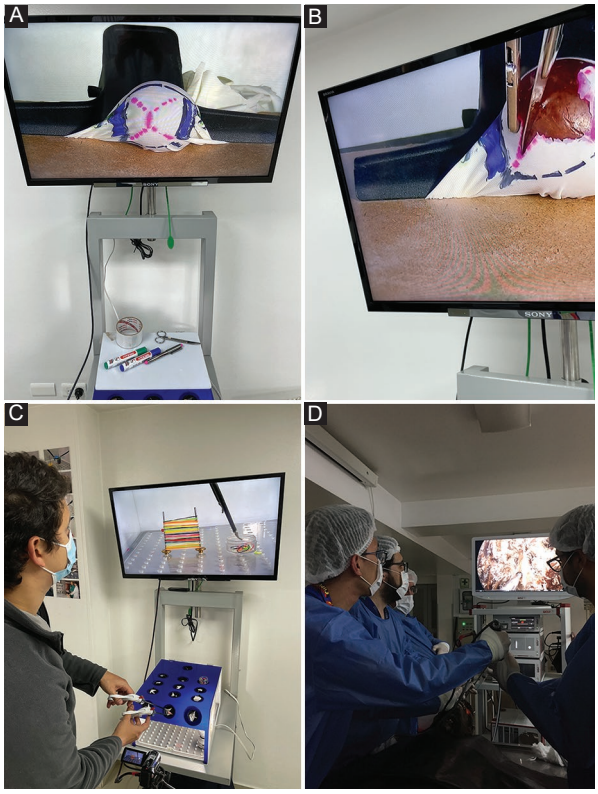

Figure 3. *Endoscopic laboratory practice with biological and non-biological exercises.* **A and B:** *a grape is wrapped with a glove, painting both cavernous sinuses and the site for "dura opening". The instruments are used for cutting both the glove and the skin of the grape for further debulking, using a single port of entry to the practice box.* **C:** *different exercises used for laparoscopic training are used through a single port for two-hand practice.* **D:** *a cadaveric laboratory practice is performed by training the 4-hand technique.*

On the other hand, regarding the surgical learning curve, some authors have defined it as "the time taken and/or the number of procedures an average surgeon needs to be able to perform a procedure independently with a reasonable outcome"[27]. When plotting a learning curve, 6 different stages have been described: (1) the commencement of training, (2) a rapidly ascending curve, (3) a point when the procedure can be performed independently and competently, (4) a step where additional experience improves outcomes by small amounts until a (4) plateau is reached, and, finally, (5) there is a fall in the level of performance[28].

For endoscopic skull base surgery (ESBS), the pioneers in the field described their first experience, showing the limitations they had 2 decades ago when endoscopes and other instruments were under important development[29-31]. More recently, Younus et al. described the curve's plateau of ESBS, integrating data of 1000 cases[32]. They described an ESBS learning curve consisting of three phases: (1) the slow ascending curve, (2) the rapidly ascending curve, and (3) a variable plateau. The three different possibilities for the ESBS learning curve's plateau they propose are (1) a "slow ascending" plateau with a persistent acquisition of complex skills, (2) a "flat" plateau with mastery (classic), and 3) a "slow descending" curve if attempting more difficult cases. This was based on the premise that the plateau may last for several years depending on the complexity of the endpoints considered. In terms of the length of the phases of the curve, the exact length of phases I and II cannot be exactly determined[32]. However, 200 cases are the upper limit of most studies of the surgical learning curve[33]. It is important to note that this should be generalized for all scenarios. However, the need for a fast adaption of new technologies is paramount, especially if the caseload is not as high as it is for some reference centers in high-income countries[31,32,34]. Hence, the learning curve for a skull base surgeon in any center with a low- or intermediate load of cases will be likely even slower, and the complexity of cases performed will be limited in the first phases of the learning curve (Fig. 4). In other specialties like robot-assisted laparoscopic surgery, there has been proposed that 30-40 cases are needed to carry out the procedure safely[35]. Here, we also propose that for ESBS~40 cases are needed to reach the safe threshold and complete the phases I and II proposed by Younus et al.[32] The time to perform these 40 cases may vary among centers, as the caseload will determine the number of patients amenable for ESBS. At the early beginning of this curve, we did not perform any extended EEA, as we strongly believe that reconstruction techniques should be mastered before opening the skull base in a wide manner. In our study, in all endoscopic and mixed cases, we performed a nasoseptal flap. We considered at the beginning of our curve that the risk of CSF leaking and/or neuroinfection outweighed the inherent risks associated to the considerable manipulation of the nasal mucosa (e.g., crusts). In addition, we consider that the length of stay as well as the impact in costs in the scenario of a reoperation due to a CSF leak would be appreciated, especially in a middle-economy health-care system, where the resources are scares and should be optimized. We consider that the use of a nasoseptal flap would be a reasonable option in this early phase of the learning curve. In terms of complications, we highlight that risks were considerable higher in the endoscopic group. This is remarkable and need to be considered when starting performing ESBS. Many aspects including manipulation of the endoscope and the instruments, as well as the lack of experience, would impact directly on surgical outcomes. We suggest to make all efforts as possible to avoid resection of large tumors in this transition, given the need of aggressive resections that may lead to avoidable complications.

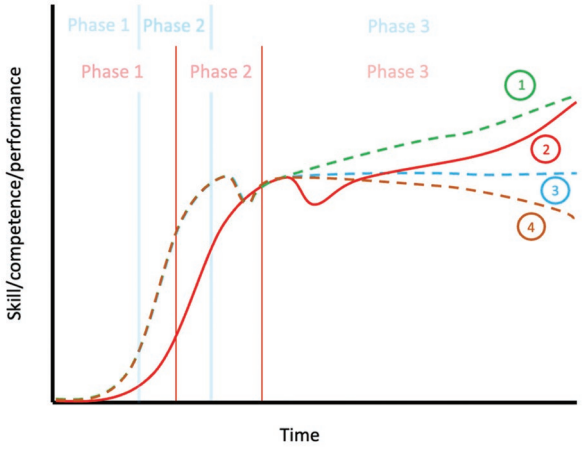

Figure 4. *The surgical learning curve for endoscopic skull base surgery. Phase 1 corresponds to the slow ascending curve, Phase 2 to the rapidly ascending curve, and Phase 3 to a variable plateau. These phases are prolonged in time for low-caseload centers (phases illustrated in red) compared to those for high-caseload centers (phases illustrated in blue). The three different possibilities of the curve's plateau proposed by Younus et al. are presented as a "slow ascending" plateau with a persistent acquisition of complex skills (green-1), a "flat" plateau with mastery-"classic" (blue-3), and a "slow descending" curve if attempting more difficult cases (brown-4). An additional curve is proposed for low-caseload neurosurgical centers (red-2), which corresponds to a slower curve. By the end, the tail of the curve would get to the same as curve 1, as the probable scenario in any center would be to perform more challenging cases over time. This final ascending curve would be related to expanded approaches in the sagittal and coronal planes.*

Our study represents an important description of overcoming barriers to trespassing the threshold of performing ESBS with reasonable outcomes. In general, in LMICs, there is a lack of high-caseload centers. Although some specific exceptions can be found, there is an urgent need to improve outcomes for ESBS in LMICs. Not only the training and the surgeon's expertise are necessary; a multidisciplinary approach including post-operative ICU care and the

endocrine approach is fundamental for good results. Unfortunately, in LMICS, the health-care systems, the socioeconomic factors[36], as well as the personal interests of neurosurgeons remain to impact the advancement of the specialty in our region.

In our series, for the transition between the two approaches, the conversion of 21% of cases was needed, as well as the constant training of ENTs and neurosurgeons. Over time, we have been able to decrease the operative time by improving surgical techniques. Special cases in which a microscopic technique is ideal for the patient still exist; some examples are surgeon's comfort and experience, extensive nasal bleeding, atypical airway, or technical problems with the endoscope[37]. Furthermore, for the first cases, we decided to have the microscope prepared in case that it was required by the surgeon. It is important to highlight that all technological aids represent a change not only for the surgeon but also for the surgical team as well, and they represent a way to maximize EOR and minimize the risk of injuring neurovascular structures[13,14]. Our study found a visual function improvement or without changes in 32% of the cases in the entire series, which is a percentage similar to what has been reported in the literature, reporting rates from 16.8% to 79%[38-40]. From an endocrine point of view, both groups had similar outcomes. Published series vary according to different variables including the pathology, intervention as a 1st-time surgery, or re-intervention for recurrent tumors[13,14,40,41]. In this study, anterior and posterior endocrine deficits were no higher than 10%, which is reasonable with those reported in other series as well.

Finally, traditional microscopic transsphenoidal surgery remains trustworthy, fast, and effective. Many neurosurgeons have published excellent results with this technique. It has low complication rates and patient satisfaction is high[41,42]. However, the transition to an endoscopic approach has been growing due to the panoramic view with clear visualization of surgical corridors, bony landmarks, and neurovascular structures, increasing neurosurgeons' confidence to perform ESBS safely[37]. Some series that have compared both approaches since 2015 are presented in table 3. Visual outcomes, EOR, and endocrine outcomes vary among studies. Despite trends in ESBS for improving EOR, there is not sufficient data to support significant variations among both techniques. Unfortunately, different aspects including socioeconomic barriers, caseload, and surgical team expertise will continue to shape surgical results.

Table 3. Studies reporting microscopic versus endoscopic endonasal approaches for sellar and suprasellar lesions after 2015

Authors	Year of publication	Type of country	Period time of the study (years.)	Total cases	EEA cases	MTA cases	Mixed cases	Type of lesions	GTR (%)		Improvement or no changes in visual function (%)		New-onset endocrine deficit (%)		Phases of learning curve assessed
									EEA	MTA	EEA	MTA	EEA	MTA	
Guo-Dong et al.[43]	2016	HIC	7	247	100	147	-	Adenoma	60	58	58[a]	88[a]	21	22	1, 2, 3
Akbari et al[44]	2018	LMIC	3	35	16	19	-	Large (≥3 cm) adenomas	81	16	NR[b]	NR[b]	31	37	1, 2
Prajapati et al[45]	2018	LMIC	NR	30	17	13	-	Adenoma	65	46	100	100	12	27	1, 2
Trevisi et al.[46]	2019	HIC	15	55	27[c]	28	-	Adenoma with parasellar extension	70	29	NR	NR	NR	NR	1, 2, 3
Phogat et al.[47]	2020	LMIC	6	198	119	79	-	Adenoma	70	48	100	98	32	28	1, 2, 3
Møller et al.[48]	2020	HIC	10	240	45	195	-	Adenoma	39	22	37[d]	35[d]	3	34	1, 2, 3
Shimony et al.[49]	2021	HIC	11	87	39	48	-	Adenoma	87	79	36[a]	42[a]	36	27	1, 2, 3
Trimpou et al.[50]	2022	HIC	15	40	26	14	-	Adenoma (Cushing's disease)	62	92	NR	NR	23	36	1, 2

[a]Reported as visual improvement. [b]Visual field improvement was comparable in both groups: 50% of the patients showed improvement in the visual fields 6 months after surgery. [c]Microsurgical sublabial transsphenoidal resection. [d]Reported as normalization of visual function.
EEA: endonasal endoscopic approach; GTR: gross total resection; HIC: high income country; LMIC: low-to-middle income country; MTA: microscopic transsphenoidal approach; NR: not reported.

Study limitations

The main limitation of this study is its retrospective nature. Second, the recurrence rate or tumor progression rate was not evaluated. Cost-effectiveness and quality of life were not addressed either. However, trends of increased costs were noted in the endoscopic group given the rent of the neuronavigation system. This information could have been useful considering the budget limitations in the health-care systems in our region and further research is necessary to contrast this remarkable aspect. No analysis of re-intervention rates due to tumor regrowth was done on follow-up. This study did not measure skill improvement in terms of surgical time but demonstrates the number of cases to feel comfortable to perform purely endoscopic approaches. It is necessary to evaluate the importance of technological help required for these cases since a vascular injury, a new-onset neurologic deficit, or a severe endocrine decline related to these procedures constitute irreparable damage.

Conclusion

The transition between MTA and EEA depends on multiple factors that include training of the surgical personnel as well as the confidence or lack thereof generated by the surgeon's change in position during the procedure, the lack of stereoscopic view of the two-dimensional images of the endoscope, and the lack of security to maximize the EOR. This is most remarkable for neurosurgeons that have prior experience using MTA in a daily manner. The use of either approach will always be based on the experience and consideration of the surgical team. Finally, the early phase of the learning curve did not affect our series significantly in terms of EOR, endocrine status, and visual outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for the analysis and publication of routinely obtained clinical data. The informed consent of the patients was not required because this was a retrospective observational study.

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ARTÍCULO ORIGINAL

Coinfecciones y comorbilidad observadas en la COVID-19 durante la temporada de influenza en el paciente pediátrico

Coinfections and comorbidities observed in COVID-19 during the influenza season in the pediatric patient

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Resumen

Objetivo: *Evaluar el impacto de la comorbilidad y de las coinfecciones presentadas por la infección por SARS-CoV-2 vs. COVID-19 en niños mexicanos.* **Método:** *Estudio prospectivo y observacional que comprendió la temporada alta de influenza 2020-2021, analizando todos los pacientes con diagnóstico de infección vs. enfermedad por SARS-CoV-2 vs. COVID-19 que ingresaron al Hospital Infantil de México. Se realizó en todos RT-PCR en tiempo real para SARS-CoV-2, determinando gen E, gen RdRp, gen RP y proteína N, y RT-PCR multiplex para detección de virus respiratorios.* **Resultados:** *Los criterios de inclusión los cumplieron 163 pacientes. El grupo con mayor riesgo de enfermar fueron los adolescentes (40.4%), seguidos de los escolares y preescolares (21.4% y 19.6% de los casos, respectivamente). Hubo tres casos con coinfección viral: dos (1.2%) con parvovirus B-19 y uno (0.6%) con herpes tipo I; hubo otros dos (1.2%) con coinfección bacteriana. La principal comorbilidad correspondió a obesidad, leucemia linfoblástica aguda e hipertensión arterial. En cuanto a mortalidad, solo hubo cuatro casos (2.4%).* **Conclusiones:** *Obesidad, cáncer, hipertensión, cardiopatías y diabetes constituyen la comorbilidad en nuestros pacientes, como se refiere en la literatura, no así las coinfecciones. En nuestro estudio no hubo casos de mortalidad relacionada con la comorbilidad.*

Palabras clave: *SARS-CoV-2. COVID-19. Coinfecciones. Comorbilidad. Morbimortalidad.*

Abstract

Objective: *To evaluate if the comorbidity and coinfections presented by SARS-CoV-2 infection vs. COVID-19 impact our Mexican children.* **Method:** *Prospective and observational study that included the 2020-2021 peak influenza season. All patients with a diagnosis of infection by SARS-CoV-2 vs. COVID-19 who were admitted to the Hospital Infantil de Mexico were analyzed. Real-time RT-PCR for SARS-CoV-2 was performed in all patients, determining E, RdRp and RP genes and protein N, as well as RT-PCR for detection of respiratory viruses.* **Results:** *The inclusion criteria were met by 163 patients. The group with the highest risk of becoming ill was adolescents (40.4%), followed by schoolchildren and preschoolers (21.4% and 19.6% of the cases, respectively). There were three cases with viral coinfection: two (1.2%) with parvovirus B-19 and one (0.6%) with herpes type I; another two (1.2%) showed bacterial coinfection. The main comorbidity were obesity, acute lymphoblastic leukemia and arterial hypertension. Regarding mortality, we only had four cases (2.4%).* **Conclusions:** *Obesity, cancer, hypertension, heart disease and diabetes are comorbidity present in our patients, as referred to in literature, but not coinfections. In our study, we did not have any associated mortality related to comorbidity.*

Keywords: *SARS-CoV-2. COVID-19. Coinfections. Comorbidity. Morbidity. Mortality.*

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Introducción

Los primeros informes de COVID-19 en pediatría fueron reportados en la provincia de Wuhan, China. Los dos iniciales consideraban que el cuadro clínico, y en sí la enfermedad, tanto en los recién nacidos como en los niños menores de 14 años, era poco frecuente que resultara grave en comparación con los adultos y los adolescentes jóvenes. El primer reporte, del centro para el control de enfermedades chino, solo reportó que el 1.3% de 72,314 pacientes diagnosticados de COVID-19 eran menores de 20 años[1]. El segundo, un informe posterior de 171 niños menores de 16 años hospitalizados en la provincia de Wuhan, destacaba que solo tres fueron ingresados en la unidad de cuidados intensivos, y de ellos solo uno falleció a causa de la enfermedad[2].

Posteriormente, el *Morbidity and Mortality Weekly Report* de los Centers for Disease Control and Prevention de los Estados Unidos, publicado el 6 de abril de 2020, hacía mención a que el 1.7% de casi 150,000 casos conocidos de COVID-19 en ese país correspondían a niños. Solo hubo 2572 casos pediátricos, de los cuales 15 (0.5%) fueron ingresados en una unidad de cuidados intensivos, y se sabe que, igual que en el reporte de Wuhan, solo tres (20%) murieron[3].

Desde el inicio del brote de coronavirus en el invierno de 2019 en Wuhan, hemos podido aprender un poco más sobre la epidemiología de la COVID-19 en niños, pero aún hay mucho que no sabemos sobre el proceso de la enfermedad y, sobre todo, aquello que la modifica[4]. A raíz de esto han aparecido diferentes informes en la literatura sobre la enfermedad en niños, asociada esta con coinfección con otros patógenos respiratorios, es decir, pacientes pediátricos infectados por SARS-CoV-2 más otro u otros virus respiratorios a la vez. En un estudio de 72 casos pediátricos infectados, al parecer por contactos domésticos, 34 de ellos fueron evaluados para coinfecciones y 19 tenían otros patógenos virales además del SARS-CoV-2. Aunque se trata de un estudio pequeño, la alta prevalencia de coinfecciones aumenta la posibilidad de que los niños compartan entre sí más de una infección viral a la vez[5].

Por otro lado, al igual que en los adultos, los niños tienen comorbilidad que puede aumentar el riesgo de gravedad e incluso de muerte. Al respecto, en una recopilación de datos de niños mexicanos diagnosticados con COVID-19, la mayor prevalencia se encontró en el sexo femenino, con 6983 casos, predominando en ambos sexos en el grupo de 15-19 años, y en menores, en el grupo de 0-4 años para los varones y de 5-9 años para las niñas. En México, a 30 de septiembre de 2020, el 9.1% (2584/28,388) de los pacientes pediátricos con COVID-19 tenían comorbilidad, el 19.1% (540/2827) de aquellos con COVID-19 hospitalizados tenían comorbilidad y el 26% (83/310) de los que fallecieron con COVID-19 tenían comorbilidad[6].

A la fecha de iniciar este estudio no encontramos reportes nacionales sobre coinfecciones virales asociadas con SARS-CoV-2 en niños mexicanos, por lo que el objetivo de nuestro estudio fue observar la presencia de coinfecciones virales y bacterianas, la comorbilidad presentada y su impacto sobre la evolución de la enfermedad en niños con COVID-19 ingresados en un hospital pediátrico de tercer nivel (Hospital Infantil de México Federico Gómez).

Método

Diseño del estudio

Se trata de un estudio prospectivo y observacional que se realizó en un lapso comprendido entre las semanas epidemiológicas de la temporada de influenza 2020-2021 (semanas 40 a 20), que comprendieron del 27 de septiembre de 2020 al 21 de mayo de 2021. Tomamos esta época presuponiendo que es la temporada de circulación de este y otros virus invernales. Se incluyeron los pacientes con diagnóstico de infección vs. enfermedad por SARS-CoV-2 vs. COVID-19 de ambos sexos, independientemente de la edad, ingresados al Hospital Infantil de México.

Consideraciones éticas y criterios de inclusión

Este estudio cumplió con los lineamientos de la Declaración de Helsinki en materia de investigación y ética. Incluimos en este estudio todos los pacientes que cumplieran con criterios de infección vs. enfermedad por SARS-CoV-2 vs. COVID-19, de acuerdo con la definición operativa de caso sospechoso de enfermedad respiratoria viral emitida el 24 de septiembre de 2020, que a la letra dice: «Persona de cualquier edad que en los últimos 10 días haya presentado al menos uno de los siguientes signos y síntomas mayores: tos, fiebre, disnea (dato de gravedad) o cefalea acompañados de al menos uno de los siguientes signos o síntomas menores: mialgias,

artralgias, odinofagia, escalofríos, dolor torácico, rinorrea, anosmia, disgeusia y/o conjuntivitis. En menores de cinco años de edad, la irritabilidad puede sustituir la cefalea»[7].

Dado que por normatividad a todos los pacientes ingresados se les debe hacer una prueba diagnóstica, no fue requisito que los pacientes contaran con carta de consentimiento informado ni autorización del padre o tutor en un momento dado. De la misma forma, ya que el estudio se realizó en un hospital de enseñanza e investigación, no se solicita autorización por el comité de ética en los estudios observacionales.

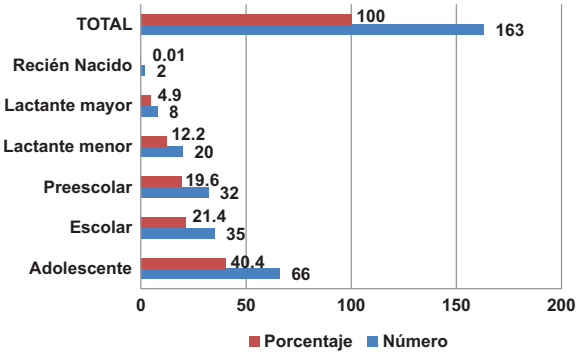

Figura 1. *Distribución de casos por grupo etario.*

Material y metodología

El procedimiento para la toma, el procesamiento, la identificación y la conservación de muestras de hisopado nasal y nasofaríngeo se realizó como a continuación se describe. Se ocupó para cada paciente un medio de transporte viral (BD Universal Viral Transport), hisopos de dacrón o rayón con mango de plástico (exudado faríngeo) e hisopos de dacrón o rayón con mango flexible (exudado nasofaríngeo). Se realizó hisopado nasal y nasofaríngeo en cada paciente ingresado al área COVID-19. Tanto el exudado faríngeo como el nasofaríngeo se colocaron en el mismo tubo para incrementar la carga viral, procurando que se transportaran a una temperatura de 2-8 °C para su procesamiento. Cada muestra fue etiquetada con el nombre y apellido del paciente, y se acompañó del estudio epidemiológico de caso sospechoso de COVID-19. Ello conforme a lo señalado por el manual para la vigilancia epidemiológica y de laboratorio de la Secretaría de Salud[8].

Las muestras fueron tomadas por personal del hospital, tanto médico como de laboratorio afín al área de atención de pacientes COVID-19. Las muestras se procesaron para realizar la prueba de reacción en cadena de la polimerasa en tiempo real (RT-PCR) para SARS-CoV-2 utilizando el equipo QuantStudio 5 para la determinación de gen E, gen RdRp, gen RP y proteína N. Así mismo, se realizó RT-PCR multiplex para detección de otros virus respiratorios, tales como influenza A, influenza A (H1N1 pdm09), influenza A (H3N2), influenza B, adenovirus, bocavirus, coronavirus endémicos (OC43, NL63,229E y HKU1), metaneumovirus, enterovirus/rinovirus y virus respiratorio sincitial (VRS).

Resultados

Al término del estudio encontramos un total de 173 pacientes ingresados con diagnóstico de infección por SARS-CoV-2 vs. enfermedad asociada (COVID-19), de los cuales se descartaron siete, ya que tres correspondieron a adultos, en otros seis no se corroboró el diagnóstico por laboratorio y en uno no se encontró su expediente. En total, quedaron 163 pacientes, los cuales mostraron una prevalencia acorde al periodo analizado del 4.5%, que correspondió al número de pacientes atendidos en el hospital (3591 pacientes vistos desde septiembre de 2020 hasta mayo de 2021), y una incidencia relacionada al número de pacientes asistidos en ese mismo tiempo de 18.1 casos por mes y 16.3 por 1000 pacientes.

De estos 163 pacientes analizados, 83 (50.9%) fueron masculinos y 80 (49.1%) femeninos, destacando el grupo de edad con mayor riesgo de enfermar, los adolescentes, con 66 casos (40.4%), seguido del grupo de escolares y preescolares con 35 (21.4%) y 32 (19.6%) casos, respectivamente (Fig. 1).

Los pacientes ingresados fueron provenientes de diferentes partes de la República; no obstante, la mayoría fueron de dos Estados: el Estado de México y la Ciudad de México, con 81 (49.6%) y 59 (36.1%) casos, respectivamente. Hubo otros siete Estados con mucho menor número de ingresos a este nosocomio (5 [3%], 4 [2.4%] y 1 [0.6%] casos). Solo en 4 (2.4%) casos se desconoció su lugar de origen (Fig. 2). Al respecto, y en consideración de que somos un hospital de la Ciudad de México, observamos que la mayor procedencia de casos correspondió a la delegación de Iztapalapa. Cabe señalar que, en segundo lugar, no se determinó bien la procedencia, ya que en su hoja de ingreso solo apareció como Ciudad de México y correspondieron al 11.8% (siete casos). Hubo dos delegaciones, Venustiano Carranza y Cuauhtémoc, con cinco casos (8.4%) cada una; otras tres

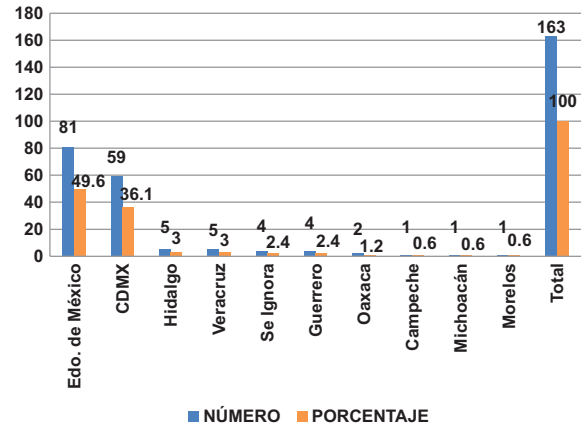

Figura 2. *Número y porcentaje de pacientes en relación al lugar de procedencia.*

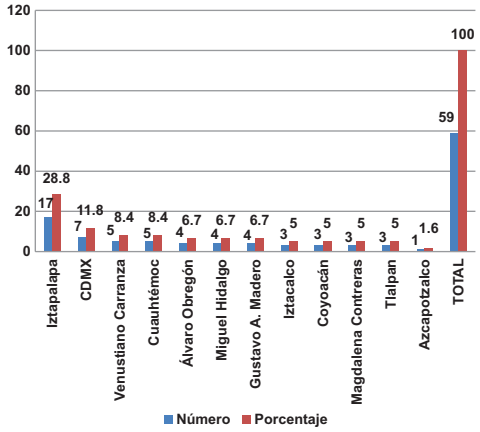

Figura 3. *Relación de casos ingresados y porcentaje en cuanto a delegación de la Ciudad de México.*

con cuatro casos (6.7%), cuatro con tres casos (5%) y una con solo un caso (1.6%) (Fig. 3).

Respecto a la morbimortalidad observada, en el global solo se registraron 4 (2.4%) casos, 3/80 (3.8%) del sexo femenino (1.8% del global) y 1/83 (1.2%) del sexo masculino (0.6% del global). Estos datos se muestran en la tabla 1 y la figura 4.

En cuanto a los objetivos del presente estudio, en relación con las coinfecciones observadas en estos 163 pacientes analizados, encontramos que solo hubo tres casos (1.8%) con coinfección viral: dos (1.2%) con parvovirus B-19 y uno (0.6%) con herpes tipo I. Hubo otros dos casos (1.2%) con coinfección bacteriana, y el resto (96.9%) no mostraron ninguna coinfección (Tabla 2).

Cabe señalar que en el paciente que cursó con coinfección por virus herpes tipo I, el diagnóstico, como tal, fue solo de infección por SARS-CoV-2 y mostró hisopados nasal y nasofaríngeo positivos para el virus, con resultados mediante RT-PCR de gen E 20.23, gen RdRp 21.230 y proteína N 21.96. Por igual, mostró un resultado para IgG > 1.10 (considerado positivo). Este paciente cursó con exantema, dolor torácico y odinofagia. Su diagnóstico de base era leucemia linfoblástica aguda (LLA), alto riesgo, e ingresó por mucositis, síndrome infiltrativo y lesiones mucocutáneas que se confirmaron producidas por virus herpes tipo I.

Los resultados de parvovirus B-19 correspondieron a un mismo paciente que presentó dos eventos: el primero en septiembre, que fue considerado como portador asintomático ya que solo tuvo como sintomatología fiebre, calosfríos y congestión nasal, con hisopados nasal y nasofaríngeo positivos, pero sin reporte cuantitativo de

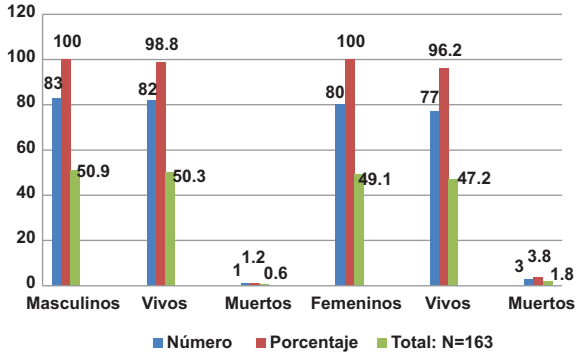

Figura 4. *Morbimortalidad por sexo.*

la prueba QuantStudio 5; y el segundo evento lo presentó en octubre y se consideró como infección por SARS-CoV-2 asociada a reactivación del parvovirus B-19, con positividad, nuevamente, de los hisopados nasal y nasofaríngeo, y con reporte cuantitativo de la prueba QuantStudio 5 (PCR en tiempo real) de gen E 32.47, gen RdRp 35.400 y proteína N 33.93. Cabe mencionar que este paciente tenía como diagnóstico de base anemia hemolítica hereditaria y que, como síntomas en este segundo cuadro, solo mostró irritabilidad. No hubo casos de coinfección con algún virus de la influenza.

Respecto a la comorbilidad presentada, encontramos ocho de importancia, destacando en primer lugar la obesidad con 24 casos (14.7%); en segundo, la LLA con 18 casos (11.04%), siendo ocho de alto riesgo y siete de riesgo habitual; en tercer lugar, hipertensión arterial en 12 casos (7.3%), seguida de otros tumores malignos y de enfermedad cardiaca con ocho casos cada una (4.9%); y finalmente, diabetes, síndrome de

Tabla 1. Morbimortalidad en casos diagnosticados con infección por SARS-CoV-2 vs. enfermedad COVID-19

Sexo	n	%	Total (n = 163)
Masculino	83	100	50.9
Vivos	82	98.8	50.3
Muertos	1	1.2	0.6
Femenino	80	100	49.1
Vivos	77	96.2	47.2
Muertos	3	3.8	1.8

Tabla 2. Coinfecciones observadas en pacientes con infección por SARS-CoV-2 vs. enfermedad COVID-19

Coinfecciones	n	%
Virus		
Ninguno	158	96.9
Herpes tipo I	1	0.6
Parvovirus B-19	2	1.2
Bacterias		
S.epidermidis	1	0.6
C. difficile	1	0.6
Total	163	100

Tabla 3. Casos con comorbilidad asociada a infección por SARS-CoV-2 vs. enfermedad COVID-19

Comorbilidad	n	%
Obesidad	23	14.1
LLA	18	11.04
Hipertensión arterial	12	7.3
Otros tumores malignos	8	4.9
Enfermedad cardiaca	8	4.9
Diabéticos	7	5.2
Síndrome de Down	6	3.6
Insuficiencia renal crónica	5	3.06
Epilepsia	3	1.8
Desnutrición	2	1.2
Hepatopatías	2	1.2
Parálisis cerebral infantil	2	1.2
Asma	2	1.2
Prematuridad	2	1.2
Crisis convulsivas	2	1.2
Dermatomiositis juvenil	1	0.6
Deficiencia de acetil coenzima A	1	0.6
BDP	1	0.6
Lupus eritematoso sistémico	1	0.6
Anemia hemolítica	1	0.6
Atresia esofágica con fístula	1	0.6
VIH	1	0.6
Hemofilia tipo A	1	0.6
Ninguna	42	25.7
No bien definida	11	6.7
Total	163	100

BDP: broncodisplasia pulmonar; LLA: leucemia linfoblástica aguda; VIH: virus de la inmunodeficiencia humana.

Down e insuficiencia renal crónica, con siete (5.2%), seis (3.6%) y cinco (3.06%) casos, respectivamente. Entre la comorbilidad hubo otras 15 afecciones más con un número menor de casos (Tabla 3), así como 11 casos (6.7%) con otra comorbilidad no bien definida y un número considerable de pacientes sin ninguna comorbilidad (25.7%; 42/163) (Fig. 5).

En cuanto a la mortalidad observada en relación con la comorbilidad en estos pacientes, notamos que, de las ocho afecciones principales referidas, no hubo ninguna muerte registrada (Tabla 4 y Fig. 6). Si bien es cierto que hubo 4/163 muertes registradas, estas se presentaron en pacientes con otro tipo de comorbilidad: un caso con parálisis cerebral infantil, uno con desnutrición crónica, otro con desnutrición crónica más retraso global del desarrollo, y un último con síndrome de lisis tumoral más síndrome infiltrativo (que se consideró como probable LLA).

Discusión

Este es un estudio observacional, como muchos de los reportes que al momento se encuentran en la literatura y que describen algunos eventos asociados con esta nueva infección-enfermedad de COVID-19. En el periodo señalado, en el cual tomamos en cuenta que incluimos los meses de alta contagiosidad de influenza, encontramos un total de 173 pacientes, de los cuales 163 cumplieron con los criterios de análisis. De estos, el mayor número de casos fueron masculinos (83; 50.9%) y el resto femeninos (80; 49.1%). En cuanto a la edad, los adolescentes ocuparon el primer lugar de asistencia médica (40.4%), seguidos de los escolares y preescolares, así como de los lactantes (menor [12.2%] y mayor [4.9%]), y en último lugar del

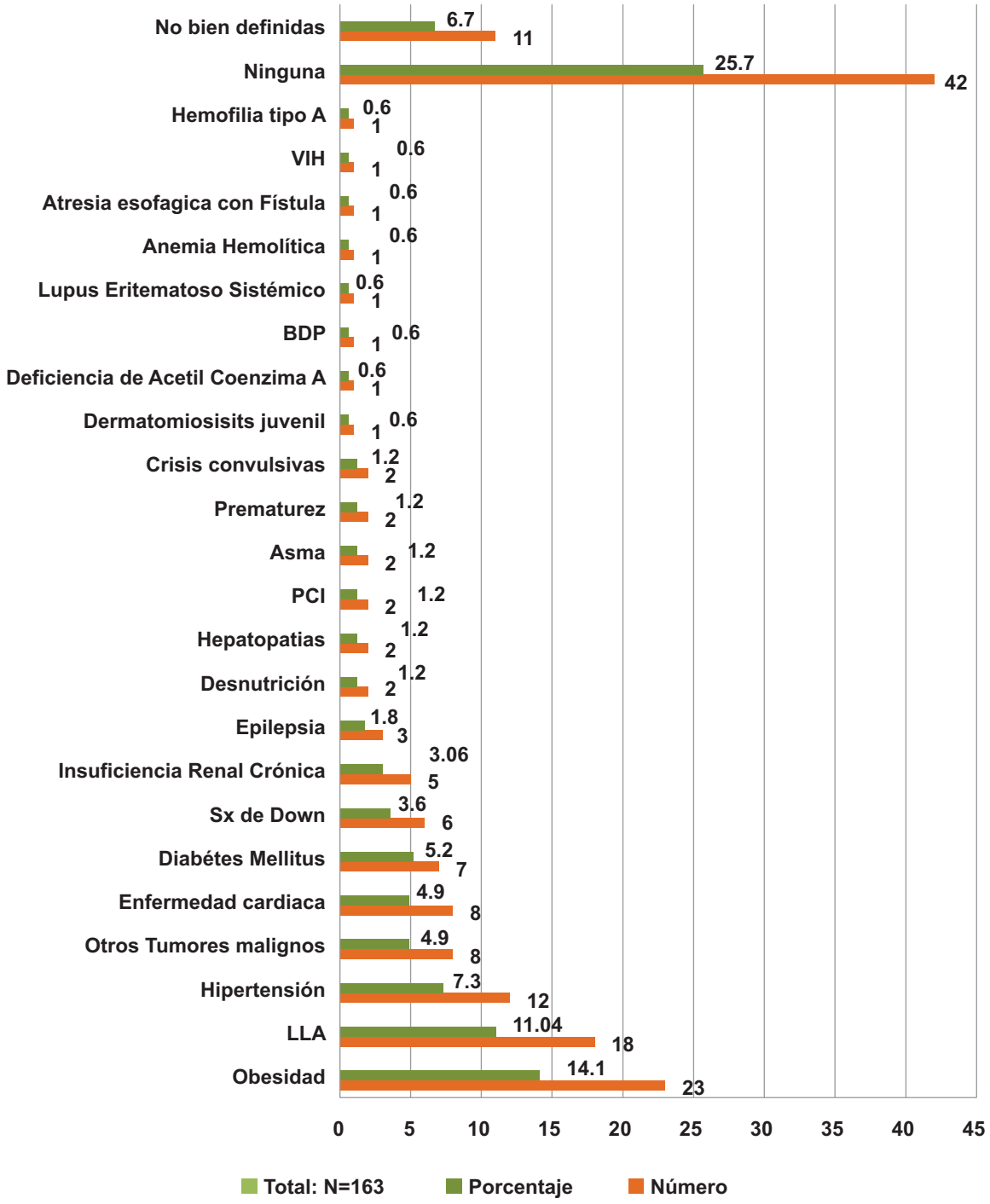

Figura 5. *Número y porcentaje de comorbilidad en pacientes ingresados por infección por SARS-CoV-2 vs. enfermedad de COVID-19.*

grupo de recién nacidos, solo con dos casos (0.01%) (Fig. 1). La procedencia de los pacientes fue de 10 Estados de nuestra república, pero hubo cuatro casos (2.4%) en los que se desconoció la procedencia, y de los nueve restantes, el Estado de México y la Ciudad de México fueron los principales sitios de procedencia, con 81 (49.6%) y 59 (36.1%) casos, respectivamente (Fig. 2). Considerando que somos un hospital de tercer nivel de la Ciudad de México, observamos que la mayoría de los casos atendidos fueron de las

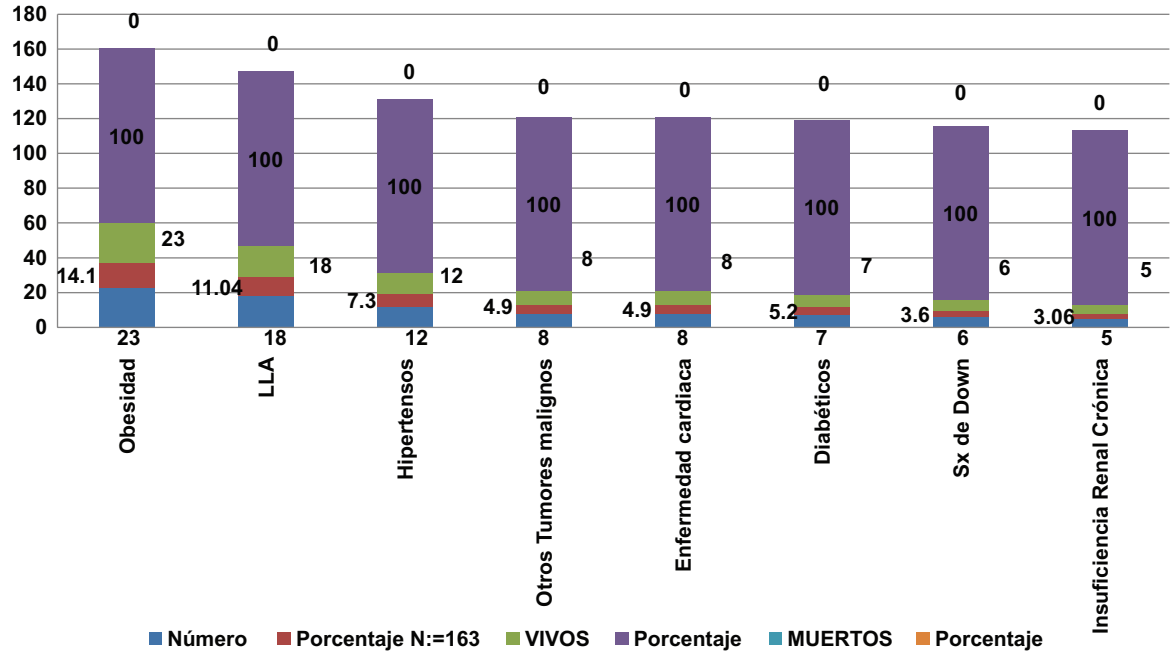

Figura 6. *Mortalidad asociada a la principal comorbilidad en pacientes ingresados al área COVID-19.*

Tabla 4. Número y porcentaje de vivos y muertos con comorbilidad asociada

Comorbilidad	n	% (n = 163)	Vivos	%	Muertos	%
Obesidad	23	14.1	23	100	0	0
LLA	18	11.04	18	100	0	0
Hipertensión arterial	12	7.3	12	100	0	0
Otros tumores malignos	8	4.9	8	100	0	0
Enfermedad cardiaca	8	4.9	8	100	0	0
Diabetes	7	5.2	7	100	0	0
Síndrome de Down	6	3.6	6	100	0	0
Insuficiencia renal crónica	5	3.06	5	100	0	0

LLA: leucemia linfoblástica aguda.

delegaciones Iztapalapa, Venustiano Carranza y Cuauhtémoc con 17 (28.8%), cinco y cinco (8.4%) casos, respectivamente. De igual manera, hubo siete casos (11.8%) en los que no se especificó su delegación y se captaron como simplemente procedentes de la Ciudad de México (Fig. 3).

En relación con la mortalidad hay que hacer notar que fue muy baja, tan solo del 2.4% (4/163), que correspondió a tres niñas y un niño (Tabla 1 y Fig. 4).

Considerando los objetivos del presente estudio en cuanto a coinfecciones registradas en estos 163 pacientes, llama la atención que solo se presentaron en cinco casos (3.06%): tres con virus (dos parvovirus B-19 y uno virus herpes tipo I) y dos bacterianas (uno con *Staphylococcus epidermidis* y otro con *Clostridioides difficile*) (Tabla 2 y Fig. 5).

En cuanto a la comorbilidad, sí encontramos un número considerable de asociación en los pacientes infectados por SARS-CoV-2 y en aquellos que desarrollaron la enfermedad COVID-19. Las principales afecciones encontradas como comorbilidad fueron ocho: obesidad, LLA, hipertensión arterial sistémica, otros tumores malignos, algún tipo de enfermedad cardiaca, diabetes, síndrome de Down e insuficiencia renal crónica; en conjunto, correspondieron al 51.04% del total de la comorbilidad registrada. Resalta que el 25.7% de los casos (42) no tenían comorbilidad alguna, y en otros 11 casos hubo otra no bien definida (6.7%). El resto (16.56%) fueron casos con diversa comorbilidad en menor número y porcentaje (Tabla 3 y Fig. 6).

Si bien es cierto que la COVID-19 se comporta de forma grave o agresiva en los pacientes con comorbilidad (sobre todo en adultos jóvenes y más aún en mayores)[9], al hacer el análisis de relación de mortalidad observada con algún tipo de comorbilidad, de las ocho que destacaron como las principales en

nuestros casos, no observamos esa relación (Tabla 4 y Fig. 6).

En cuanto al objetivo de identificar coinfecciones, como ya mencionamos, solo hubo cinco casos, pero en uno de ellos la misma coinfección se identificó en dos ocasiones, mismas en que el paciente presentó un cuadro asociado con infección por SARS-CoV-2 vs. enfermedad COVID-19, como se comentó en el apartado de resultados. Al respecto de las coinfecciones virales, es importante señalar que prácticamente no hubo ningún caso asociado con algún tipo de virus influenza, a pesar de haber tomado como un parámetro del estudio la temporada alta de influenza 2020-2021, a diferencia de lo reportado en otros estudios de la literatura donde se hace mención a la identificación de casos de coinfección con VRS , metapneumovirus humano, rinovirus o virus parainfluenza, entre otros[10]. En un estudio de Wu et al.[11] se encontró en 34/74 niños muestreados para patógenos respiratorios que solo 19 (51.4%) tuvieron coinfección con *Mycoplasma pneumoniae* (16; 84.2%), VRS (3; 15.8%), virus de Epstein-Barr (3; 15.8%), citomegalovirus (3; 15.8%) o influenza A y B (1; 5.3%). En otro reporte de Kumar et al.[12] se refieren 30 casos analizados de coinfección tanto viral como bacteriana, destacando 12 con *Salmonella typhi,* seis con meningitis por *Streptococcus pneumoniae*, tres con infección de vías urinarias por *Escherichia coli*, dos con *Salmonella paratyphi* A, dos con fiebre tifosa asociada a *Typhus/ Rickettsia,* dos positivos para virus de la hepatitis A y uno positivo para virus de la hepatitis E, un evento de artritis séptica por *Staphylococcus aureus* y una neumonía por *S. pneumoniae*[9-12]. Al parecer, las coinfecciones más frecuentes o comunes reportadas en la literatura corresponden a procesos bacterianos, destacando en 17 estudios como más frecuente *Mycoplasma pneumoniae* (42%), seguido de *Pseudomonas aeruginosa* (12%), *Haemophilus influenzae* y *Klebsiella pneumoniae* igual con 12%, respectivamente[13]. En nuestro estudio solo encontramos dos eventos asociados: uno con *S. epidermidis* (infección asociada a catéter venoso central) y otro con *C. difficile* (diarrea crónica).

En lo que respecta a la comorbilidad, hay quizás algunos más estudios y con mayor número de casos analizados. Destaca la diferencia de los primeros reportes, de los cuales en uno[14] solo se mencionaban cinco casos de niños de 0-16 años admitidos al King's College Hospital, en Londres, Reino Unido, entre el 25 de febrero y el 28 de abril de 2020, señalando que la comorbilidad preexistente incluyó parálisis cerebral, prematuridad (dos casos), enfermedad de Wilson y cardiomiopatía dilatada. Sin embargo, más recientemente, un reporte retrospectivo[15] con 12,306 niños analizados describe que la principal comorbilidad consistió en problemas respiratorios, sin especificar cuáles, pero se detectaron en 2310 casos (19.9%), seguidos de eventos gastrointestinales (334; 2.9%), neurológicos y neuromusculares (252; 2.2%), renales y urológicos (175; 1.5%), defectos congénitos o genéticos (127; 1.1%), problemas cardiovasculares (94; 0.8%), metabólicos (79; 0.8%), hematológicos o inmunológicos (57; 0.5%), y procesos malignos (51; 0.4%). Por igual, en un metaanálisis de 2021[16] se hace mención a que la principal comorbilidad observada en niños fue obesidad, enfermedad crónica respiratoria, enfermedad cardiovascular, trastornos neurológicos, trastornos inmunitarios, enfermedades metabólicas, trastornos hematológicos, cáncer, falla renal y afecciones gastrointestinales. Así mismo, como factores de riesgo para manifestaciones graves de la enfermedad por SARS-CoV-2 y riesgo de fallecer por COVID-19 se encontraron la diabetes, la hipertensión y la obesidad, al igual que en el adulto, resaltando que la obesidad fue un factor importante para desarrollar manifestaciones graves de la infección por SARS-CoV-2 e incluso de morir por COVID-19.

Conclusiones

A la fecha hay pocos reportes en la literatura de pacientes pediátricos con coinfecciones asociadas, mas no así con comorbilidad presente, por lo que consideramos importante llevar a cabo un monitoreo estrecho e incluso un estudio multicéntrico de las coinfecciones presentadas en pacientes pediátricos con infección por SARS-CoV-2 vs. enfermedad COVID-19, con lo cual tendríamos un panorama epidemiológico y geográfico de la situación que acontece en nuestros niños mexicanos y podríamos compararlo con lo reportado en la literatura internacional. Con los resultados obtenidos en nuestro estudio podemos concluir que las coinfecciones, tanto virales como bacterianas, son poco comunes en nuestro hospital. En cuanto a la comorbilidad, acorde con los principales estudios que reportan un gran número de casos analizados, podemos decir que tanto la obesidad como el cáncer (pacientes con LLA y diversos tumores malignos), así como la hipertensión, las enfermedades cardiacas y la diabetes, son importantes afecciones presentadas por nuestros pacientes estudiados. No obstante, de lo descrito en el reporte de

Tsankov et al.[16], en nuestros niños estudiados ninguna comorbilidad representó un riesgo para fallecer.

Por igual, consideramos que tomando como base este estudio pudiese ser de utilidad realizar o valorar en cualquier temporada del año si se debe realizar una prueba de coinfección junto con una prueba para detectar infección por SARS-CoV-2 en todos los pacientes pediátricos que ingresen con cuadro respiratorio agudo, o si solo debe hacerse en pacientes gravemente enfermos que requieran hospitalización o intubación. También, si se sospecha o corrobora que un niño tiene VRS o influenza según el historial clínico-epidemiológico de contacto y las pruebas iniciales, si debería realizarse la prueba del SARS-CoV-2. Estas cuestiones quizás puedan resolverse si se hace un estudio de seguimiento multicéntrico.

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Conflicto de intereses

Para la elaboración de este manuscrito los autores declaran que no hubo ni hay conflicto de intereses, comerciales ni económicos.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido la aprobación del Comité de Ética para el análisis y publicación de datos clínicos obtenidos de forma rutinaria. El consentimiento informado de los pacientes no fue requerido por tratarse de un estudio observacional retrospectivo.

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ORIGINAL ARTICLE

Can direct bilirubin-to-lymphocyte ratio predict surgery for pediatric adhesive small bowel obstruction?

¿La relación bilirrubina directa-linfocitos puede predecir la cirugía para la obstrucción adhesiva del intestino delgado en niños?

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Abstract

Objective: *Estimating which patients might require surgical intervention is crucial. Patients with complete bowel obstructions exhibit disrupted enterohepatic cycles of bile and bacteremia due to bacterial translocation. The goal of this study was to develop a prediction index using laboratory inflammatory data to identify patients who may need surgery.* **Materials and methods:** *The patients were divided into two groups based on their management strategy: Non-operative management (Group 1) and surgical management (Group 2).* **Results:** *The indirect bilirubin, direct bilirubin, and total bilirubin were significantly higher in Group 2 than in Group 1 ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-NLR (PNLR), and direct bilirubin-to-lymphocyte ratio (DBR) were significantly higher in Group 2 compared to Group 1 ($p = 0.041$, $p = 0.020$, and $p < 0.001$, respectively). In group 2, 78% have viable bowels. Resection was performed in 40% of cases, with 12% mortality and a 10-day average hospital stay. DLR performs the best overall accuracy (72%), demonstrating a well-balanced sensitivity (62%) and specificity (81%).* **Conclusions:** *This study suggested that DBR is a more accurate predictive index for surgical intervention in pediatric adhesive small bowel obstruction patients compared to NLR and PNLR, providing valuable guidance for treatment strategies.*

Keywords: *Neutrophil-to-lymphocyte ratio. Platelet-to-neutrophil-to-lymphocyte ratio. Direct bilirubin-to-lymphocyte ratio. Adhesive small bowel obstruction.*

Resumen

Objetivo: *Desarrollar un índice de predicción utilizando datos inflamatorios de laboratorio para identificar qué pacientes podrían necesitar cirugía.* **Método:** *Los pacientes se dividieron en dos grupos según su estrategia de manejo: no quirúrgico (grupo 1) o quirúrgico (grupo 2).* **Resultados:** *Las bilirrubinas indirecta, directa y total fueron significativamente más altas en el grupo 2 que en el grupo 1 ($p = 0.001$, $p < 0.001$ y $p < 0.001$, respectivamente). Las relaciones neutrófilos-linfocitos, plaquetas-neutrófilos-linfocitos y bilirrubina directa-linfocitos fueron significativamente más altas en el grupo 2 que en el grupo 1 ($p = 0.041$, $p = 0.020$ y $p < 0.001$, respectivamente). En el grupo 2, el 78% tenían intestino viable. Se realizó resección en el 40% de los casos, con un 12% de mortalidad y una estancia hospitalaria promedio de 10 días. La relación bilirrubina directa-linfocitos tuvo la mejor precisión general (72%), demostrando una sensibilidad bien equilibrada (62%) y una buena especificidad (81%).*

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Conclusiones: *Este estudio sugiere que la relación bilirrubina directa-linfocitos es un índice predictivo más preciso para la intervención quirúrgica en pacientes pediátricos con obstrucción adhesiva de intestino delgado en comparación con la de neutrófilos-linfocitos y la de plaquetas-neutrófilos-linfocitos, proporcionando una valiosa orientación para las estrategias de tratamiento.*

Palabras clave: *Relación neutrófilos-linfocitos. Relación plaquetas-neutrófilos-linfocitos. Relación bilirrubina directa-linfocitos. Obstrucción adhesiva de intestino delgado.*

Introduction

A complicated combination of cellular elements involved in inflammation and tissue repair results in post-operative adhesion development. According to the current theory, altering the serosal surfaces and being exposed to non-organic substances disrupt the mesothelium, causing a localized inflammatory reaction and an influx of fibroblasts that promote the formation of fibrin-based adhesions[1,2]. Although the actual prevalence of adhesive small bowel obstruction (ASBO) in children is unknown, reports suggest that it can range from 1.1 to 8.3%, with the majority of cases occurring during the 1st year following surgery[3-5]. Compared to adults, children have a higher lifetime risk of developing adhesion-related issues because of their age. The success rate of non-operative management has been reported to range substantially from 0 to 63%[4-6].

Estimating which patients might require surgical intervention is crucial. ASBO, a common intra-abdominal infection, is frequently associated with *Escherichia coli* and *Bacteroides fragilis*[6]. Bacteremia caused by these bacteria can lead to endotoxemia and impaired bilirubin excretion, increasing direct bilirubin (DB) levels in ASBO patients. Furthermore, patients with complete bowel obstructions exhibit disrupted enterohepatic cycles of bile and bacteremia due to bacterial translocation. These conditions contribute to both inflammation and neutrophil-to-lymphocyte ratio (NLR) and platelet-to-neutrophil-to-lymphocyte ratio (PNLR) and increased DB and direct bilirubin-to-lymphocyte ratio (DLR), levels, particularly in complete obstructions[7,8].

In this study, receiver operating characteristic (ROC) curve analysis was used to investigate the predictive value of several biomarker combinations related to the requirement for surgical treatment for ASBO.

Methods

This study comprises patients who presented with ASBO to the Pediatric Surgery Clinic at Dicle University between 2010 and 2022. The study commenced following the approval of the ethics committee (no: 211, date: April 12, 2023). Variables such as patients' age, sex, prior surgery (primary pathology), physical examination findings at the time of presentation, duration of symptoms, laboratory blood test results, radiological findings, performed surgery, viability status of the intestines, surgery duration, post-operative complications, mortality, and length of stay were retrospectively evaluated.

Some patients with ASBO were managed nonoperatively, successfully following a non-operative management approach. However, a portion of the patients required surgery. The patients were divided into two groups based on their management strategy: non-operative management (Group 1) and surgical management (Group 2). The aforementioned factors were compared between the two groups.

Inclusion criteria

Patients under the age of 18, those with a previous history of surgery, and those with consistent and accurate data in retrospective file scans were included in this study.

Exclusion criteria

Patients over the age of 18, neonates (due to highly variable laboratory parameters), and those presenting with COVID-19, upper respiratory tract diseases, or any other diseases affecting laboratory parameters beyond the diagnosis of ASBO were excluded from the study.

Clinical monitoring

All patients presenting with vomiting, absence of fecal output, and abdominal distension (Fig. 1), who had a previous history of surgery, underwent a physical examination. This was followed by laboratory blood tests. Subsequently, every patient underwent radiography (Figs. 2 and 3) and ultrasonography. Advanced imaging techniques such as computed

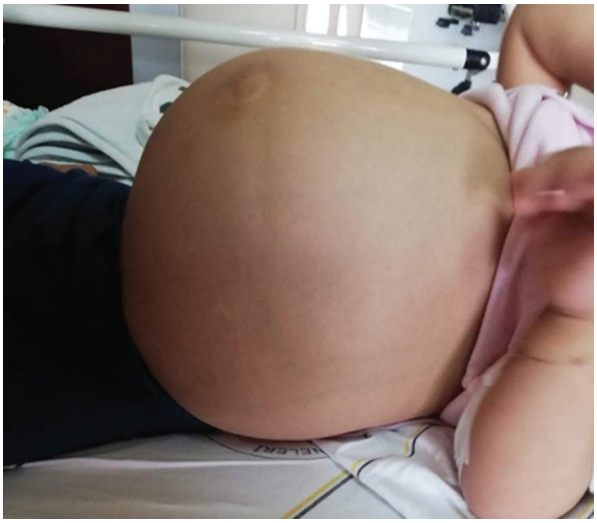

Figure 1. *Distended abdomen in a patient with adhesive small bowel obstruction.*

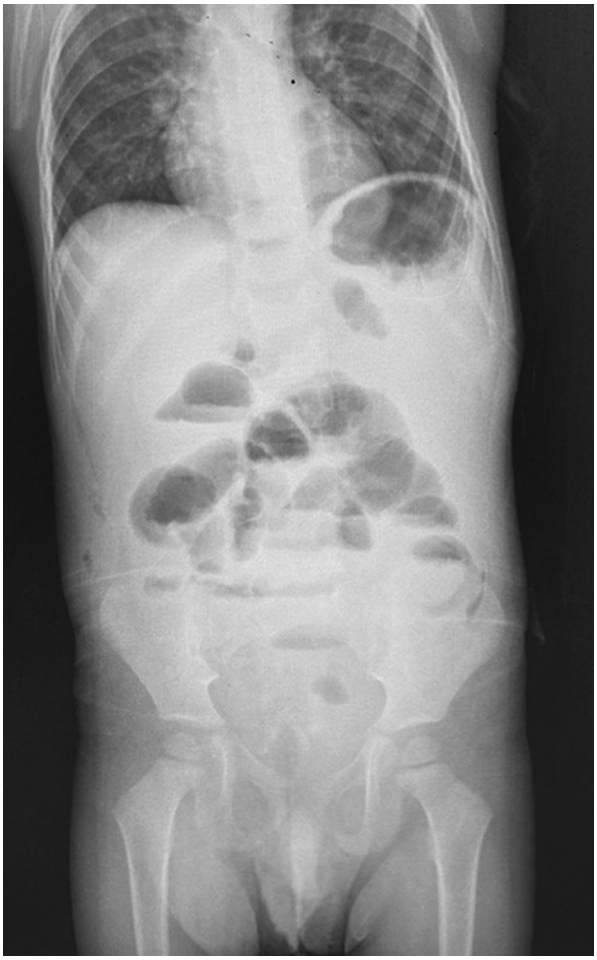

Figure 2. *Pre-opertaive radiograph from a patient who treated non-operatively (Group 1).*

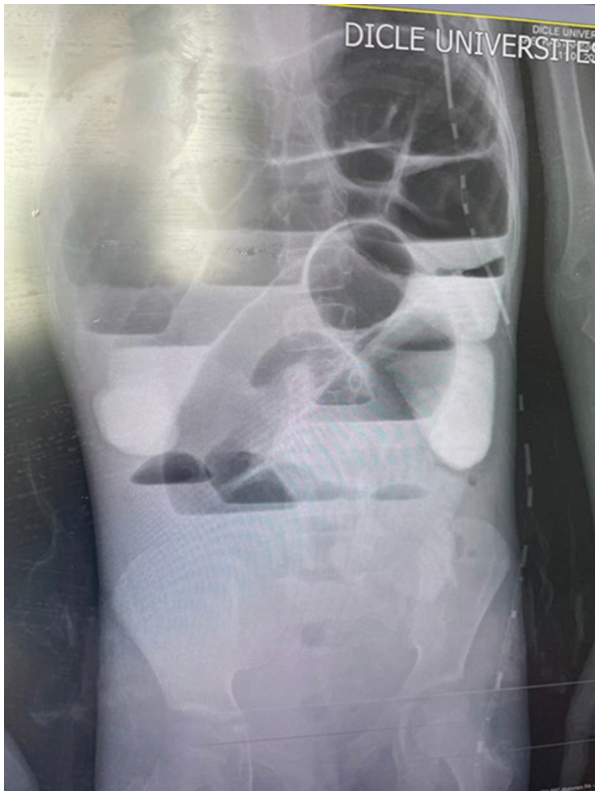

Figure 3. *Pre-operative radiograph from a patient who was treated with surgical intervention (Group 2).*

tomography were utilized where necessary. Dehydrated patients, which constituted the majority of cases, were rehydrated with 20 mL/kg of 0.09% NaCl saline. All patients were put on nil per os and a nasogastric tube was inserted. Suitable antibiotic therapy was administered, and adequate analgesia was ensured. Patients in poor general condition were monitored in intensive care. Initially, all patients were followed up with enema administration. Those patients who had gas and fecal output after the enema, and showed a reduction in distension, continued to be nonoperatively managed. However, patients who persisted in vomiting (those continuing to produce bile from the nasogastric tube) and showed no decrease in distension were subjected to surgical intervention.

Statistical analysis

The statistical analysis of patient data employed descriptive statistics, frequency, and other characteristics for all items. Mean and standard deviation were used for displaying continuous data. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to determine whether continuous data were normal. When data varied from a normal distribution, non-parametric

tests were used instead of the Student's t-test for continuous and regularly distributed variables. For categorical variables, Chi-square tests were utilized, and Fisher's exact tests were applied as necessary. The diagnostic performance of the NLR, PNLR, and DLR was investigated using ROC analysis. SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA), was used to analyze the data. A $p < 0.05$ was considered statistically significant.

Results

The mean age of patients in Group 1 was 4.40 ± 3.85 years, while in Group 2, it was 4.64 ± 3.43 years ($p = 0.745$). Regarding gender, 50% of patients in Group 1 and 58% in Group 2 were men ($p = 0.418$). White blood cell count was significantly higher in Group 2 (15.47 SD2.54) compared to Group 1 (13.16 ± 3.32) ($p < 0.001$). Similarly, the neutrophil count (NEU) was also significantly higher in Group 2 (12.34 ± 3.19) compared to Group 1 (10.01 ± 3.48) ($p < 0.001$). Lymphocyte (LYM) counts and platelet counts were slightly higher in Group 2 than Group 1, but the difference was not statistically significant ($p = 0.307$ and $p = 0.082$, respectively). The indirect bilirubin, DB, and total bilirubin were significantly higher in Group 2 than in Group 1 ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Although the C-reactive protein (CRP) level was higher in Group 2 (68.39 ± 57.59) than in Group 1 (63.1 ± 25.52), the difference was not statistically significant ($p = 0.065$). The NLR and PNLR were significantly higher in Group 2 compared to Group 1 ($p = 0.041$ and $p = 0.020$, respectively). However, the PLR was not significantly different between the groups ($p = 0.195$). DLR was significantly higher in Group 2 (0.224 ± 0.124) than in Group 1 (0.147 ± 0.113) ($p < 0.001$) (Table 1).

The surgical management group consisted of 50 patients. Evaluation of bowel status revealed that in the majority of the cases (n = 39, 78%), the bowel was viable, whereas in a smaller proportion of cases (n = 11, 22%), the bowel was gangrenous. Of the surgical procedures performed, intestinal resections were carried out in 20 patients (40%), while non-resection procedures were conducted in the remaining 30 patients (60%). In cases where a resection was performed, further procedures involved anastomosis in 8 patients (16%) and stoma creation in 12 patients (24%). At post-operative period, 16 patients (32%) need to be observed in intensive care unit. Post-operative complications were observed in 12 patients (24%). The mortality rate was 12% (n = 6). The mean length of hospital stay was reported as 10 SD7 days (Table 2).

Table 1. Comparison of non-operative management and surgical group

	Group 1 (n = 52)		Group 2 (n = 50)		p-value
	Mean	SD	Mean	SD	
Age	4.40	3.85	4.64	3.43	0.745
Gender (M)*	26	50%	29	58%	0.418
WBC	13.16	3.32	15.47	2.54	<0.001
NEU	10.01	3.48	12.34	3.19	<0.001
LYM	2.08	0.96	1.89	0.90	0.307
PLT	266	55	287	64	0.082
IB	0.33	0.23	0.49	0.25	0.001
DB	0.23	0.11	0.33	0.12	<0.001
TB	0.57	0.32	0.83	0.83	<0.001
CRP	63.12	25.52	68.39	57.59	0.065
NLR	6.47	5.23	8.76	5.89	0.041
PLR	159	86	181	81	0.195
PNLR	1692	1354	2360	1487	0.020
DLR	0.147	0.113	0.224	0.124	< 0.001

*n(%), Chi-square test; other items, Independent T-test. SD: standard deviation; WBC: white blood cell count; NEU: neutrophil; LYM: lymphocyte; PLT: platelet; IB: indirect bilirubin; DB: direct bilirubin; TB: total bilirubin; CRP: c-reactive protein; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; PNLR: platelet neutrophil–lymhocyte ratio; DLR: direct bilirubin lymphocyte ratio.

Table 2. Characteristics of the patients underwent surgery

Surgical group	n = 50 (%)
Bowel status	
Viable	39 (78)
Gangrenous	11 (22)
Procedure performed	
Resection	20 (40)
Non-resection	30 (60)
Procedure after resection	
Anastomosis	8 (16)
Stoma	12 (24)
Post-operative ICU	16 (32)
Post-operative complication	12 (24)
Mortality	
Dead	6 (12)
Survived	44 (88)
Lenght of stay (days)*	10 (7)

*mean (SD); other items: n(%). ICU: intensive care unit.

In this study, the NLR, PLNR, and DLR indices tested using ROC analysis to identify patients who require surgery. Accordingly, the NLR was observed to have a cut-off value of 4.1. The area under the ROC curve (AUC) for this index was 0.630, which signifies moderate predictive accuracy. The sensitivity was quite high at 86%, indicating a substantial ability to correctly identify positive cases. However, the specificity was observed to be relatively low at 40%, suggesting a moderate rate of accurately identifying negative cases. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 58% and 75%, respectively, while the overall accuracy of the NLR was found to be 63%. The PNLR was evaluated at a cut-off value of 2137. This index had a higher AUC value of 0.662 compared to NLR, implying a somewhat improved predictive accuracy. The sensitivity was lower at 48%, but the specificity was considerably high at 83%. This suggests that the PNLR has a strong ability to accurately classify negative cases, despite a lower ability to detect positive cases. The PPV and NPV for PNLR were 73% and 62%, respectively, and the overall accuracy came out to be 65%. The DLR demonstrated the highest AUC value of 0.711 among the indices, indicating superior predictive accuracy. The cut-off value was set at 0.2. The sensitivity and specificity for DLR were recorded at 62% and 81%, respectively, showing a well-balanced ability to correctly identify both positive and negative cases. The PPV and NPV were 75% and 69%, respectively. Notably, DLR outperformed both NLR and PNLR in terms of overall accuracy, with a rate of 72% (Table 3 and Fig. 4).

Table 3. Indeces diagnostic test analysis

Index	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR	4.1	0.630	86%	40%	58%	75%	63%
PNLR	2137	0.662	48%	83%	73%	62%	65%
DLR	0.2	0.711	62%	81%	75%	69%	72%

NLR: neutrophil–lymphocyte ratio; PNLR: platelet neutrophil–lymhocyte ratio; DLR: direct bilirubin–lymphocyte ratio.

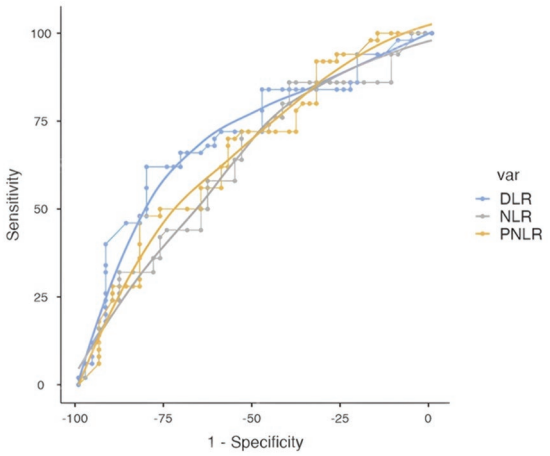

Figure 4. *ROC graph of the indexes.*

Discussion

ASBO can result in strangulation, triggering bowel ischemia and necrosis due to obstructed blood flow[9]. A recent single-center review demonstrated that 54% of pediatric cases were successfully managed nonoperatively, while 12% required immediate surgical intervention, and another 34% needed abdominal surgery later during their hospital stay[10]. These findings contrast with a multi-center study using the Kids' Inpatient Database, which reported that 85% of pediatric ASBO patients required surgical intervention, with 16.5% undergoing bowel resection[11]. However, in this study, 50% of patients were needed surgical intervention. In 22% of the cases, the patients' bowels were gangrenous. In 40% of these cases, an intestinal resection was performed. Meanwhile, stoma formation was carried out in 12 (24%) patients.

In the current study, investigated the discriminating ability of various factor combinations, particularly the up and down combinations, identified with pre-operative regular laboratory work and defined many discoveries. The main finding of this study was that patients who had surgical management had considerably greater DLR levels than patients who were managed nonoperatively, where DLR is defined as the sum of LYM counts and DB levels. The DLR was a more accurate indicator for ASBO who received surgical management when compared to other metrics, such as the NLR and PNLR levels.

Studies are collected that show a number of elements play a role in systemic inflammatory states, which can be used to assess the presence of ischemia. Measurable inflammatory factors, which were responses from and released by the local ischemic intestinal wall, were found in the peripheral blood as a result of strangulation[7,8]. Various inflammatory indicators have been reported to be helpful in the diagnosis and treatment monitoring in different disease types[7,8].

ASBO patients can use peripheral blood systemic inflammatory factor analysis to predict intestinal ischemia and necrosis, although the most accurate parameters for this analysis are still unknown.

In the research conducted by Chen et al.,[12] it was discovered that the inflammatory response's intensity was discernibly higher in patients who underwent intestinal resection. This was demonstrated by increased values of CRP and leukocyte count and decreased levels of albumin and LYMs, suggesting an inflammatory reaction to intestinal ischemia and necrosis. Prior studies on inguinal hernias noted that the lymphocyte-to-CRP ratio (LCR) was generally higher in patients experiencing strangulation, indicating its potential as a predictor for the necessity of bowel resection[13]. Another multivariate study also confirmed the NLR as being significantly linked with hernia strangulation and clear bowel ischemia[14]. The findings concluded that specific surrogate markers could be utilized to anticipate intestinal necrosis and have clinical relevance. In addition, it has been observed that the LCR is related to the prognosis of certain types of cancer patients, like those with stomach cancer and colorectal cancer[14,15]. A retrospective study revealed an elevation in the levels of CRP and NLR in patients suffering from acute pancreatitis[16]. Another piece of research indicated a significant correlation between NLR levels and patients with acute mesenteric ischemia who had undergone intestinal resection[17,18]. The study led by Chen et al. found a noticeable rise in NLR, CRP levels, and NEU in patients who had an intestinal resection[12]. However, this study found that NLR, PNLR, and DLR were significantly higher in surgical group. This suggests that in the surgical group, the bowel ischemia risk is more closely, indicating that these patients need surgery. Indeed, this study observed that patients with lower NLR, PLNR, and DLR values, whose bowels have not ischemia and necrosis, are in better general condition and these inflammatory indexes are lower.

Recently, there have been numerous retrospective and a few prospective studies that have investigated hyperbilirubinemia as an indicator of acute appendicitis and perforation[8]. It is common to observe elevated serum bilirubin levels and jaundice in patients with a septic condition. ASBO is one of the most frequent intra-abdominal infections. *E. coli* and *B. fragilis* are the most commonly isolated bacteria in these situations. Bacteremia, which these bacteria cause, can lead to endotoxemia, thus impairing bilirubin excretion from the bile canaliculi. Consequently, direct bilirubin levels increase in ASBO patients[7,8]. In another perspective, patients with complete bowel obstruction (surgical group) have impaired enterohepatic cycles of bile due to the lack of intestinal transit and experience bacteremia due to bacterial translocation[7,8]. All these mechanisms result in an increase in both direct bilirubin and DLR, especially in complete obstructions (surgical group). This study is the first and only research that investigates the diagnostic value of DLR in ASBO patients. Among the tested indices, DLR demonstrated the highest AUC value of 0.711, indicating superior predictive accuracy. The cut-off value was established at 0.2. The sensitivity and specificity for DLR were documented at 62% and 81%, respectively, displaying a balanced capability to correctly identify both positive and negative cases. The PPV and NPV were calculated at 75% and 69%, respectively. Remarkably, in terms of overall accuracy, DLR outperformed both NLR and PNLR, with a success rate of 72%.

The study's limitations include its retrospective design and single-center data, which may limit generalizability. In addition, selection bias may exist in choosing management strategies. The exclusion of neonates and individuals with other diseases impacting laboratory parameters could influence results. Unaccounted confounding factors such as surgeon's experience and patients' underlying health conditions might affect outcomes. Finally, the study relies heavily on the accuracy of past medical records.

In conclusion, DLR is a more accurate predictive index for surgical intervention in pediatric ASBO patients compared to NLR, PNLR, providing valuable guidance for treatment strategies. To date, no other study has addressed this issue specifically in pediatric patients with ASBO.

Author's contributions

Research concept and design: MA, SA, EB, MHO, BA, MK, TOK, Data analysis and interpretation: MA, SA, TOK, Collection and/or assembly of data: MHO, EB, BA, MK, Writing the article: MA, TOK, BA, MHO, Critical revision of the article: EB, MA, SA, MK, Final approval of the article: MA, MHO, SA, BA, TOK, MK, EB, All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

Funding source

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Informed consent

Written informed consent was obtained from all individual participants and/or their gaurdians.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Comparison of clinical efficacy of different colon anastomosis methods in laparoscopic radical resection of colorectal cancer

Comparación de la eficacia clínica de diferentes métodos de anastomosis de colon en la resección radical laparoscópica del cáncer colorrectal

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Abstract

Objective: *The objective of this study was to investigate the clinical effect of overlap anastomosis and functional end-to-end anastomosis (FEEA) in laparoscopic radical resection of colorectal cancer (CRC).* **Methods:** *The clinical data of 180 patients who underwent laparoscopic radical resection of CRC and side-to-side anastomosis were retrospectively collected; the patients were divided into the Overlap group and FEEA group, according to the anastomosis method that was used to treat them.* **Results:** *The Overlap group had a shorter operation time, anastomosis time, post-operative hospital stay, post-operative feeding time, and post-operative exhaust time than the FEEA group ($p < 0.05$). The total incidence of post-operative complications was 14.4% (13/90) in the FEEA group and 0.7% (6/90) in the Overlap group, and there was no significant difference between the two groups ($p > 0.05$).* **Conclusions:** *Overlapping anastomosis can shorten the operation time and accelerate the recovery of intestinal function without increasing the incidence of post-operative complications, and it will not affect the quality of life and survival of patients in the short term after surgery.*

Keywords: *Colon/colorectal cancer. Laparoscopy. Overlap anastomosis. Functional end-to-end anastomosis.*

Resumen

Objetivo: *Investigar el efecto clínico de la anastomosis superpuesta y de la anastomosis funcional de extremo a extremo (AFEE) en la resección radical laparoscópica del cáncer colorrectal (CCR).* **Método:** *Se recolectaron retrospectivamente los datos clínicos de 180 pacientes sometidos a resección radical laparoscópica de CCR y anastomosis de lado a lado. Los pacientes se dividieron en grupo de anastomosis superpuesta y grupo AFEE, según el método de anastomosis que se utilizó para tratarlos.* **Resultados:** *El grupo de anastomosis superpuesta tuvo un tiempo de operación, un tiempo de anastomosis, una estancia hospitalaria posoperatoria, un tiempo de alimentación posoperatorio y un tiempo de escape posoperatorio más cortos que el grupo AFEE ($p < 0.05$). La incidencia total de complicaciones posoperatorias fue del 14.4% (13/90) en el grupo AFEE y del 0.7% (6/90) en el grupo de anastomosis superpuesta, y no hubo diferencias significativas entre los dos grupos ($p > 0.05$).* **Conclusiones:** *La anastomosis superpuesta puede acortar el tiempo operatorio y acelerar la recuperación de la función intestinal sin aumentar la incidencia de complicaciones posoperatorias, y sin afectar la calidad de vida y la supervivencia de los pacientes a corto plazo después de la cirugía.*

***Palabras clave*:** *Cáncer de colon/colorrectal. Laparoscopia. Anastomosis superpuesta. Anastomosis funcional de extremo a extremo.*

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Introduction

Colorectal cancer (CRC) is a common malignant tumor of the digestive tract. According to global cancer statistics, there were more than 1.9 million new CRC cases and more than 935,000 deaths in 2020, accounting for around 1/10 of cancer cases and deaths[1]. The incidence and mortality rates of CRC in China are among the highest in the world[2]. The disease is caused by the abnormal proliferation of colorectal glandular epithelial cells. In addition to the aging population and the dietary habits in high-income countries, adverse factors such as obesity, lack of physical exercise, and smoking increase the likelihood of CRC[3].

At present, the treatment of CRC is still based on surgery, supplemented with radiotherapy, chemotherapy, or targeted therapy[4-6]. Radical resection of the tumor and digestive tract reconstruction are two key steps for successful laparoscopic CRC surgery[7]. In terms of radical resection, it is necessary to determine the extent of resection according to the clinical stage of the tumor; however, due to the development of complete mesocolic resection (CME) and lymph node dissection specifications[8-10], radical resection of cT1-4N0-2M0 CRC has been achieved in clinical practice[11]. Digestive tract reconstruction determines the success rate of surgery, operation time, post-operative recovery, incidence of anastomotic complications, and other issues[12,13]. Traditional digestive tract reconstruction of the colon has three anastomosis methods: end-to-end, end-to-side, and side-to-side anastomosis[14,15]. Side-to-side anastomosis is the predominant method, and functional end-to-end anastomosis (FEEA) and overlap anastomosis are the two most important anastomosis methods for side-to-side anastomosis[16,17].

FEEA can reduce the incidence of anastomotic stricture, post-operative pain and intraoperative blood loss, and its short-term efficacy is better. However, it is a difficult and time-consuming endoscopic operation, requiring the free length of the intestinal canal and an experienced medical team. This anastomosis method of reconstruction is also performed against the physiological peristaltic direction of the intestinal tract[18,19]. In 2010, Inaba et al.[17] proposed an overlap anastomosis method that has the advantages of FEEA in digestive tract reconstruction during laparoscopic total gastrectomy but low requirements for free bowel length. The operation is also simple and follows the direction of physiological peristalsis of the intestine, meaning it has been widely used in clinical surgery. Previous studies have found that overlap anastomosis takes less time and patients recover faster after surgery and have a shorter post-operative hospital stay. Moreover, it does not increase the incidence of anastomosis-related complications compared with FEEA surgery and anastomosis[20,21]. However, there are still few studies on laparoscopic overlap anastomosis and FEEA in terms of surgical conditions, incidence of complications, and post-operative quality of life (QOL) for patients, and no unified criteria for digestive tract reconstruction have been developed. This study explores the intraoperative conditions, post-operative recovery, post-operative complications, and post-operative QOL of patients undergoing laparoscopic CRC overlapping anastomosis and FEEA to identify an anastomosis method that improves patient QOL and reduces their pain and to provide new reference suggestions for laparoscopic anastomosis of CRC.

Study participants and methods

Study participants

The convenience sampling method was used to select 180 patients who underwent laparoscopic radical resection of CRC and lateral anastomosis in the gastrointestinal surgery department of the authors' hospital between March 2020 and May 2023 as the study participants. The patients were divided into the Overlap group (n = 90) and the FEEA group (n = 90), according to the anastomosis method that was used. The study inclusion criteria were as follows: patients (1) aged 18-75 years; (2) with CRC confirmed by pre-operative colonoscopy and pathological examination; (3) with CRC without intestinal obstruction and with pre-operative bowel preparation; (4) who underwent total laparoscopic radical resection of CRC, intraoperative standard lymph node dissection and CME; and (5) with complete medical records. The exclusion criteria were as follows: patients (1) with a history of other malignant tumors or CRC combined with other malignant tumors within the previous 5 years; (2) with any distant metastasis; (3) with a history of previous abdominal surgery or inflammatory bowel disease; (4) whose surgery involved a forced conversion to laparotomy; (5) with uncontrolled nutritional disorders and mental illness; and (6) who were unable to complete the follow-up for 12 months after the surgery. The screening process of the research participants is shown in figure 1.

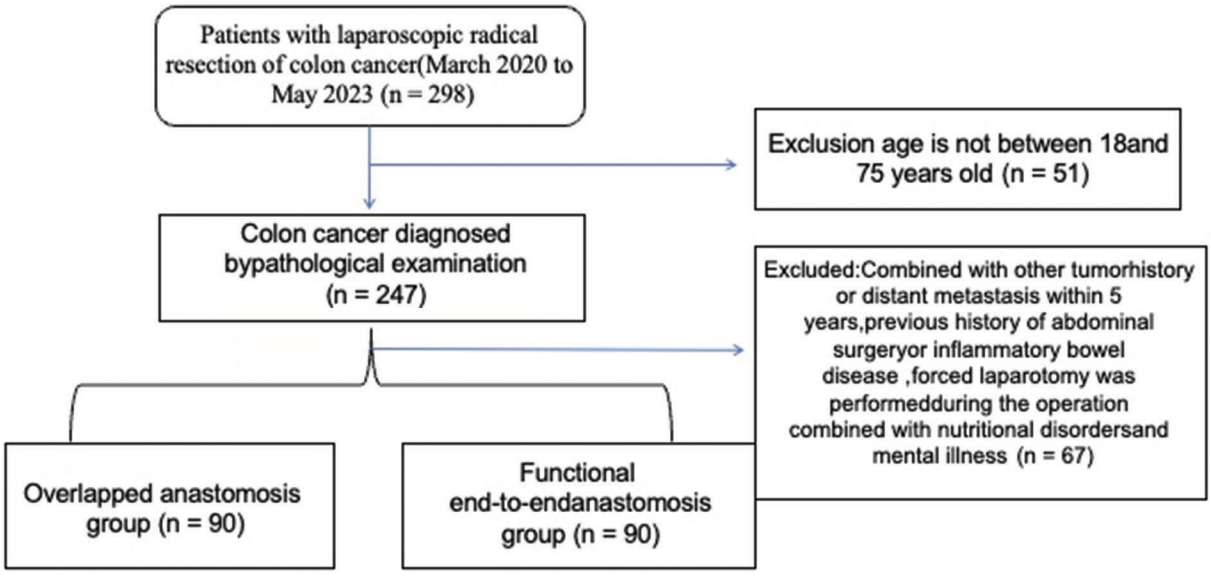

Figure 1. *Research subject screening flow chart.*

Study methods

The pre-operative preparation was as follows. (1) For patients with underlying diseases, such as hypertension, diabetes, and coronary heart disease, multidisciplinary consultation was conducted to assess the risk of surgery; for patients with low protein, anemia, electrolyte imbalance, and malnutrition, levels had to be adjusted to a reasonable range; for patients with small non-invasive serous tumors, pre-operative colonoscopic carbon nanoparticle localization was routinely performed. (2) A liquid diet was started 1 day before surgery, and polyethylene glycol electrolyte powder solution was taken orally to clean the intestine one night beforehand. Fasting and drinking were prohibited for 12 h and 4 h, respectively. (3) Prophylactic antibiotics were administered 30 min before the operation.

In terms of surgical methods, during the operation, CME and standardized lymph node dissection were performed under laparoscopy, and intestinal anastomosis was fully mobilized. For overlapping anastomosis, the small intestine and colon were cut off at their pre-resection sites. The ileum was placed in parallel with the transverse colon, and a small hole was made in the intestinal wall. Ileal-transverse side-to-side closure anastomosis was performed with an endoscopic cutting closure device. A barbed wire interrupted suture was used to strengthen the stump and anastomosis, and when the anastomosis was unobstructed and tension-free and the blood supply was good, the mesangial hole was closed (Fig. 2). In terms of FEEA, the right colon was pulled out through the incision, the ileum mesentery was separated from it, and the mesentery was also detached from the middle of the transverse colon. The mesentery was clamped with a purse-string forceps 15 cm from the ileocecal junction, and a purse-string needle was inserted. A 25# tubular stapler was placed at the ileum stump, and the purse-string line was tightened. After the intended resection of the transverse colon was removed, a 25# tubular stapler was placed through the stump, and the ileum-transverse colon end-to-side anastomosis was performed. To close the transverse colon residue, the transverse colon stump was reinforced with barbed wire, and the transverse-colon ileal anastomosis was strengthened with 4-0-line interrupted sutures (Fig. 3).

The post-operative treatment was as follows: (1) bed rest with close monitoring of the patient's vital signs; (2) regular re-examination of blood, liver and kidney function and electrolytes, and the wearing of elastic stockings to prevent lower extremity deep venous thrombosis; (3) post-operative fasting and parenteral nutrition to control blood pressure and blood glucose and maintain water and electrolyte balance; (4) patient-controlled analgesia within 48 h of surgery, and non-steroidal anti-inflammatory drug administration for rescue analgesia; (5) daily assessment of pain levels using Visual Analog Scale (VAS) criteria for pain (no pain = 0 points, mild pain = 1-3 points, moderate pain = 4-6 points, severe pain = 7-9 points, and intolerable pain = 10 points); (6) monitoring and evaluation of the patient's defecation and feces to assess his/her intestinal recovery status (the patient received a liquid

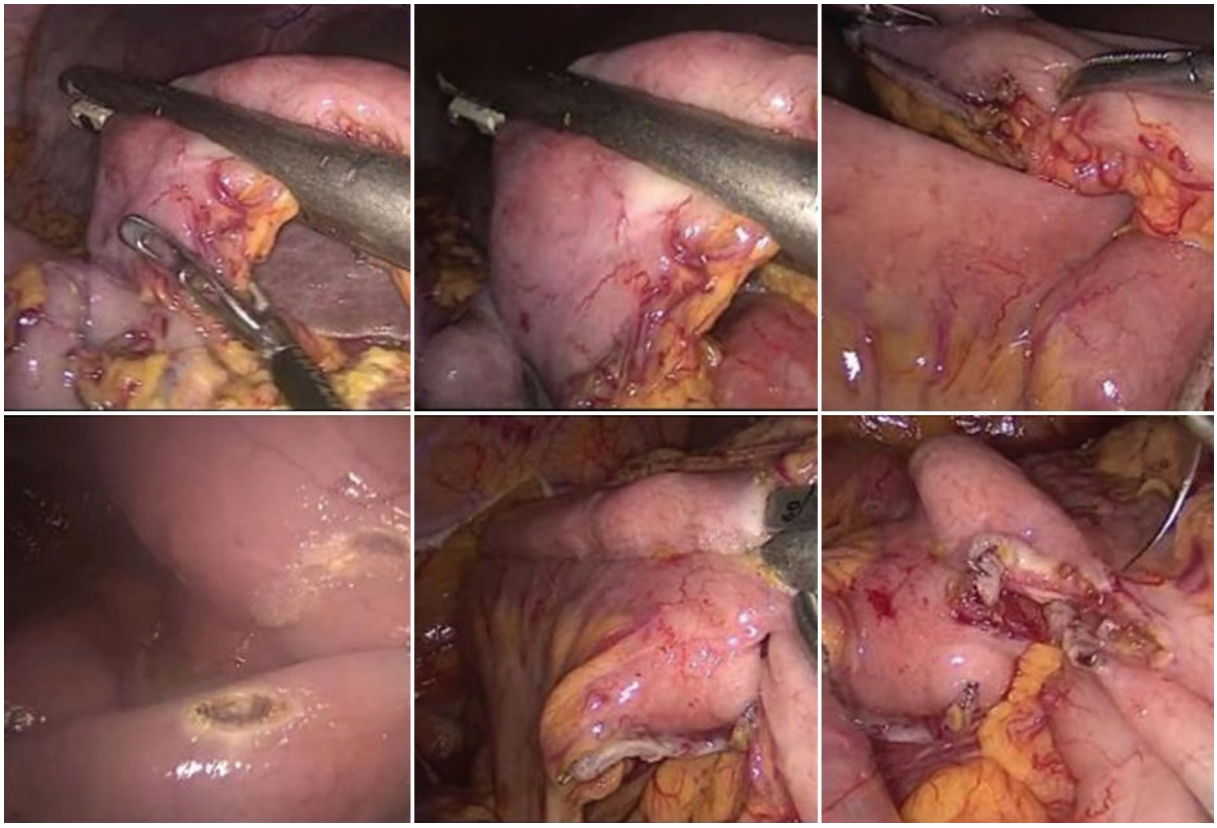

Figure 2. *Overlapping anastomosis method.*

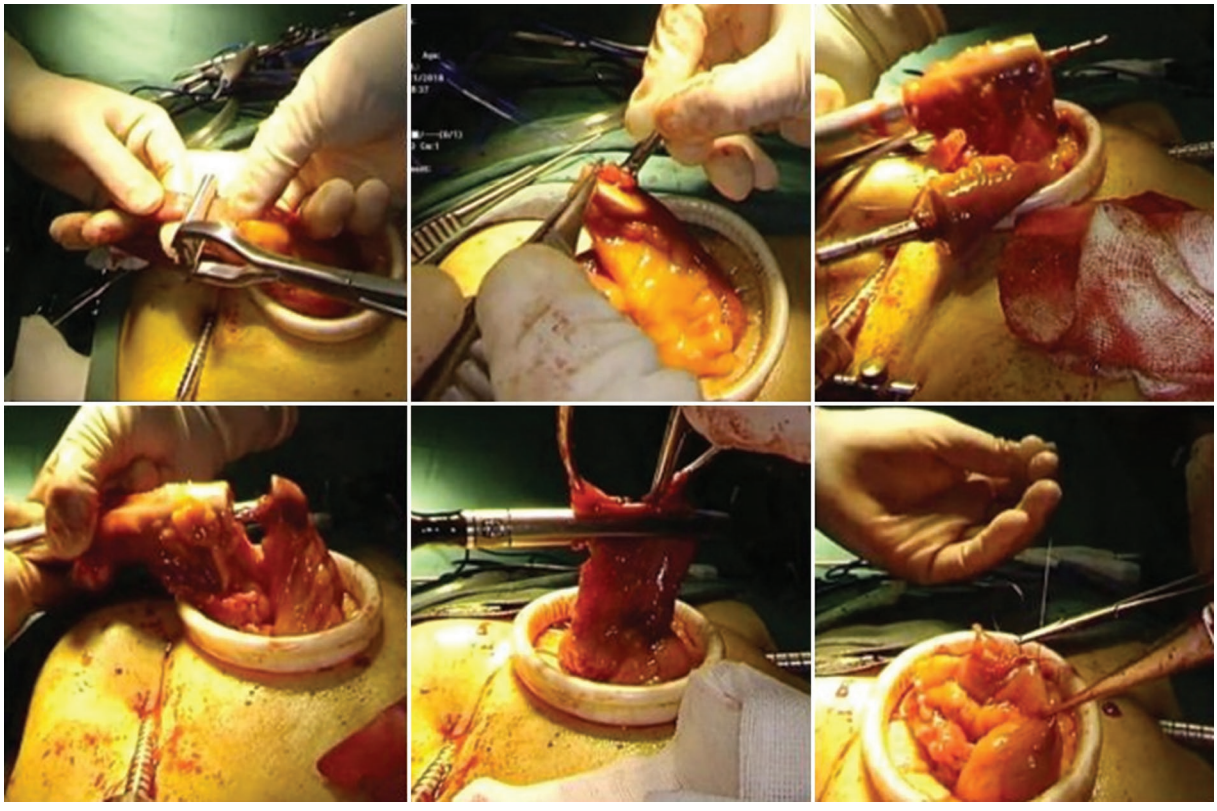

Figure 3. *Functional end-to-end anastomosis method.*

diet once defecation commenced and gradually transitioned to a regular diet); (7) the monitoring of abdominal drainage fluid and drainage volume, where once the drainage fluid was non-bloody, non-purulent, and non-chylous and < 30 mL/d, the drainage tube was removed; and (8) the discharge of patients who were asymptomatic and eating well with unobstructed defecation.

Data collection

General patient data consisting of age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, tumor location, size and stage, history of hypertension, diabetes and abdominal surgery, intraoperative conditions, post-operative recovery, post-operative perioperative complications, post-operative follow-up, and post-operative pathological results were gathered.

The intraoperative conditions included data on operation and anastomosis duration, intraoperative blood loss and abdominal incision length, and post-operative recovery included data on post-operative hospital stay, feeding and defecation times, and the post-operative 24 h pain score. Pain scores 24 h after surgery were measured using the VAS, with 0 indicating no pain, 1-3 mild pain, 4-6 moderate pain, 7-9 severe pain, and 10 intolerable pain.

Post-operative perioperative complications pertained to whether there was an incision, abdominal or lung infection, abdominal bleeding, incisional hernia, anastomotic leakage, bleeding or stenosis, and intestinal obstruction. The post-operative pathological results concerned the number of dissected and positive lymph nodes, nerve, and vascular invasion, specimen length, and tumor differentiation and growth patterns.

Regarding the 12-month post-operative follow-up, the QOL score table was used to evaluate the QOL of the two groups at 3, 6, 9, and 12 months after the operation. Every 3 months after surgery, carcinoembryonic antigen levels were assessed and enhanced computed tomography scans of the chest and abdomen were taken. Enteroscopy was performed every 6 months to ascertain whether the patients had tumor recurrence and metastasis, and the follow-up also recorded whether the patient died within 12 months of the surgery.

Statistical analysis

Data analysis was performed using SPSS 26.00, and measurement data conforming to the normal distribution were expressed in the form of mean ± standard deviation (± s) and compared using the independent samples t-test. Enumeration data were presented as absolute numbers or percentages (n [%]) and compared using χ^2 or Fisher's exact tests, with $p \leq 0.05$ was considered statistically significant.

Results

Comparison of general data

The FEEA group included 90 patients, 52 men and 38 women, with a mean age of 58.34 ± 7.51 years, and the Overlap group included 90 patients, 49 men and 41 women, with a mean age of 57.32 ± 6.35 years. There was no significant difference between the two groups in terms of age, gender, BMI, ASA grade, tumor location, size and stage, and history of hypertension, diabetes, and abdominal surgery ($p > 0.05$), as shown in table 1, meaning that the two groups were comparable.

Comparison of intraoperative and post-operative recovery

The results showed that there were significant differences between the FEEA group and the Overlap group in operation time (197.36 ± 31.91 vs. 182.14 ± 23.32 min), anastomosis time (24.23 ± 5.34 vs. 16.32 ± 6.77 min), post-operative hospital stay (10.21 ± 2.31 vs. 8.31 ± 2.41 days), post-operative feeding time (4.93 ± 1.12 vs. 4.51 ± 1.03 days), and post-operative defecation time (4.12 ± 1.31 vs. 3.81 ± 1.03 h) ($p < 0.05$). There was no significant difference between the two groups in intraoperative blood loss, abdominal incision length, and post-operative 24 h pain score ($p > 0.05$), as shown in table 2.

Comparison of post-operative perioperative complications

The results showed that there was one case of incision infection, one case of abdominal infection, one case of abdominal hemorrhage, one case of incisional hernia, one case of anastomotic leakage, two cases of anastomotic bleeding, one case of anastomotic stricture, and five cases of intestinal obstruction in the FEEA group, making 13 cases in total. There was one case of incision infection, one case of abdominal hemorrhage, one case of pulmonary infection, one case of incisional hernia, one case of anastomotic leakage, and one case of intestinal obstruction in the Overlap group, with six cases

Table 1. Comparison of general data between the two groups

Item	FEEA group (n = 90)	Overlap group (n = 90)	χ^2/t value	p-value
Gender (male/female)	52/38	49/41	0.203	0.652
Age (years, $\bar{X} \pm s$)	58.34 ± 7.51	57.32 ± 6.35	0.832	0.751
Body mass index (kg/m^2, x ± s)	21.19 ± 2.61	21.73 ± 3.14	0.713	0.988
ASA grade (n)			0.425	0.808
Grade II	41	43		
Grade III	32	28		
Grade IV	17	19		
Tumor site (n)			0.114	0.736
Right colon	65	67		
Left colon	25	23		
Tumor size (cm, $\bar{X} \pm s$	5.14 ± 1.60	4.96 ± 1.57	0.925	0.138
TNM stage (n)			0.696	0.706
Phase I	11	13		
Phase II	48	51		
Phase III	31	26		
Hypertension history	10	15	1.161	0.281
Diabetes history	7	9	0.274	0.788
Abdominal surgery history	6	8	0.310	0.579

ASA: American Society of Anesthesiologists; FEEA: functional end-to-end anastomosis; TNM: tumor-node-metastasis.

Table 2. Comparison of intraoperative and post-operative recovery between the two groups

Item	FEEA group (n = 90)	Overlap group (n = 90)	t-value	p-value
Operative time (min)	197.36 ± 31.91	182.14 ± 23.32	3.431	0.024
Anastomosis time (min)	24.23 ± 5.34	16.32 ± 6.77	14.321	< 0.001
Intraoperative blood loss (mL)	52.95 ± 14.42	54.41 ± 10.53	0.841	0.753
Abdominal wall incision length (cm)	6.53 ± 1.31	6.82 ± 1.23	0.823	0.814
Post-operative hospital stay (day)	10.21 ± 2.31	8.31 ± 2.41	3.451	0.022
Post-operative feeding time (day)	4.93 ± 1.12	4.51 ± 1.03	3.211	0.017
Post-operative exhaust time (h)	4.12 ± 1.31	3.81 ± 1.03	3.321	0.009
Pain score 24 h after surgery	3.92 ± 1.24	3.89 ± 1.20	0.987	0.475

FEEA: functional end-to-end anastomosis.

in total. Overall, there was no significant difference in post-operative perioperative complications between the two groups ($\chi^2 = 2.883$, $p = 0.091$), as shown in table 3.

Comparison of post-operative pathological results

The number of dissected normal lymph nodes was comparable between the two groups (31.00 ± 17.92 vs. 27.04 ± 14.00, $p > 0.05$). The results showed that there was no significant difference between the two groups in the number of positive lymph nodes, nerve and vascular invasion, specimen length, tumor differentiation, and tumor growth patterns ($p > 0.05$), as shown in table 4.

Comparison of post-operative follow-up

The results of the post-operative follow-up showed that there were no significant differences between the Overlap and the FEEA groups in QOL scores at 3, 6,

Table 3. Comparison of post-operative perioperative complications between the two groups

Item	FEEA group (n = 90)	Overlap group (n = 90)	χ^2 value	p-value
Post-operative complications (n)	13	6	2.883	0.091
Incision infection	1	1		
Abdominal infection	1	0		
Abdominal bleeding	1	1		
Lung infection	0	1		
Incisional hernia	1	1		
Anastomotic leakage	1	1		
Anastomotic bleeding	2	0		
Anastomotic stricture	1	0		
Ileus	5	1		

FEEA: functional end-to-end anastomosis.

Table 4. Comparison of post-operative pathological results between the two groups

Item	FEEA group (n = 90)	Overlap group (n = 90)	t/χ^2-value	p-value
Dissected lymph nodes (number, x ± s)	31.00 ± 17.92	27.04 ± 14.00	1.213	0.084
Positive lymph nodes (number, x ± s)	2.13 ± 1.24	2.34 ± 1.46	0.931	0.089
Nerve invasion (n)	22	25	0.259	0.611
Vascular invasion (n)	30	40	2.338	0.126
Specimen length (cm, x ± s)	23.98 ± 3.01	25.22 ± 3.19	0.932	0.176
Tumor differentiation (n)			0.111	0.946
High	11	10		
Mid	63	65		
Low	16	15		
Tumor growth pattern (n)			0.375	0.829
Ulcerated type	51	55		
Elevated type	32	29		
Infiltrative	7	6		

FEEA: functional end-to-end anastomosis.

9, and 12 months after surgery ($p > 0.05$). The FEEA group had one case of recurrence and two cases of metastasis, while the Overlap group had one case of recurrence and three cases of metastasis, meaning there was no significant difference in recurrence and metastasis between the two groups ($p > 0.05$). There was no recurrence followed by death within 12 months of follow-up in either group, as shown in Table 5.

Discussion

This study retrospectively analyzed the intraoperative and post-operative conditions of patients undergoing laparoscopic CRC anastomosis in the gastrointestinal department of the authors' hospital. It was found that there were significant differences between the FEEA group and the Overlap group in terms of operation, anastomosis post-operative defecation times, and

Table 5. Comparison of post-operative follow-up between the two groups

Item	FEEA group (n = 90)	Overlap group (n = 90)	t-value	p-value
QOL of 3 months after operation (score, x ± s)	48.92 ± 5.34	48.34 ± 4.48	0.423	0.545
QOL of 6 months after operation (score, x ± s)	50.37 ± 5.65	50.83 ± 5.55	0.531	0.453
QOL of 9 months after operation (score, x ± s)	51.84 ± 4.87	51.32 ± 4.64	0.511	0.624
QOL of 12 months after operation (score, x ± s)	52.74 ± 4.31	52.52 ± 4.55	0.948	0.122
Recurrence (n)	1	1	-	1.000
Metastases (n)	2	3		
Death (n)	0	0		

FEEA: functional end-to-end anastomosis.

post-operative hospital stay. However, there was no significant difference between the two groups in intra-operative blood loss, abdominal incision length, post-operative 24 h pain scores, QOL score at 3, 6, 9, and 12 months after surgery, the recurrence and metastasis rate, and the recurrence and death rate during the 12 months of follow-up.

The results of this study showed that the operation and anastomosis times of the Overlap anastomosis group were shorter than those of the FEEA group. The main reason for this was that FEEA involved closing and aligning the distal bowel before lifting it and performing the anastomosis, meaning more bowel needed to be freed and more mesentery cut to avoid excessive anastomotic tension. In contrast, the overlap anastomosis only required lifting the distal bowel and overlapping the proximal bowel, and, thus, without the need to free more bowel and mesentery, the operation time was shorter. Post-operative defecation and feeding times and post-operative hospital stays were shorter for the Overlap group than the FEEA group. There was no significant difference between the two groups in the VAS pain score at 24 h after surgery, which may be because there was little difference in the length of the abdominal incision of the two groups.

In this study, intestinal obstruction and pulmonary infection occurred in the Overlap group, and intestinal obstruction occurred in the FEEA group. All the patients who developed intestinal obstruction had an incomplete intestinal obstruction caused by post-operative adhesions, and they recovered after fasting, the inhibition of digestive juice secretion, and intravenous nutritional support. There were some cases of anastomotic leakage, abdominal infection, and anastomotic bleeding in the FEEA group, which may have been caused by an insufficiently free proximal and distal intestinal canal or an excessive opening in the left colon during the FEEA and poor strengthening sutures. These circumstances would have resulted in high anastomotic tension and greater distal transverse stress, which would have led to anastomotic leakage and abdominal infection. A total laparoscopic FEEA has previously been reported to increase the risk of uncontrollable intestinal fluid spillage, post-operative intestinal leakage, and abdominal infection due to the large opening it requires[22].

Although total laparoscopic surgery is increasingly used in CRC surgery, its oncologic effect is unclear. Because intra-abdominal manipulation is difficult, many surgeons feel uncomfortable performing laparoscopic intra-abdominal anastomosis. For patients with CRC, oncologic outcomes may be compromised if the use of intra-abdominal anastomosis results in shorter specimen lengths or fewer lymph node dissections[23]. In this study, the principle of radical resection of the tumor, precisely completed CME and D3 lymph node dissection using three-dimensional laparoscopy and the clear identification of subtle structures, was strictly adhered to in both groups of patients, which not only ensured the safety of the surgery but also improved its quality. In addition, the preferred caudomedial approach combined with the intermediate approach can accurately enter the anatomical level for page lymph node dissection and standardized ligation of mesangial root vessels[24]. In terms of the number of dissected lymph nodes, there was no significant difference in the results between the two groups in this study, and the average number of dissected lymph nodes was > 12 in both groups, meeting the radical cure requirements for CRC in US National Comprehensive Cancer Network guidelines. There was also no significant difference in the number of positive lymph nodes or nerve and vascular invasion. Finally, a patient who underwent another

operation for a bypass in the terminal ileum recovered after a temporary emptying of the bowel during the anastomosis. We followed up the QOL of 180 patients at 1, 3, and 6 months after surgery and found that there were no significant differences between the two groups in QOL.

This study does have some limitations. First, this is a single-center study, and it is difficult to ensure consistent baseline assurance when cohorts are compared, and patients are likely to have other comorbidities that could affect prognosis. Second, this study is retrospective, making it difficult to determine the sequence of influencing factors and the occurrence of outcomes and, in turn, to determine the causal association. Finally, due to the limitation of time and manpower, the sample size is small; meaning the representativeness of the sample may be poor. Further exploration is needed through a large-sample, multicenter prospective study.

Conclusion

Overlap anastomosis can shorten the operation time and accelerate the recovery of post-operative intestinal function without increasing the incidence rate of post-operative complications compared with FEEA, and it will not affect the QoL and survival status of patients after surgery in the short term. Therefore, overlap anastomosis is safe and effective and has certain advantages for colorectal reconstruction, making it worthy of clinical use.

Authors' contributions

Conception and design of the work: Sun WM; Data collection: Sun WM, Zhang J; Supervision: Sun WM; Analysis and interpretation of the data: Sun WM, Zhang J; Statistical analysis: Sun WM; Drafting the manuscript: Sun WM; Critical revision of the manuscript: Sun WM, Zhang J; Approval of the final manuscript: Sun WM, Zhang J.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Xuyi People's Hospital.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

The authors declare that they have not received funding.

Conflicts of interest

They declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the approval of the Ethics Committee for the analysis and publication of clinical data obtained routinely. The informed consent of the patients was not required because it was a retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Could the thick of retinal nerve fiber layer be a potential measure of axonal loss in hearing loss?

¿Podría el espesor de la capa de fibras nerviosas de la retina ser una potencial medida de la pérdida axonal en la pérdida auditiva?

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Abstract

Objective: *The objective of the study is to compare the optic coherence tomography (OCT) parameters of the healthy and affected sides of patients with idiopathic sudden sensorineural hearing loss (ISSNHL) and to investigate the relationships between these and the improvement in hearing levels.* **Methods:** *A bilateral eye evaluation of patients diagnosed with ISSNHL was performed with OCT. The ganglion cell complex (GCC) and retina nerve fiber layer (RNFL) thickness values were recorded and the differences between the two eyes were examined.* **Results:** *An evaluation was made of 39 patients with a mean age of 44.82 ± 14.90 years. The RNFL thickness of the eyes was determined to be mean 89.87 ± 3.65 µm on the affected side and 103.87 ± 3.98 µm on the healthy control side (p = 0.0001). The mean GCC was determined to be mean 90.46 ± 3.49 µm on the affected side and 103.77 ± 3.96 µm on the healthy control side (p = 0.0001).* **Conclusions:** *A statistically significant difference was observed between the healthy and affected eyes of patients with ISSNHL with respect to mean GCC and mean RNFL thickness. OCT could be a useful technique for measuring this neural degeneration.*

Keywords: *Ganglion cell complex. Retinal nerve fiber layer. Optic Coherence Tomography. Sudden hearing loss.*

Resumen

Objetivo: *Comparar e investigar los parámetros de la tomografía de coherencia óptica (OCT) de los lados sanos y afectados de pacientes con pérdida auditiva neurosensorial súbita idiopática (PANSI).* **Método:** *La evaluación ocular bilateral de los pacientes diagnosticados con PANSI se realizó con OCT. Se registraron los valores de espesor del complejo de células ganglionares (CCG) y de la capa de fibras nerviosas de la retina (CFNR), y se examinaron las diferencias entre los dos ojos.* **Resultados:** *Se evaluaron 39 pacientes, con una edad media de 44.82 ± 14.90 años. Se determinó que el grosor de la CFNR de los ojos era una media de 89.87 ± 3.65 µm en el lado afectado y 103.87 ± 3.98 µm en el lado de control sano (p = 0.0001). Se determinó que el CCG medio era 90.46 ± 3.49 µm en el lado afectado y 103.77 ± 3.96 µm en el lado de control sano (p = 0.0001).* **Conclusiones:** *Se encontró una diferencia estadísticamente significativa entre los ojos sanos y afectados de pacientes con PANSI con respecto al CCG medio y al espesor medio de la CFNR. La OCT podría ser una técnica útil para medir esta degeneración neuronal.*

***Palabras clave*:** *Complejo de células ganglionares. Capa de fibras nerviosas de la retina. Tomografía de coherencia óptica. Pérdida auditiva repentina.*

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is an emergency ear, nose, and throat (ENT) condition characterized by hearing loss of more than mean 30 dB in at least 3 consecutive frequencies within 72 h[1]. ISSNHL is seen at a frequency of 5-20/100,000/year, and studies have reported an increasing incidence[2]. When the etiological factors are examined, a cause cannot be determined in < 5% of cases[3]. Potential causes include viral infections, vascular disorders, metabolic disorders, trauma, autotoxicity, autoimmune diseases, developmental anomalies, and psychogenic disorders[3]. The most commonly accepted etiologies are immune system-mediated mechanisms, vascular disorders, and viral infections[4,5]. Secondary sensorineural hearing loss can occur due to causes such as neoplasm, stroke, or irradiation[5]. Despite high rates of spontaneous recovery, such as 40-65%, reported in the literature, the etiology and pathogenesis have not yet been fully clarified[4]. The point most focused on in studies of etiology and pathogenesis is vascular disorders. When it is taken into consideration that the cochlear microvascular system cannot be measured *in vivo*, recent studies have concluded that indirect evaluation of the cochlear microvascular system using retinal imaging may present an alternative[6]. In such circumstances, the findings obtained with optic coherence tomography (OCT) may be explanatory for the etiology of sudden hearing loss.

OCT is an imaging technique with good patient compliance that can be easily applied and provides information in depth and high resolution about the internal structure of the retina using the optic reflective characteristics of the tissues with the aid of an 830 nm diode laser light close to infrared[7,8]. The axial resolution of OCT is extremely high at 8-10 microns, and as slices can be obtained similar to a microscopic image, it is defined as a non-invasive tissue biopsy[7]. Therefore, with the measurement of the morphology of the retina nerve fiber layer (RNFL), evidence is provided of neurodegeneration with the visualization of myelin loss in the retina[9].

OCT is used in the diagnosis and follow-up of many diseases that have accompanying degeneration. These include anterior ischemic optic neuropathies (ON), other toxic and inflammatory ON, multiple sclerosis (MS), neuromyelitis optica, pseudotumor cerebri, migraine, optic nerve head drusen, and Alzheimer's disease. To the best of our knowledge, there is no study in the literature showing whether or not there is neurodegeneration using optic imaging in ISSNHL patients.

The aim of this study was to use OCT to determine whether or not there was neurodegeneration in ISSNHL patients and, if so, how early-determined neurodegeneration changed with treatment.

Materials and methods

This prospective, monocentric study was conducted in the ENT clinic of a training and research hospital. Approval for the study was granted by the Local Ethics Committee (100/05: December 14, 2020). Informed consent was provided by all the study participants. The study included patients who presented at our clinic with the complaint of sudden hearing loss and were diagnosed with ISSNHL as a result of an audiometric examination. Before treatment, both eyes of each patient were evaluated separately with OCT by an ophthalmologist.

The patients included in the study were those with symptom duration of < 30 days, who started treatment because of ISSNHL, and completed the treatment protocols appropriately. Before and after treatment, all the patients underwent an audiogram, a full ENT examination, and temporal contrast magnetic resonance imaging (MRI). Patients were excluded from the study if symptoms had been ongoing for longer than 30 days, if they had Meniere's disease, acoustic trauma, chronic middle ear inflammation, cerebellopontine angle pathologies, SNHL associated with autotoxic drug use, a history of autological surgery, bilateral ISSNHL, newly diagnosed vestibular Schwannoma, glaucoma, macula degeneration, uveitis, retinal or choroidal vascular disease, a history of retinal surgery, ocular trauma or optic neuropathy, optic nerve head or retinal anomaly, or who were referred to our clinic after having started treatment.

The patients included in the study were started on treatment with 1 mg/kg/day oral methylprednisolone, and this was reduced by 16 mg every 3 days. Audiological tests were performed before and after treatment. Speech discrimination scores (SDS) were recorded, and pure tone average (PTA) values were calculated at 0.5, 1, 2, and 4 kHz. The change in PTA values after treatment was analyzed according to the Furuhashi criteria (Table 1)[10].

OCT

OCT scanning was performed on the same day as the ophthalmological examination by experienced

Table 1. Furuhashi criteria for the assessment of audiological hearing outcomes

	Criteria
Complete recovery	PTA < 20 dB or identical to contralateral non-affected ear
Marked improvement	PTA improvement > 30 dB
Slight improvement	PTA improvement between 10 and 30 dB
No recovery	PTA improvement < 10 dB

PTA: pure tone threshold average (500, 1000, 2000, and 4000 Hz).
Source: Furuhashi, A., et al., Sudden deafness: long-term follow-up and recurrence. Clin Otolaryngol Allied Sci, 2002. 27(6): p. 458-63.

operators using the RTVue SD-OCT system (RTVue-XR 100 Avanti software v.6.1, Optovue, Inc., Fremont, CA, USA). OCT was performed in a dark room on both eyes after dilatation of the pupils. The macula and optic nerve head were evaluated, while the RNFL and ganglion cell complex (GCC) thicknesses were measured separately. Measurements were repeated three times for each eye to reduce measurement errors. The RNFL 3.45 protocol was used for peripapillary RNFL analysis, with the thickness measured at a diameter of 3.45 mm around the center of the optic disc. The total number of A-scans with a circumference was 2225. The results were displayed on a color map with customized software, with normative data adjusted for age and optic disc size (Fig. 1). A peripapillary RNFL thickness map was expressed as a numerical value. GCC thickness was measured using the GCC protocol, composed of 15 vertically oriented B scans 7.0 mm in length (800 A scans each), separated by 0.50 mm, together with a single horizontally oriented B scan 7.0 mm in length (12,934 A-scans), all centered on the macula by the operator. The center of the GCC scan was shifted 1.0 mm temporally to be able to better sample the temporal peripheral macula with the nasal visual field.

Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, version 22.0 for Windows; SPSS Inc., Chicago, Illinois, USA) was used to perform all analyses. Kolmogorov–Smirnov and P-P plot tests were used to verify the normality of the distribution of continuous variables. The results were reported as means standard deviations, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were presented as percent. The comparison of categorical variables between the groups was done using Pearson's chi-square and Fischer's exact test, whereas continuous variables were compared using an independent sample t-test and the Mann–Whitney U test according to homogenity. SDS values before and after treatment were evaluated with the Wilcoxon signed-rank test. A $p < 0.05$ was considered statistically significant.

Results

The study started with a total of 62 patients. Of these, 23 were excluded; 4 did not complete follow-up, 17 were newly diagnosed with comorbidity, and 2 had hearing loss in the ear that was thought to be healthy. Thus, the evaluations were completed with 39 patients, comprising 16 (41%) females and 23 (59%) males with a mean age of 44.82 ± 14.90 years. The patients were diagnosed, treated, and followed up for ISSNHL on the left side in 15 cases and on the right side in 24.

The PTA values of the patients were mean 61.25 before treatment and 30.00 after treatment. The SDS was 68% before treatment and 88% after treatment. When the patients were evaluated according to the Furuhashi criteria, full recovery was seen in 15 (38.4%) patients. Full recovery and significant improvement were accepted as treatment successes, and 23 patients were determined to have benefited from the treatment. The treatment was not successful for 16 patients. A slight improvement was seen in 6 of these patients and no improvement in 10 (Table 2).

The RNFL thickness of the eyes was determined to be mean 89.87 ± 3.65 μm on the affected side and 103.87 ± 3.98 μm on the healthy control side ($p = 0.0001$). The mean GCC was determined to be mean 90.46 ± 3.49 μm on the affected side and 103.77 ± 3.96 μm on the healthy control side ($p = 0.0001$).

The patients were separated into two groups according to their response to treatment: those with full recovery-significant improvement, and those with slight or no improvement. The mean RNFL thickness was found to be 89.72 ± 3.59 μm in the successful group and 90.05 ± 3.66 μm in the group with an unsuccessful response to treatment, with no statistically significant difference observed ($p = 0.991$). The GCC values were mean 90.38 ± 3.47 μm in the successful treatment group and 90.07 ± 3.55 μm in the unsuccessful group ($p = 0.991$).

When the affected eyes of only the patients showing full recovery (n: 15) were compared with those of the

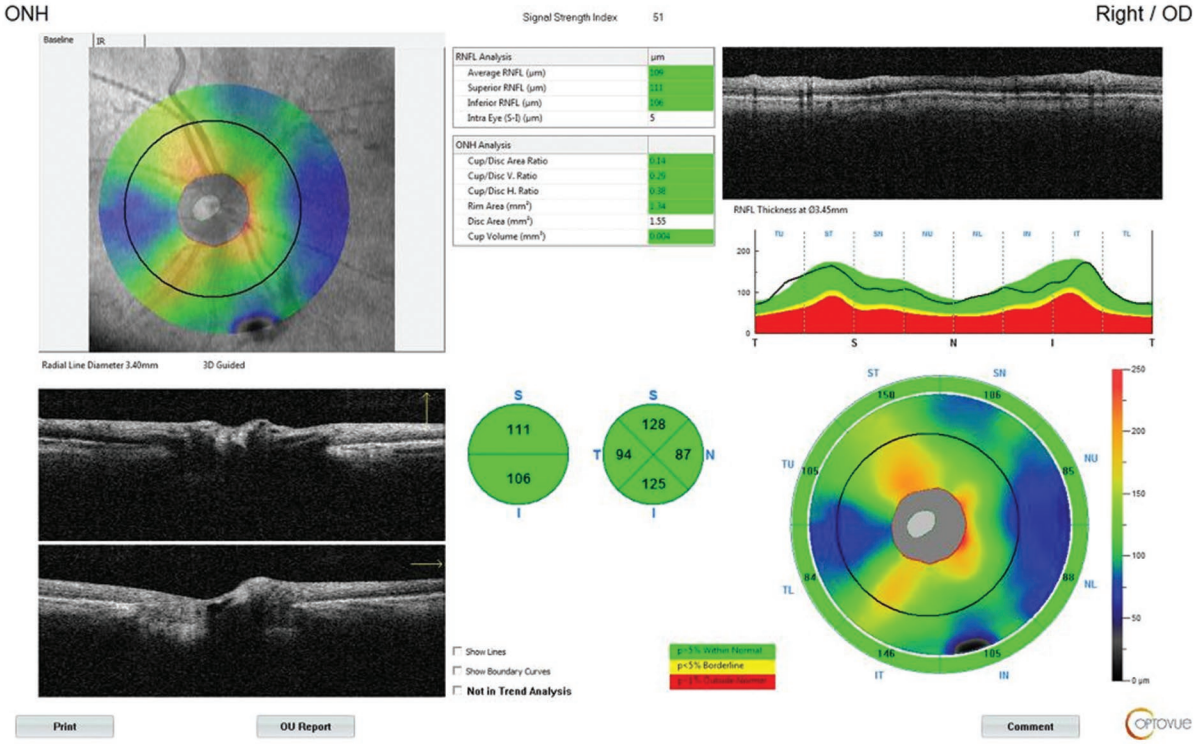

Figure 1. *Optic coherence tomography sample of a patient.*

Table 2. Post-treatment categorization according to the Furuhashi criteria

	Number of patients (%)
Complete recovery (1)	15 (38.4)
Marked improvement (2)	8 (20.7)
Slight improvement (3)	6 (15.3)
No recovery (4)	10 (25.6)

Table 3. The OCT findings according to the responses to treatment

	GCC	RFNL	p-value
Complete recovery (n: 15)	90.01 ± 3.49	89.61 ± 3.64	0.989
Marked improvement (n: 8)	89.21 ± 3.51	89.01 ± 3.71	
Slight improvement (n: 6)	90.52 ± 3.39	89.98 ± 3.60	
No recovery (n: 10)	88.89 ± 3.41	89.71 ± 3.59	
Successful (n: 23)	90.38 ± 3.47	89.72 ± 3.59	0.991
Not successful (n: 16)	90.07 ± 3.55	90.05 ± 3.66	
Full recovery (n: 15)	90.51 ± 3.41	89.66 ± 3.52	0.993
No full recovery (n: 24)	90.23 ± 3.51	90.1 ± 3.55	

other patients (n: 24), the mean RNFL thickness values were 89.66 ± 3.52 µm and 90.1 ± 3.55 µm, respectively, with no statistically significant difference determined (p = 0.993) (Table 3).

Discussion

The results of this study showed that the RNFL thickness measured with OCT in patients with ISSNHL was statistically significantly thinner in the eye on the affected side, as if accompanied by neurodegeneration, compared to the healthy side (affected side: 89.87 ± 3.65 µm, healthy side: 103.87 ± 3.98 µm, p = 0.0001). The GCC thickness was also statistically significantly thinner in the eye of the affected side compared to the healthy side (affected side: 90.46 ± 3.49 µm, healthy side: 103.77 ± 3.96 µm, p = 0.0001). A significant improvement was determined in these patients in the PTA values (from 61.25 to 30) and the SDS (from 68 to 88%). The etiology of neurodegeneration, which progresses with the loss of nerve cells, causing dysfunction of the nerve or organ associated with this loss, has not been fully determined. The results of this study

showed a statistically significant level of neurodegeneration in the eye on the affected side in patients with ISSNHL.

In a study that examined the cardiovascular risk factors of patients with sudden hearing loss, it was stated that ISSHNL could be associated with vascular endothelial dysfunction[11]. In studies by Fusconi et al. to determine the prevalence of thrombophilic risk factors in stroke associated with sudden hearing loss, central retinal vein occlusion, and small vessel disease, and to investigate the vascular hypothesis in the pathogenesis of sudden hearing loss, it was concluded that hyperhomocysteine, which is a common cause of thrombophilia, was associated with sudden hearing loss. That study also suggested that it was necessary to confirm the hypothesis that the small peripheral vessels of the ears, eyes, and brain provided by all the supra-aortic branches are affected by the same thrombotic factors. Ophthalmic symptoms may be the only finding in Susac syndrome, which is an uncommon cause of recurrent retinal artery occlusion and emerges with sensorineural hearing loss[12]. In the current study, vascular endothelial dysfunction, which can be a cause of ISSNHL, may have caused neurodegeneration. The RNFL was statistically significantly thinner in the eye on the affected side, as if accompanied by neurodegeneration, compared to the healthy side (affected side: 89.87 ± 3.65 μm, healthy side: 103.87 ± 3.98 μm, p = 0.0001).

A study of an elderly population in southern Italy investigated the relationship between macular vascular density and age-related peripheral sensorineural hearing loss (presbycusis) and determined an association between retinal vascularity and central hearing processing pathology[13]. There are also studies that have concluded that when it is taken into consideration that the cochlear microvascular system cannot be measured *in vivo*, indirect evaluation of the cochlear microvascular system using retinal imaging may present an alternative[6]. In such conditions, the findings obtained with OCT may be explanatory for the etiology of sudden hearing loss.

OCT entered ophthalmology practice in the 1990s and now has a wide range of uses in the diagnosis and follow-up of glaucoma, diabetic retinopathy, and especially in many different retinal diseases affecting the macula. OCT imaging can reveal axonal loss with RNFL thickness measurements and neuronal damage with GCC measurements[14]. In recent years, there has been great interest in the use of OCT in neurodegenerative diseases. Clinical studies have shown that these diseases lead to a decrease in RNFL thickness, which is mainly formed from retinal ganglion cells and the axons of these cells[15]. The RNFL shows a similarity to gray matter in the brain, and changes in thickness are only due to axon damage. When examined in this respect, the retina is accepted as a part of the brain that can be easily observed. Changes in retinal vascular density have the potential to be an ocular biomarker for neurodegenerative conditions.

A series of studies conducted on Alzheimer's disease, which is the most common form of neurodegeneration, have shown that the disease is not limited to the brain, but the retina is also greatly affected[16,17]. The thickness of the RNFL and GCC has been shown to be reduced in Alzheimer's patients compared to healthy individuals[18]. The current study results showed that the RNFL and GCC thickness values were 89.87 ± 3.65 μm and 90.46 ± 3.49 μm, respectively, on the affected side and were determined to be statistically significantly thinner than the healthy side.

The RNFL thickness measured with OCT was compared with MRI findings in a study of MS patients, and it was determined that this test could indirectly show brain atrophy[19]. When compared with a control group, the RNFL thickness was found to be significantly thinner in the MS patients[20]. Hearing loss can also be seen in this disease, for which early diagnosis is important, and some patients may present with hearing loss as the first complaint[21]. Just as the determination of OCT findings in this disease could contribute to the etiology, they could also make a difference in the early identification of patients. However, it is difficult to draw clear conclusions from the available data, and there is a need for further studies of specific groups diagnosed with sudden hearing loss.

To be able to observe a change in RNFL values, there has to be at least 50% cell damage in the GCC[22]. This development in idiopathic optic neuritis cases is a process. The pattern and degree of loss in GCC number and RNFL thickness can be useful in differentiating the underlying etiology[23]. The determination of a significant difference in RNFL thickness within a short time of presenting with sudden hearing loss makes it possible to be able to interpret the emergence of the disease with different pathophysiologies, or the severity of the disease, or it suggests the possibility of experiencing an asymptomatic process that will reveal this effect.

PTA is a value that is calculated by taking the mean values of 500, 1000, 2000, and 4000 Hz frequencies in the audiogram. These frequencies are the frequencies at which people perceive speech. In the current study group with full recovery and significant recovery according to the Furuhashi criteria (59%), GCC of 90.38 ± 3.47 and RFNL of 89.72 ± 3.59 were determined, and in the unsuccessful group with slight or no improvement, GCC was 90.07 ± 3.55 and RFNL was 90.05 ± 3.66 (p = 0.991). Although not statistically significant, this change was observed to be positive and was considered to be promising with respect to the possibility that neurodegeneration can be improved with treatment.

The primary limitation of this study was the low number of patients. The main reason for this was that the prevalence of ISSNHL patients in the general population is 5-20/100,000, and with advancing age, these patients have comorbidities that could affect the vascular base. Another limitation was that there were no post-treatment and long-term serial OCT data. However, this study can be considered valuable as the first study in the literature to have presented the OCT results of patients diagnosed with ISSNHL, and it could be a foundation for further studies.

Conclusion

There have been many previous studies of ISSNHL, which is an ENT emergency requiring early diagnosis and treatment. In respect of etiology, diagnosis, and referral for treatment, neurodegeneration and perhaps the degree of this degeneration can be diagnosed earlier, and more rapid interventions can be made with the use of OCT to take RNFL and GCC measurements.

Author contributions

Kaya Celik E: conceptualization, methodology, software. Doluoglu S: Data curation, Writing-Original draft preparation, Writing-Reviewing and Editing Acar M, Keseroglu K: visualization, investigation. Bayir O: software, validation. Mutlu M, Saylam G.: supervision.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ARTÍCULO ORIGINAL

Evaluación de complicaciones posquirúrgicas de la técnica «Rendez-vous» vs. el manejo estándar en pacientes con coledocolitiasis

Evaluation of post-surgical complications between "Rendez-vous" technique vs. standard care in patients with choledocholithiasis

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Resumen

Antecedentes: *La técnica de «Rendez-vous» (RV) es una técnica mixta en la que se combinan las habilidades endoscópicas y laparoscópicas. La evidencia es contradictoria respecto al uso de RV frente a la técnica secuencial en dos tiempos (colangiopancreatografía retrógrada endoscópica [CPRE] seguida de colecistectomía laparoscópica [CL]) para el manejo de la coledocolitiasis.* **Objetivo:** *Estimar la asociación entre el uso de la técnica RV y la presencia de complicaciones posquirúrgicas como desenlace primario, en comparación con la técnica secuencial.* **Método:** *Se realizó un estudio observacional analítico retrospectivo que tomó como cohorte expuesta las historias clínicas de pacientes con diagnóstico de colelitiasis, colecistitis o pancreatitis leve de origen biliar sometidos a la técnica RV, y se compararon con registros en los que se realizó la técnica de dos tiempos.* **Resultados:** *La tasa de complicaciones posquirúrgicas en el grupo de RV fue del 0%, frente al 10.1% (p = 0.3617) en el grupo control. Además, la RV presentó menor tiempo de hospitalización global (p = 0.0377) y posquirúrgica (p < 0.0001).* **Conclusiones:** *La técnica RV es superior a la técnica secuencial de CPRE seguida de CL, por su mayor tasa de éxito, menor tasa de complicaciones y menor tiempo hospitalario.*

***Palabras clave*:** «*Rendez-vous*». *CPRE. Colecistectomía laparoscópica. Complicaciones quirúrgicas.*

Abstract

Background: *"Rendez-vous" (RV) technique is a mixed-technique which uses both laparoscopic and endoscopic skills; however, the evidence is contradictory regarding the implementation of this technique or the 2-step sequential technique (endoscopic retrograde cholangiopancreatography [ERCP] followed by laparoscopic cholecystectomy [LC]) in the management of cholecysto-choledocholitiasis.* **Objective:** *To estimate the association between the implementation of RV technique and the presence of post-surgical complications as primary outcome, using as comparator the 2-step sequential technique.* **Method:** *An observational, analytical, retrospective study was conducted, using as exposed cohort the medical records from patients with a diagnosis of cholelithiasis, cholecystitis, or mild biliary pancreatitis. The exposed cohort underwent RV technique, while the unexposed cohort were those which underwent two step technique.* **Results:** *There was a lower post-surgical complication rate in the RV group (0%) compared with the 10.1% (p = 0.3617) in the control group. Also, RV technique showed a lesser*

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hospitalization time (p = 0.0377) and a lesser post-surgical hospitalization time (p < 0.0001) **Conclusions:** *RV technique is superior when compared with the 2-step sequential technique (ERCP followed by LC), based on a better surgical success rate, a fewer complications rate and less hospitalization time.*

Keywords: **"***Rendez-vous". ERCP. Laparoscopic cholecystectomy. Surgical complications.*

Introducción

La colelitiasis es la presencia de masas (litos) compuestas por colesterol o bilirrubina localizadas en la vesícula biliar, y afecta al 10-20% de la población adulta en los Estados Unidos de América[1]. Del total de los casos, un 11-20% corresponden a cálculos sintomáticos[2,3] y la colecistectomía laparoscópica (CL) es la técnica de referencia para su tratamiento[4,5]. La coledocolitiasis se define como la migración de dichos litos hacia el árbol biliar, lo que ocurre en un 10-15% de los pacientes que van a ser sometidos a colecistectomía. En este caso, la colangiopancreatografía retrógrada endoscópica (CPRE) seguido de CL es el procedimiento secuencial más utilizado para su resolución. El diagnóstico y el enfoque del tratamiento de estas patologías dependen de múltiples factores, incluidos el nivel de sospecha de la coledocolitiasis, el estado hemodinámico del paciente, los recursos disponibles, las preferencias del paciente y la experticia de los profesionales[6].

Dentro de los recursos disponibles se encuentra la técnica «Rendez-vous» (RV), una técnica mixta en la que se combinan habilidades endoscópicas y laparoscópicas para extraer los cálculos retenidos en el colédoco y realizar una CL en el mismo tiempo quirúrgico. La maniobra disminuye el tiempo de canulación y las complicaciones asociadas a la manipulación endoscópica de la papila duodenal mayor[7].

Deslandres et al.[8], en 1993, fueron los primeros en informar sobre este tratamiento laparo-endoscópico combinado, consistente en la inserción transcística de una guía para llegar a la ampolla de Vater, con una canulación más fácil, y eventual esfinterotomía y extracción endoscópica con una canastilla o un globo de los cálculos retenidos en la vía biliar. Su implementación se inició en 1994 con 12 pacientes[9,10] y fue conocida como RV a partir de 1997[11]. En nuestro caso, la técnica implementada es realizar una CL parcial, disecando el triángulo de Calot, colocando un clip a nivel de la arteria cística y ubicando el conducto cístico, posteriormente colocando un clip distal y realizando una sección parcial del conducto cístico. Por el puerto subxifoideo se dispone una pinza de Olsen, ubicándola en la sección realizada, y a través de esta se pasa una guía de punta hidrófila de 0.89 mm de diámetro y 450 cm de largo, desplazándola hasta alcanzar la ampolla de Vater y llegando así la luz duodenal. Posteriormente, con la mínima insuflación necesaria, se desplaza el duodenoscopio hasta la segunda porción del duodeno, y teniendo la guía bajo visión directa, con una punta libre de aproximadamente 5-7 cm, se enlaza utilizando un asa de polipectomía sobre los 2-3 cm proximales a la papila, para tener un margen de maniobrabilidad cuando haya tracción. Una vez atrapada, se coloca la guía fuera del canal de trabajo del duodenoscopio y se introduce la totalidad del esfínterotomo dentro del colédoco. Tras ubicarlo, se realiza la esfinterotomía y a continuación el esfínterotomo es reemplazado por una canastilla de Dormia para extraer los litos. Tras esto, se realizan revisiones sucesivas y en retirada, confirmando la permeabilidad de la vía biliar con la salida de bilis, y radiológicamente con colangiografía en búsqueda de defectos de llenado. Al dar por terminada la CPRE, se aspira el aire insuflado mientras se retira el equipo, disminuyendo lo más posible la distensión de asas, para que el cirujano pueda concluir la CL.

Actualmente, la técnica en dos tiempos es la más utilizada por la mayoría de los cirujanos en su práctica diaria, pese a que la evidencia aportada por los ensayos aleatorizados prospectivos sugiere la superioridad del manejo en un tiempo (RV), con variables significativas que incluyen una mayor tasa de extracción de litos, tiempos de hospitalización más cortos, una recuperación más rápida, mayor confort y comodidad para el paciente, y una menor tasa de complicaciones, en particular de pancreatitis[12,13].

En contraste, al evaluar la evidencia disponible en estudios retrospectivos, la CPRE presenta una mayor tasa de falla para canular la ampolla de Vater (4-18%), una canulación e inyección inadvertida de medio contraste al conducto pancreático con la consecuente mayor tasa de pancreatitis (2-9%), una manipulación excesiva de la ampolla de Vater y de la vía biliar con sangrado secundario (10-30%), y riesgo de perforación (< 1%)[14,15].

Pese a los beneficios demostrados para la técnica RV, hay evidencia que muestra limitaciones para su implementación, incluyendo una mayor dificultad en

la realización de la CL, un mayor tiempo quirúrgico y unas considerables necesidades logísticas[16], que introducen dificultades a la estructuración de los deberes de los cirujanos y los endoscopistas[14,17]. Por todo esto, el presente estudio tiene como objetivo estimar el desarrollo de complicaciones posquirúrgicas tomando como intervención la técnica RV y comparándola con la técnica convencional (CPRE + CL).

Método

Se realizó un estudio observacional analítico, de cohorte retrospectiva, en el que se usó como cohorte expuesta las historias clínicas de pacientes incluidos en el programa *Round List,* que asistieron a varios centros hospitalarios en las ciudades de Bucaramanga y Floridablanca, en Colombia, durante el período comprendido entre enero de 2016 y enero de 2018, cuyos diagnósticos fuesen colelitiasis, colecistitis o pancreatitis leve de origen biliar, y que presentaran clínicamente alta sospecha de coledocolitiasis basándose en la presencia de predictores muy fuertes (criterios de la American Society for Gastrointestinal Endoscopy [ASGE])[18], con posterior confirmación del diagnóstico por imágenes (ecografía hepatobiliar, tomografía computarizada abdominal contrastada o colangiografía por resonancia magnética). La cohorte expuesta correspondió a los pacientes que fueron sometidos a la técnica de RV, mientras que la cohorte no expuesta (control) correspondió a los pacientes que fueron sometidos a la técnica secuencial de CPRE seguida de CL. Se establecieron como resultado primario el desarrollo de complicaciones posquirúrgicas y como resultados secundarios el tiempo de la cirugía, el tiempo de realización de la CPRE, la capacidad resolutiva del procedimiento y los tiempos de hospitalización total y poscirugía, considerando variables como la edad, el sexo y la indicación de la técnica.

Criterios de inclusión

Pacientes mayores de 18 años que tuvieran diagnóstico de colelitiasis, colecistitis o pancreatitis de origen biliar leve (criterios de Atlanta[19], al menos uno de los tres), cuyo diagnóstico de coledocolitiasis fue comprobado por estudio de imágenes (ecografía, tomografía computarizada, resonancia magnética) y clínicamente con presencia de predictores muy fuertes (clasificación ASGE) para coledocolitiasis.

Criterios de exclusión

Pacientes menores de 18 años o con al menos una de las siguientes condiciones: pancreatitis moderada-grave (criterios de Atlanta[19]), colangitis, hallazgo endoscópico o imagenológico de neoplasia, vesícula en porcelana, coledocolitiasis primaria, síndrome de Mirizzi, fístula biliar o categorización III/IV de la ASA (American Society of Anesthesiologists)[20].

Análisis estadístico

El análisis descriptivo se realizó mediante el cálculo de frecuencias absolutas y relativas para las variables cualitativas, y para las variables cuantitativas se usaron medidas de tendencia central tipo mediana con su respectiva medida de dispersión (rango intercuartílico [RIC]) por la naturaleza no paramétrica de estas variables, estimada por la prueba de Shapiro-Wilk. Para comparar las características clínicas y los resultados posquirúrgicos se utilizaron la prueba χ^2 o el test exacto de Fisher para las variables cualitativas según fuese necesario; las variables cuantitativas se compararon con la prueba U de Mann-Whitney y se consideró estadísticamente significativo un valor de $p < 0.05$. Finalmente, se estimaron los riesgos relativos (RR) crudos y ajustados por regresión de Poisson con sus respectivos intervalos de confianza del 95% (IC95%), para analizar la asociación de la técnica con la aparición de complicaciones.

Resultados

El estudio se realizó en una población de 127 pacientes, de los cuales el 91% eran mujeres y el 9% eran hombres. El promedio de edad fue de 48 años (RIC: 30-66; p = 0.9421) en el grupo de RV y de 50 años (RIC: 30-66; p = 0.9421) en el grupo de CPRE seguida de CL. Del total de los pacientes, el 14.1% fueron llevados a RV, de los cuales el 83.3% eran mujeres y el 16.7% eran hombres. Al restante 85.9% se les practicó la técnica secuencial de CPRE seguida de CL, de los cuales el 76.2% eran mujeres y el 23.8% eran hombres (Tabla 1).

En el grupo de RV, la indicación principal para realizar el procedimiento quirúrgico fue la coledocolitiasis en el 88.9% (p = 0.0191), de los cuales 6 (p = 0.3615) cursaron concomitantemente con colelitiasis. El 11.1% (p = 0.0191) cursaron con pancreatitis leve de origen biliar. En el grupo de control, en el 100% (p = 0.0191)

Tabla 1. Características generales de las cohortes de estudio

	Grupo RV (n = 18) n (%)	CPRE+CL (n = 109) n (%)	p
Edad. años, media (rango)	48 (30-55)	50 (30-66)	0.9421
Sexo			
Femenino	15 (83.3)	83 (76.2)	0.7622
Masculino	3 (16.7)	26 (23.8)	0.9520

CL: colecistectomía laparoscópica; CPRE: colangiopancreatografía retrógrada endoscópica; RV: «Rendez-vous».

la indicación principal fue la coledocolitiasis, de los cuales 23 (p = 0.3615) cursaron concomitantemente con colecistitis, y no fueron incluidos pacientes con pancreatitis.

Cuando se evaluó la tasa de extracción endoscópica de cálculos, el 100% de los pacientes (p = 0.6844) a quienes se realizó la técnica de RV tuvieron un resultado favorable, en comparación con el 98.1% (p = 0.6844) del grupo control. En el 1.8% de los pacientes (p = 0.5639) no se logró la extracción completa del cálculo, considerándose un procedimiento fallido, con posterior inserción de un *stent* biliar.

Respecto a las complicaciones del procedimiento quirúrgico, en el grupo de RV no se presentaron, mientras que en el grupo control hubo una tasa de complicaciones del 10.1% (p = 0.3617), de los cuales el 4.6% (p = 0.3557) presentaron pancreatitis, el 1.8% (p = 0.5639) perforación y el 3.7% (p = 0.4107) sangrado (Tabla 2).

Con respecto al tiempo de hospitalización global, el grupo de RV presentó un promedio de 7 días (RIC: 5-10; p = 0.0377) y el grupo control un promedio de 9 días (RIC: 7-12; p = 0.0377). El tiempo de hospitalización poscirugía fue de 2 días (RIC: 1-2; p < 0.0001) en el grupo de RV y 4 días (RIC 2-6; p = 0.0001) en el grupo control.

Con relación a los tiempos quirúrgicos, para la CPRE fue de 34 minutos (RIC: 26-50; p = 0.9390) en el grupo de RV y de 35 minutos (RIC: 22-60; p = 0.9390) en el grupo control; y el tiempo de CL fue de 100 minutos (RIC: 90-104; p = 0.0008) en el grupo de RV y de 70 minutos (RIC: 52-90; p = 0.0008) en el grupo control. El tiempo quirúrgico total fue de 131 minutos (120-160; p = 0.0156) en el grupo de RV y de 110 minutos (RIC: 84-150; p = 0.0156) en el grupo control (Tabla 2). Destaca que la asociación cruda entre la técnica de RV y la técnica secuencial de CPRE seguida de CL solo fue estadísticamente significativa cuando se compararon el tiempo quirúrgico de la CL (RR crudo: 1.44; IC95%: 0.45-4.64; RR ajustado: 1.78; IC95%: 0.31-10.31) y el tiempo quirúrgico total (RR crudo: 1.37; IC95%: 0.44-4.25; RR ajustado: 1.03; IC95%: 0.19-5.63). En el resto de los ítems no se observaron datos estadísticamente significativos (Tabla 3).

Discusión

La CPRE seguida de CL representa hoy en día la técnica de referencia[4,5,21] para la resolución de la coledocolitiasis asociada a colelitiasis, colecistitis y pancreatitis de origen biliar; sin embargo, la mejor estrategia resolutiva aún se debate.

Varios estudios[8,15] han demostrado la superioridad de la técnica RV, por su alta tasa de éxito, alta tasa de eliminación de cálculos, baja tasa de incidencia de complicaciones, menor tiempo hospitalario y necesidad de un único tiempo quirúrgico. Uno de los factores que avala su implementación es la teoría de que, tras la esfinterotomía endoscópica durante la CPRE, la contaminación biliar a través del ascenso de bacterias yeyunales[22] puede conducir a la inflamación del ligamento hepatoduodenal, obstaculizando la disección laparoscópica del triángulo de Calot y dificultando la realización de la CL en un segundo tiempo quirúrgico; sin embargo, evidencia reciente ha demostrado que esto no es un factor predictor independiente de colecistectomía catalogada como difícil[23].

Por otra parte, la técnica RV ha sido discutida, dado que en estudios retrospectivos se ha demostrado que aumenta significativamente el tiempo dentro del quirófano, además de requerir operadores cualificados y capacitados[24], y presenta unas dificultades intraoperatorias propias de la técnica, como son la posición supina, que dificulta la canulación de la papila, o la insuflación endoscópica intestinal, que interfiere con la CL. Por esto, Basso et al.[25], al encontrar beneficios en la aplicación de la técnica RV, consideraron importante realizar una disección total de la vesícula biliar antes de realizar el procedimiento endoscópico, con el fin de disminuir la dificultad técnica tras la insuflación intestinal con el endoscopio. Otras recomendaciones incluyen usar una pinza laparoscópica intestinal aplicada en el primer bucle yeyunal[26], o minimizar el inflado y prolongar la aspiración antes de extraer el endoscopio[27], facilitando así la implementación de esta técnica.

Ahora bien, al comparar los desenlaces clínicos de las dos técnicas, en cuanto a la tasa de extracción endoscópica del cálculo en estudios retrospectivos,

Tabla 2. Comparación de los resultados clínicos observados en las cohortes de estudio

	Grupo RV (n = 18) n (%)	Grupo CPRE + CL (n = 109) n (%)	p
Extracción endoscópica de cálculos	18 (100.0)	108 (99.1)	0.6844
Inserción de *stent*	0 (0.0)	2 (1.8)	0.5639
Complicación de CPRE	0 (0.0)	11 (10.1)	0.3617
Pancreatitis	0 (0.0)	5 (4.6)	0.3557
Perforación	0 (0.0)	2 (1.8)	0.5639
Sangrado	0 (0.0)	4 (3.7)	0.4107
Días totales de hospitalización, media (rango)	7 (5-10)	9 (7-12)	0.0377
Días de hospitalización posquirúrgica, media (rango)	2 (1-2)	4 (2-6)	< 0.0001
Tiempo quirúrgico de CPRE, min, media (rango)	34 (26-50)	35 (22-60)	0.9390
Tiempo quirúrgico de CL, min, media (rango)	100 (90-104)	70 (52-90)	0.0008
Tiempo quirúrgico total, min, media (rango)	131 (120-160)	110 (84-150)	0.0156

CL: colecistectomía laparoscópica; CPRE: colangiopancreatografía retrógrada endoscópica; RV: «Rendez-vous».

Tabla 3. Asociación cruda y ajustada por regresión de Poisson del uso de la técnica «Rendez-vous» frente al tiempo quirúrgico

	RR crudo	IC95%	RR ajustado	IC95%
Tiempo quirúrgico de CL, min	1.44	0.45-4,64	1.78	0.31-10.31
Tiempo quirúrgico total, min	1.37	0.44-4.25	1.03	0.19-5.63

CL: colecistectomía laparoscópica; IC95%: intervalo de confianza del 95%; RR: riesgo relativo.

la CPRE tiene una tasa de falla en la canulación que puede alcanzar hasta un 18%[14], mientras que con la técnica RV es < 1%, con una tasa de fracaso de la técnica secuencial del 12.3% contra un 0.7% de la técnica RV (p = 0.001)[27,28]. En relación con la tasa de éxito, los reportes para la técnica RV varían entre un 90% y un 100%, frente al 82-96% que alcanza la técnica secuencial de CPRE seguida de CL[26], pero con un riesgo de eliminación incompleta de los cálculos de hasta un 20% con esta última, producto de la incapacidad para canular la ampolla de Vater[14,15]. En nuestro estudio, cuando se comparó la tasa de extracción endoscópica del cálculo, se evidenció un 100% de resolución en los pacientes en quienes se realizó la técnica de RV, frente al 98.1% en el grupo control; sin embargo, este 1.9% restante requirió dos tiempos para la resolución de su patología biliar, inicialmente manejado con la colocación de un stent biliar y posteriormente con nuevo tiempo de CPRE para la extracción endoscópica de los cálculos.

Rábago et al.[29] evaluaron la morbilidad al aplicar estas técnicas y encontraron que fue mayor con la técnica secuencial que con la técnica RV (23% vs. 8.5%), con una necesidad de repetición de la CPRE de casi un 100% más en la técnica secuencial (10.2% vs. 5.2%). En nuestro trabajo, en el grupo RV no se presentaron complicaciones, pero al aplicar la técnica secuencial reportamos complicaciones en el 10.1% de los pacientes, repartido así: un 4.6% (que representa un 45.5% de los pacientes con complicaciones) cursaron con pancreatitis, pero consideramos este hallazgo esperable, dada la asociación entre la manipulación de la ampolla de Vater y el desarrollo de esta complicación, que no parece variar respecto al enfoque quirúrgico[28,29]. Sin embargo, la tasa de pancreatitis es significativamente mayor con la CPRE convencional que al realizar la técnica de RV (12.7% vs. 1.7%)[30]. En nuestro estudio, al aplicar la técnica secuencial hubo una tasa de sangrado del 3,7%, y, de perforación del 1.8% (36.6% y 17.8% del total respectivo de pacientes con complicaciones); consideramos que esto deriva de la dificultad para la canulación

de la ampolla de Vater, que representa una mayor manipulación endoscópica. La técnica RV confiere un efecto protector frente a estas complicaciones, dado que la canulación se realiza bajo visión indirecta de la vía biliar, en relación con la guía introducida retrógradamente por vía transcística[11].

En cuanto al tiempo quirúrgico de CPRE, en el grupo de RV fue de 34 minutos (p = 0.9390) y en la técnica de dos tiempos fue de 35 minutos (p = 0.9390), sin diferencia estadísticamente significativa. Sin embargo, cuando se evaluó la duración de la CL, esta fue mayor en el grupo de RV (100 vs. 70 minutos) que en el de la técnica secuencial (p = 0.0008), probablemente relacionado con la dificultad técnica del procedimiento, lo cual coincide con lo descrito en la literatura[14,28]. Siguiendo con el tiempo de hospitalización, en nuestro estudio el tiempo global con la técnica RV fue menor, con una media de 7 días (p = 0.0377), mientras que con la técnica secuencial la media fue de 9 días (p = 0.0377). El tiempo de hospitalización posquirúrgica fue de 2 días (p < 0.0001) en el grupo de RV y de 4 días (p < 0.0001) en el grupo control. Esta diferencia media de 4 días de hospitalización entre las técnicas, en favor de la RV, representa una reducción de costos de aproximadamente 2000 euros por paciente[28]. Con base en esto, y estableciendo que en nuestro estudio la p fue estadísticamente significativa en favor de la técnica RV, podemos extrapolar que también hubo un costo hospitalario menor. Además, según lo descrito en la literatura[31], el manejo temprano de la patología litiásica biliar disminuye las tasas de readmisión, mejora la organización técnica del procedimiento[32] e incrementa la satisfacción del paciente, haciendo que al analizar la terapia ideal para el manejo de la colecisto-coledocolitiasis sea la técnica RV la que aparezca como la más ventajosa[33].

La técnica RV ha demostrado una mayor tasa de éxito quirúrgico, menor tasa de complicaciones, hospitalizaciones más cortas, menores costos y mayor satisfacción de los pacientes. Pese a ello, su implementación en general es baja debido a varias razones, de las cuales la primera es la curva de aprendizaje, pues dada la necesidad de implementar una curva de aprendizaje individual[34] es difícil en la medida en que este procedimiento se realiza en centros especializados, y que lo usual es que este manejo sea conjunto con el equipo de gastroenterología, suscitando otra dificultad en relación con poder disponer de un especialista en endoscopia al momento del acto quirúrgico[35,36], o cuya segunda opción debería ser el entrenamiento de cirujanos en la técnica endoscópica[35]. Lo anterior, sumado a la necesidad de una estructuración multidisciplinaria intrahospitalaria, facilitando que los equipos y materiales adicionales se encuentren disponibles a necesidad. Además, se han reportado beneficios en cuanto a costos[37], aunque cabe señalar que este beneficio solo es valorable en relación con el manejo de la coledocolitiasis, pero no cuando se evalúa en conjunto con la CL.

Conclusiones

La coledocolitiasis asociada a colelitiasis, colecistitis o pancreatitis de origen biliar es una patología frecuente en los servicios quirúrgicos. Su manejo se puede realizar en un tiempo quirúrgico único o en dos tiempos. La técnica laparoendoscópica o RV es la que ha mostrado superioridad en relación con una mayor tasa resolutiva, una menor presencia de complicaciones, un menor tiempo hospitalario y una mayor satisfacción al paciente. Sin embargo, es necesario realizar más estudios multicéntricos, con cohortes mayores, para establecer si hay otros beneficios, o si ampliando su uso aparecen otros eventos adversos. De igual manera, se requiere mayor entrenamiento a los cirujanos en esta técnica, con base en los beneficios que ofrece, permitiendo así ampliar su implementación.

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Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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ORIGINAL ARTICLE

The effect of pre-operative biliary drainage in resectable periampullary lesions: a systematic review and meta-analysis

Efecto del drenaje biliar pre-operatorio en lesiones periampulares resecables: revisión sistemática y metaanálisis

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Abstract

Objective: *The effect of a pre-operative biliary stent on complications after pancreaticoduodenectomy (PD) remains controversial.* **Materials and method***: We conducted a meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses guidelines, and PubMed, Web of Science Knowledge, and Ovid's databases were searched by the end of February 2023. 35 retrospective studies and 2 randomized controlled trials with a total of 12641 patients were included.* **Results***: The overall complication rate of the pre-operative biliary drainage (PBD) group was significantly higher than the no-PBD group (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.22-1.74; p < 0.0001), the incidence of post-operative delayed gastric emptying was increased in patients with PBD compared those with early surgery (OR 1.21, 95% CI: 1.02-1.43; p = 0.03), and there was a significant increase in post-operative wound infections in patients receiving PBD with an OR of 2.2 (95% CI: 1.76-2.76; p < 0.00001).* **Conclusions:** *PBD has no beneficial effect on post-operative outcomes. The increase in post-operative overall complications and wound infections urges the exact indications for PBD and against routine pre-operative biliary decompression, especially for patients with total bilirubin < 250 umol/L waiting for PD.*

Keywords: *Pre-operative biliary drainage. Resectable. Periampullary lesions. Meta-analysis.*

Resumen

Objetivo: *El efecto de una endoprótesis biliar pre-operatoria sobre las complicaciones después de la pancreaticoduodenectomía sigue siendo controvertido.* **Materiales y método:** *Se llevó a cabo un metaanálisis siguiendo las directrices PRISMA y se realizaron búsquedas en PubMed, Web of Science Knowledge y la base de datos de Ovid hasta finales de febrero de 2023. Se incluyeron 35 estudios retrospectivos y 2 ensayos controlados aleatorizados, con un total de 12,641 pacientes.* **Resultados:** *La tasa global de complicaciones del grupo drenaje biliar pre-operatorio (PBD) fue significativamente mayor que la del grupo no-PBD (odds ratio [OR]: 1.46; intervalo de confianza del 95% [IC 95%]: 1.22-1.74; p < 0.0001), la incidencia de vaciado gástrico retardado posoperatorio fue mayor en los pacientes con PBD en comparación con los de cirugía precoz (OR: 1.21; IC95%: 1.02-1.43; p = 0.03), y hubo un aumento significativo de las infecciones posoperatorias de la herida en los pacientes que recibieron PBD (OR: 2.2; IC 95%: 1.76-2.76; p < 0.00001).* **Conclusiones:** *El drenaje biliar pre-operatorio no tiene ningún efecto beneficioso sobre el resultado posoperatorio. El aumento de las complicaciones posoperatorias globales y de las infecciones de la herida urge a precisar las indicaciones de PBD y a desaconsejar la descompresión biliar pre-operatoria sistemática, en especial en pacientes con bilirrubina total inferior a 250 μmol/l en espera de pancreaticoduodenectomía.*

Palabras clave: *Drenaje biliar pre-operatorio. Resecable. Lesiones periampulares. Metaanálisis.*

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Introduction

Obstructive jaundice is the most common manifestation of pancreatic head and other periampullary lesions, which is related to disturbed coagulation, decreased hepatic function, and the development of cholangitis following pancreaticoduodenectomy (PD)[1].

The management of pre-operative biliary drainage (PBD) in patients undergoing PD is controversial. PBD is mostly performed by placing a biliary stent in the common bile duct or percutaneous transhepatic biliary drainage in the pre-operative diagnosis of endoscopic retrograde cholangiopancreatography[2]. Early studies have suggested a beneficial effect of treating obstructive jaundice with PBD on post-operative outcomes with regard to mortality and morbidity. However, previous data and systematic reviews have shown that PBD for distal biliary obstruction leads to increased perioperative complications after PD[3].

In order to evaluate the incidence of complications and mortality, we conducted a meta-analysis to compare surgery after PBD and single surgery.

Materials and methods

Using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, PubMed, Web of Science, and Ovid's database were searched for studies published by the end of February 2023. The search terms used were "preoperative biliary drainage," "pancreaticoduodenectomy," "resectable periampullary lesions," "complication", and "mortality."

Manually check the reference list of relevant studies to locate any missing studies. The two co-authors independently chose to include and exclude studies and reached a consensus when they did not reach an agreement at first.

Inclusion criteria and exclusion criteria

The inclusion criteria are as follows: (1) Study of patients with periampullary lesions undergoing PD; (2) Comparison of prognosis between PBD and no-PBD; (3) Mortality or complications were mentioned. Exclusion of a study using the following criteria: (1) summary, correspondence, editorial, expert opinion, review, case report; (2) no data or control studies are available; (3) including studies of unresectable periampullary lesions; and (4) patients with palliative R2 resection.

Study selection

By reviewing the titles, abstracts, keywords, and full text of each retrieved record, we evaluated whether the identified studies were qualified to be included in the review. The research is limited to papers published in English.

Data extraction

Data were extracted from two independent observers (Tiequan Yang and Yangjun Li) using standardized tables. Record the following variables: author, journal and publication year, number of patients, total sample size, age, gender, tumor size, complications, re-operation, and mortality. If necessary, contact the corresponding authors of the study to obtain supplementary information.

Quality assessment

Review Manager 5.3 by the Cochrane Collaboration was used for analysis. The risk of bias was assessed using the Cochrane Risk of Bias 2.0 assessment tool for randomized controlled trials (RCTs)[4] and the Cochrane Risk of Bias in non-randomized studies of interventions tool for non-RCTs[5].

Statistical analysis

A formal meta-analysis was carried out for all included studies for periampullary lesions with or without PBD. The outcomes of our study were complications, re-operation, and mortality. Outcomes were encoded as dichotomous variables, and odds ratios (OR) were calculated by assessing the incidence of respective outcomes. The Mantel–Haenszel statistical method with a randomized or fixed effects model was not based solely on statistical heterogeneity but also on clinical heterogeneity between the trials. Sensitivity analyses were also performed by removing individual studies from the data set and analyzing the effect on the overall results to identify sources of significant heterogeneity.

Potential publication bias was assessed by the application of contour-enhanced funnel plots[6], Egger's linear regression test[7], and Begg's rank correlation

test at the $p < 0.05$ level of significance[8]. If publication bias was indicated, we further evaluated the number of missing studies in a meta-analysis by the application of the trim and fill method and recalculated the pooled risk estimate with the addition of those missing studies. Except where otherwise specified, a $p < 0.05$ was considered significant.

Results

We followed the PRISMA guidelines to conduct the literature search and the selection of included studies, as presented in the PRISMA flow diagram (Fig. 1). Finally, 37[9-45] studies met the requirements and were included in this meta-analysis. Of these, 35 were retrospective studies, and 2 were RCTs (Table 1).

The basic characteristics of the included studies are shown in table 1. All the included studies demonstrated a relatively high quality.

The 27 included studies comprised 10376 patients, of whom 6380 received PBD and 3996 proceeded directly to surgery. Overall complications were significantly higher in the PBD group (46.3%) than in the no-PBD group (40.8%), with an OR of 1.46 (95% CI 1.22-1.74; $p < 0.001$). In the RCTs, the OR for the incidence of overall complications in the PBD group versus the no-PBD group was 2.69 (95% CI: 0.84-8.63; $p = 0.1$) (table 2).

In the 29 included studies, 1154 out of 6640 (17.4%) patients with PBD developed a pancreatic fistula in contrast to 701 of 4921 (14.2%) patients in the no-PBD group with an OR of 1.1 (95% CI: 0.9-1.35; $p = 0.34$), showing no significant difference in the incidence of post-operative pancreatic fistulas between patients receiving PBD and the no-PBD group. In the RCT, pancreatic fistula rates were 8/102 (7.8%) and 11/94 (11.7%) in the PBD and no-PBD groups, respectively, resulting in an OR of 0.64 (95% CI: 0.25-1.67; $p = 0.36$) (Table 2).

In the 20 included studies, biliary fistulas were 117/3404 (3.4%) and 116/2944 (3.9%) in the PBD and no-PBD groups, respectively, with an OR of 0.87 (95% CI: 0.66-1.15; $p = 0.32$). In the RCT, biliary fistula rates were 1/102 (1.0%) and 3/94 (3.2%) in the PBD and no-PBD groups, respectively, resulting in an OR of 0.3 (95% CI: 0.03-2.94; $p = 0.3$) (Table 2).

We elucidated the incidence of intra-abdominal abscess, intraperitoneal bleeding, and digestive tract bleeding. No significant differences were observed between the groups in terms of intra-abdominal abscess (OR 0.88, 95% CI: 0.53-1.46; $p = 0.63$), intraperitoneal bleeding (OR 1.11, 95% CI: 0.65-1.88; $p = 0.7$), and digestive tract bleeding (OR 0.79, 95% CI: 0.58-1.08; $p = 0.14$) (Table 2).

We investigated the influence of PBD on the incidence of post-operative delayed gastric emptying. As demonstrated in our study, the incidence of post-operative delayed gastric emptying was increased in patients with PBD (12.7%) compared those with early surgery (11.9%), with an OR of 1.21 (95% CI: 1.02-1.43; $p = 0.03$) (Table 2). In the RCT, 18 out of 102 (17.6%) and 9 out of 94 (9.6%) patients suffered post-operative delayed gastric emptying in the PBD and no-PBD groups, respectively, resulting in an OR of 2.02 (95% CI: 0.86-4.76; $p = 0.11$) (Table 2).

A total of 26 included studies revealed 1144 wound infections in 6373 patients in the PDB group (18.0%) in comparison to 363 in 4203 patients in the no-PBD group (8.6%), with an OR of 2.2 (95% CI:1.76-2.76; $p < 0.00001$) in favor of the no-PBD group, indicating that post-operative wound infection in PBD patients increased significantly. The incidence of wound infections in the RCT was 13 of 102 (12.7%) and 7 of 94 (7.4%) in the PBD and no-PBD groups, respectively, resulting in an OR of 1.82 (95% CI: 0.69-4.77; $p = 0.23$) (Table 2).

17 studies assessed patients for re-operation. The prevalence of re-operation was 5.3% (165/3094) in the PBD group versus 5.9% (148/2513) in the no-PBD group. However, this difference was not statistically significant (OR 0.78, 95% CI: 0.61-1.0; $p = 0.05$). In the RCT, re-operation rates were 12/102 (11.7%) and 13/94 (13.8%) in the PBD and no-PBD group, respectively, resulting in an OR of 0.83 (95% CI: 0.36-1.92; $p = 0.67$) (Table 2).

We evaluated the effect of PBD on post-operative mortality within 30 days after surgery. Among the 24 included studies, 126 (2.1%) of the 5774 cases in the PBD group died, while 103 (2.4%) of the 4051 cases in the no-PBD group died, with an OR of 0.84 (95% CI: 0.63-1.11, $p = 0.22$) (Table 2).

Regarding the patients with mean total bilirubin > 150 umol/L and < 250 umol/L, 5 studies were included for overall complications, and 3 studies were included for mortality. The prevalence of overall complications was 56.1% (202/360) in the PBD group versus 40.9% (143/350) in the no-PBD group. However, this difference was not statistically significant (OR 1.75, 95% CI: 0.99-3.11; $p = 0.06$) (Fig. 2). In the RCTs, the OR for the incidence of overall complications in the PBD group versus the no-PBD group was 2.69 (95% CI: 0.84–8.63; $p = 0.1$), depicting an overall complication rate of 120/197 (60.9%) and 70/184 (38.0%) in the PBD and no-PBD groups, respectively. A total of 3

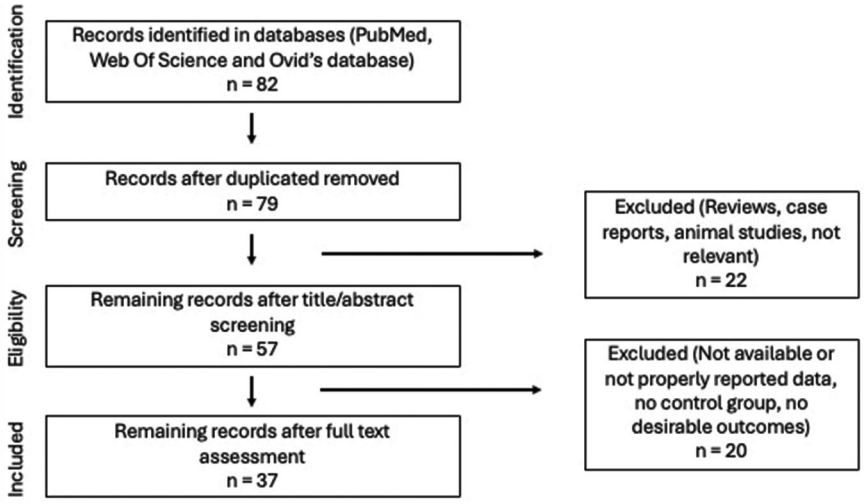

Figure 1. *Flowchart of the results of the literature search.*

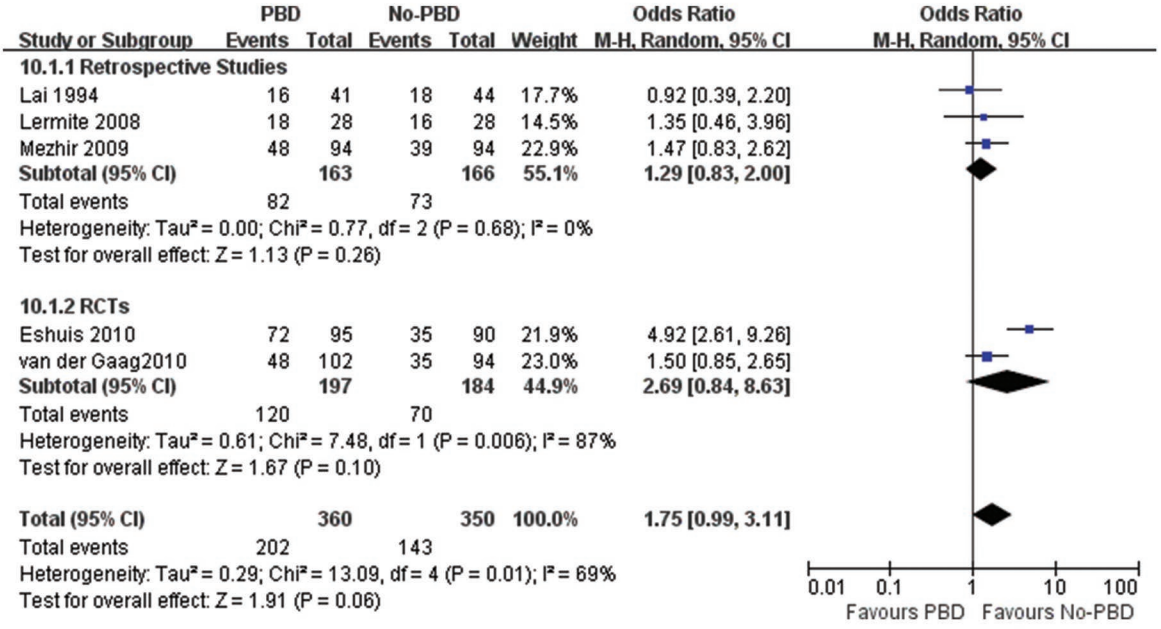

Figure 2. *Forest plots of the comparison of the overall complications between pre-operative biliary drainage (PBD) and no-PBD with patients' mean total bilirubin between 150 umol/L and 250 umol/L.*

included studies revealed 7 died in 165 patients in the PDB group (4.2%) in comparison to 13 in 166 patients in the no-PBD group (7.8%), with an OR of 0.53 (95% CI:0.21-1.36; p = 0.19) (Fig. 3).

Discussion

Biliary drainage increases patient comfort by reducing bilirubin levels, thereby alleviating the common problem symptoms of pruritus. In addition, biliary drainage can be used as a temporary measure to allow liver function tests and normalization of liver function if the operation is delayed for a considerable period of time. However, biliary stents induce bacterial contamination and enhance the risk of cholangitis because a connection between the bowels and the bile ducts is created.

Table 1. Demographic characteristics of patients and study design as reported in the included studies

Author, year	Country	Groups	No. of patients	Sex (male/female)	Mean age (year)	Total bilirubin (umol/L)	Tumor diameter (cm)	Perioperative antibiotic prophylaxis	Study design
Liu et al. 2015[9]	China	PBD No-PBD	47 288	28/19 166/122	59 ± 2 57 ± 1	363.2 ± 18.0 136.0 ± 8.4	3.5 ± 0.2 4.3 ± 0.4	-	Retrospective
Pisters et al. 2000[10]	USA	PBD No-PBD	172 93	102/70 45/48	-	-	-	Cephalosporin or ciprofloxacin	Retrospective
Howard et al. 2006[11]	USA	PBD No-PBD	86 52	52/34 33/19	61 ± 13 59 ± 14	-	-	-	Retrospective
Coates et al. 2009[12]	USA	PBD No-PBD	56 34	31/25 17/17	66 ± 12 65 ± 15	236 ± 142 101 ± 147	2.8 ± 1.5 3.3 ± 2.0	-	Retrospective
Mullen et al. 2005[13]	USA	PBD No-PBD	170 92	-	-	-	-	Cephalosporin or ciprofloxacin	Retrospective
Lai et al. 1994[14]	China	PBD No-PBD	43 44	31/12 28/16	67 66	266 209	-	-	Retrospective
Morris-Stiff et al. 2011[15]	UK	PBD No-PBD	118 162	-	-	-	-	Cephalosporin	Retrospective
Huang et al. 2015[16]	China	PBD No-PBD	100 170	- 113/57	- 57.8 ± 8.6	- 209.9 ± 136.7	- 2.2 ± 1.1	-	Retrospective
Eshuis et al. 2010[17]	Netherlands	PBD No-PBD	95 90	51/44 63/27	64.7 ± 10.3 64.6 ± 9.5	160 ± 57.9 149 ± 54.5	-	-	RCT
Singhirunnusorn et al. 2013[18]	France	PBD No-PBD	38 62	22/16 30/32	68 68	114 17	-	-	Retrospective
Arkadopoulos et al. 2014[19]	Greece	PBD No-PBD	76 76	50/26 45/31	57 ± 12 58 ± 11	-	-	-	Retrospective
Hodul 2003[20]	USA	PBD No-PBD	154 58	95/59 33/25	66 ± 11 64 ± 10	92.34 ± 102.6 157.3 ± 135.1	-	-	Retrospective
Mezhir et al. 2009[21]	USA	PBD No-PBD	94 94	48/46 47/47	68 ± 10 69 ± 9	201.78 191.52	-	-	Retrospective
Van der Gaag et al. 2010[22]	Netherlands	PBD No-PBD	102 94	53/49 66/28	64.7 ± 10.5 64.7 ± 9.5	154 ± 59.5 151 ± 58.7	-	-	RCT
Abdullah et al. 2009[23]	Singapore	PBD No-PBD	35 47	14/21 26/21	65 62	112.4 ± 116.1 91.6 ± 110.2	1 12	-	Retrospective
Agalianos et al. 2016[24]	Greece	PBD No-PBD	99 105	58/41 62/43	67.1 65.2	- -	- -	-	Retrospective
Barnett and Collier 2006[25]	Australia	PBD No-PBD	49 52	- -	- -	- -	- -	-	Retrospective
Bhati et al. 2007[26]	India	PBD No-PBD	21 27	10/11 15/12	50 48	134.24 ± 95.59 201.11 ± 154.76	- -	-	Retrospective
Cavell et al. 2013[27]	USA	PBD No-PBD	220 289	120/100 149/140	- 65	- -	- -	-	Retrospective
De Pastena et al. 2018[28]	Italy	PBD No-PBD	714 258	419/295 147/111	66 65	22.1 100.89	- -	Ampicillin/ sulbactam	Retrospective
El Nakeeb et al. 2018[29]	Egypt	PBD No-PBD	314 274	183/131 169/105	- -	239.4 138.5	- -	-	Retrospective
Gavazzi et al. 2016[30]	Italy	PBD No-PBD	89 91	57/32 51/40	- -	- -	- -	Cefazolin	Retrospective

(Continues)

Table 1. Demographic characteristics of patients and study design as reported in the included studies *(continued)*

Author, year	Country	Groups	No. of patients	Sex (male/female)	Mean age (year)	Total bilirubin (umol/L)	Tumor diameter (cm)	Perioperative antibiotic prophylaxis	Study design
Heslin et al. 1998[31]	USA	PBD	39	17/22	67 ± 2	160 ± 14	-	-	Retrospective
		No-PBD	35	24/11	62 ± 2	118 ± 18	-		
Jagannath et al. 2004[32]	India	PBD	74	50/24	50	140	-	-	Retrospective
		No-PBD	70	48/22	50	70	-		
Lermite et al. 2008[33]	France	PBD	28	22/6	64.8 ± 9.3	200 ± 158	-	Cefazolin	Retrospective
		No-PBD	28	17/11	64.4 ± 9.5	169 ± 155	-		
Marcus et al. 1998[34]	USA	PBD	22	13/9	67.5	23.94	-	-	Retrospective
		No-PBD	30	19/11	71.5	189.81	-		
Martignoni et al. 2001[35]	Switzerland	PBD	99	52/47	69	145	-	-	Retrospective
		No-PBD	158	86/72	64	14	-		
Ng et al. 2017[36]	Australia	PBD	30	19/12	66.5	24.5	-	-	Retrospective
		No-PBD	21	9/11	64	7.0	-		
Pešková and Gürlich 2005[37]	Czech Republic	PBD	144	-	63	118	-	Cefoperazone	Retrospective
		No-PBD	160	-	53.2	81	-		
Sahora et al. 2016[38]	USA	PBD	500	273/227	66	18.81	-	Cefoxitin	Retrospective
		No-PBD	500	237/263	61	6.84	-		
Shaib et al. 2020[39]	Lebanon	PBD	1803	1055/748	66.52 ± 10.26	107.6 ± 77.5	-	-	Retrospective
		No-PBD	503	272/231	66.43 ± 10.14	48.1 ± 49.1	-		
Sohn et al. 2000[40]	USA	PBD	408	220/188	63.8 ± 0.6	-	-	-	Retrospective
		No-PBD	159	78/81	61.4 ± 1.2	-	-		
Yanagimoto et al. 2014[41]	Japan	PBD	112	73/39	-	-	-	-	Retrospective
		No-PBD	73	42/31	67	10.26	-		
Ozgun et al. 2021[42]	Turkey	PBD	574	236/206	59.43 ± 11.27	104.3	-	-	Retrospective
		No-PBD	231	131/100	59.24 ± 12.87	17.1			
di Mola et al. 2014[43]	Italy	PBD	53	33/20	67	-	-	-	Retrospective
		No-PBD	40	29/11	66.5				
Ray et al. 2021[44]	India	PBD	175	115/60	52.46 ± 9.90	234.6 ± 118.5	-	-	Retrospective
		No-PBD	229	139/90	48.23 ± 11.22	115.3 ± 129.6			
Wu et al. 2019[45]	Taiwan	PBD	237	136/101	65.2 ± 12.7	179.55 ± 141.93	-	Cefmetazole	Retrospective
		No-PBD	662	346/316	60.4 ± 13.5	47.88 ± 87.21	-		

PBD: pre-operative biliary drainage.

Through our meta-analysis, we can provide evidence that the overall complications in patients receiving PBD before surgical intervention are higher than those in patients without PBD. In addition, we can indicate that PBD is related to the increase in post-operative wound infection rate and delayed gastric emptying but has no effect on biliary fistula, pancreatic fistula, abdominal abscess, intraperitoneal hemorrhage, gastrointestinal bleeding, and perioperative mortality.

The underlying mechanism of DGE remains unclear, but many authors believe that pancreatic enzyme leakage may play an important role in local inflammation[46,47].

Post-operative wound infection is defined as purulent drainage with or without bacterial culture positive, or any drainage that was culture positive. Bacterial cultures of infected wounds showed a strong correlation with the microorganisms found on bile cultures obtained at the time of surgery. For example, Sahora et al. reviewed a series of patients and reported that the presence of Citrobacter and Enterobacteriaceae in bile culture significantly increased the incidence of wound infection in stent patients[38]. Gavazzi et al.

Table 2. Comparison of outcomes associated with PBD versus no-PBD

Outcomes	No. of studies	No. of patients		OR	95% CI	p-value	I^2
		PBD	No-PBD				
Overall complications							
Retrospective	25	6183	3812	1.39	1.17,1.65	0.0002	67
RCTs	2	197	184	2.69	0.84,8.63	0.1	87
Total	27	6380	3996	1.46	1.22,1.74	< 0.0001	70
Pancreatic fistula							
Retrospective	28	5736	4327	1.12	0.92,1.37	0.27	48
RCT	1	102	94	0.64	0.25,1.67	0.36	-
Total	29	5838	4421	1.1	0.90,1.35	0.34	48
Biliary fistula							
Retrospective	19	3302	2850	0.89	0.67,1.17	0.4	3
RCT	1	102	94	0.3	0.03,2.94	0.3	-
Total	20	3404	2944	0.87	0.66,1.15	0.32	2
Intraabdominal abscess							
Retrospective	18	2540	2508	0.9	0.53,1.51	0.68	76
RCT	1	102	94	0.61	0.1,3.71	0.59	-
Total	19	2642	2602	0.88	0.53,1.46	0.63	75
Intraperitoneal bleeding							
Retrospective	5	757	1016	1.23	0.7,2.15	0.47	0
RCT	1	102	94	0.45	0.08,2.52	0.36	-
Total	6	859	1110	1.11	0.65,1.88	0.7	0
Digestive tract bleeding							
Retrospective	6	1369	1050	0.79	0.58,1.08	0.14	0
Delayed gastric emptying							
Retrospective	16	3039	2436	1.18	0.99,1.4	0.06	0
RCT	1	102	94	2.02	0.86,4.76	0.11	-
Total	17	3141	2530	1.21	1.02,1.43	0.03	0
Wound infection							
Retrospective	25	5469	3609	2.22	1.76,2.81	< 0.00001	40
RCT	1	102	94	1.82	0.69,4.77	0.23	-
Total	26	5571	3703	2.2	1.76,2.76	< 0.00001	37
Re-operation							
Retrospective	15	2817	2190	0.78	0.6,1.01	0.06	0
RCT	1	102	94	0.83	0.36,1.92	0.67	-
Total	16	2919	2284	0.78	0.61,1.0	0.05	0
Mortality							
Retrospective	23	5599	3822	0.84	0.63,1.11	0.22	0

PBD: pre-operative biliary drainage; OR: odds ratio; CI: confidence interval; RCT: randomized controlled trials.

analyzed 180 patients to explore the risk factors for wound infection after PD. Multivariate analysis showed that biliary stents significantly increased the incidence of wound infection, among which Enterococcus, Escherichia coli, and Klebsiella were the most common bacteria in bile culture[30].

Moreover, we also confirmed that the wound infection rate in the PBD group was higher than that in the no-PBD group, resulting in an increase in overall complications. The longer the time of biliary stent is implanted, the more intestinal bacteria flow back into the biliary tree, thus increasing the risk of bacterial colonization. In addition, biliary drainage itself also has complications, including pancreatitis, cholecystitis, cholangitis, and perforation[33].

One previous study illustrated that overall morbidity and mortality were not influenced by the presence or absence of severe jaundice[35]. Another study reported patients with serum bilirubin levels between 40 and 250 μmol/l had no benefit from PBD in patients with serum bilirubin levels < 170 μmol/l, and only higher values were associated with intraoperative or

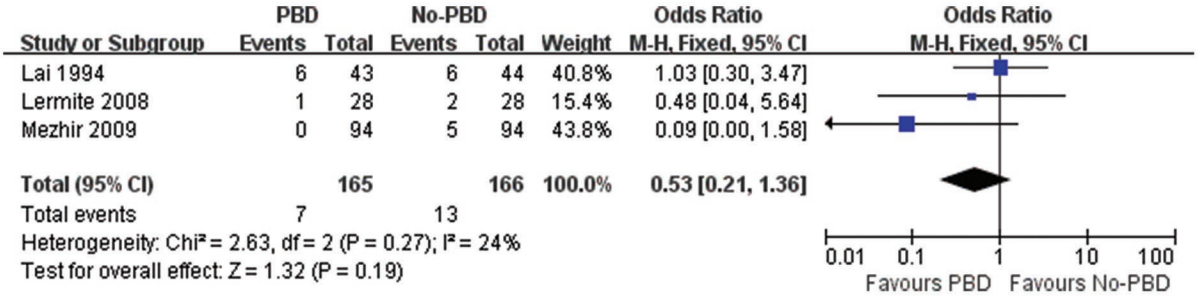

Figure 3. *Forest plots of the comparison of the mortality between pre-operative biliary drainage (PBD) and no-PBD with patients' mean total bilirubin between 150 umol /L and 250 umol /L.*

post-operative complications[17]. In our meta-analysis, patients with mean total bilirubin between 150 umol/L and 250 umol/L showed no statistically significant difference in overall complications and mortality between the PBD and no-PBD groups. However, there was no high-quality evidence for the indication of PBD by serum bilirubin thresholds.

The present analysis also has limitations that should be taken into consideration. First, only two RCTs were included in the meta-analysis. Non-RCTs may exaggerate the effect of the approaches, either by external factors or by intrinsic flaws. Second, heterogeneity was high among the included studies, possibly due to different definitions of complications, ways of stent placement, stent types, and materials. Third, some relevant data, such as stent-related complications, drainage interval, and post-operative hospital stay, were not included in this study. Therefore, more RCTs using standardized assessments, a single pre-operative drainage method, and limited surgical procedures are needed.

Conclusion

In conclusion, the use of PBD has not been proven to be beneficial for patients, especially for patients with total bilirubin < 250 umol/L waiting for PD.

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Conflicts of interest

There are no conflicts of interest exits regarding the submission of this manuscript.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Assessment of inflammatory parameters as predictive markers for malignancy in thyroid nodules: a study on the correlation with Bethesda classification

Evaluación de los parámetros inflamatorios como marcadores predictivos de malignidad en nódulos tiroideos: un estudio sobre su correlación con la clasificación de Bethesda

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Abstract

Objective: *The study aimed to assess the predictive significance of inflammatory parameters as potential markers for malignancy in individuals with thyroid nodules.* **Method:** *Nine hundred and ninety-one patients with thyroid nodules who had undergone thyroid fine-needle aspiration biopsy were included and classified according to the Bethesda system. Neutrophil lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) values obtained from hemogram parameters were determined for each patient. The study examined the correlation between the Bethesda classification and NLR/SII levels. In addition, a comparison was made between the inflammatory parameters of the benign and malignant Bethesda groups.* **Results:** *Five hundred and seventy-three patients were classified as Bethesda 2 (benign), 34 as Bethesda 6 (malignant). A correlation was observed between the Bethesda classification and NLR and SII levels (r: 0.230, $p < 0.001$; r: 0.207 $p < 0.001$, respectively). NLR and SII values were significantly higher in the malignant group ($p < 0.001$). The cutoff value for SII in predicting benign and malignant thyroid nodules was 489.86 × 10^3/mm^3 with a sensitivity of 88.2% and a specificity of 63.7%. The cutoff value for NLR for the same prediction was 2.06 with a sensitivity of 82.4% and a specificity of 83.4%.* **Conclusions:** *The findings of this study indicate that SII and NLR may be valuable prognostic markers for predicting the malignancy of thyroid nodules.*

Keywords:*Thyroid nodüle. Thyroid cancer. Fine needle aspiration biopsy. Systemic immune-inflammation index.*

Resumen

Objetivo: *Evaluar parámetros inflamatorios como posibles marcadores de malignidad en individuos con nódulos tiroideos.* **Método:** *Se incluyeron 991 pacientes con nódulos tiroideos que se sometieron a biopsia por aspiración con aguja fina y se clasificaron según el sistema de Bethesda. Se determinaron los valores de la relación neutrófilo-linfocito (NLR) y el índice de inflamación inmunitaria sistémica (SII). El estudio exploró la correlación entre la clasificación de Bethesda y los valores de NLR/SII, y comparó los parámetros inflamatorios de los grupos benignos y malignos de Bethesda.* **Resultados:** *Se clasificaron 573 pacientes como Bethesda 2 (benigno) y 34 como Bethesda 6 (maligno). Se observó una correlación entre la*

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clasificación de Bethesda y los valores de NLR y SII (r: 0.230; r: 0.207). Los valores de NLR y SII fueron mayores en el grupo maligno (p < 0.001). El valor de corte para SII en la predicción de nódulos tiroideos benignos y malignos fue de 489.86 × 10^3/mm^3, con una sensibilidad del 88.2% y una especificidad del 63.7%; para NLR fue de 2.06, con una sensibilidad del 82.4% y una especificidad del 83.4%. **Conclusiones:** *El SII y el NLR pueden ser valiosos marcadores pronósticos para predecir la malignidad de los nódulos tiroideos.*

Palabras clave: *Nódulo tiroideo. Cáncer de tiroides. Biopsia por aspiración con aguja fina. Índice de inflamación inmunitaria sistémica.*

Introduction

Thyroid nodules are a frequently encountered clinical finding, with prevalence estimates of up to 60% in certain populations[1]. Despite the majority of nodules being benign, a significant proportion of them, ranging from 5% to 15%, is malignant[2]. The most accurate diagnostic procedure for evaluating the malignancy of thyroid nodules is performing a thyroid fine-needle aspiration biopsy (FNAB) on nodules that are considered to be at high risk[3]. The Bethesda System, which categorizes thyroid nodules into six categories based on the cytological findings of FNAB, is the standard reporting system used to classify the results of thyroid FNAB[4]. However, there is still significant overlap between benign and malignant nodules, leading to the need for additional practical and non-invasive markers to improve diagnostic accuracy and prevent unnecessary surgeries.

In recent years, the hematological parameters have gained attention as potential markers to enhance the diagnosis and prognosis of various inflammatory conditions, including cancers[5-12]. Systemic immune-inflammation index (SII) is a composite index based on the absolute counts of neutrophils, lymphocytes, and platelets and has been found to be associated with the prognosis of several cancers. In a previous study, it was observed that the SII of patients with differentiated thyroid cancer was significantly higher when compared to a control group (6). Similarly, in a recent study, it has been reported that elevated neutrophil–lymphocyte ratio (NLR) values in patients with nodules can predict malignancy[11]. However, there is insufficient and conflicting data about predicting value of NLR and SII in malign thyroid nodules.

The aim of this study was to assess the predictive significance of inflammatory parameters, specifically NLR and SII, as potential markers for malignancy in individuals with thyroid nodules. By evaluating the correlation between inflammatory parameters and the Bethesda classification, this investigation aimed to contribute to the existing knowledge and potentially enhance the diagnostic accuracy and risk assessment of thyroid nodules.

Methods

This study was conducted in compliance with the principles of the Helsinki Declaration and with the approval of Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital Ethics Committee, with a number of 2022/137.

Patients included in this study were 18 years of age or older who underwent thyroid FNAB at Sancaktepe Sehit Professor Doctor Ilhan Varank Training and Research Hospital between March 2018 and October 2022. Only patients with available data, including demographic information, laboratory parameters, and cytological results were included in this study. Exclusion criteria for this study were pre-defined to include patients with unavailable medical data, active infection, chronic infection (tuberculosis, hepatitis B, C etc.), acquired immunodeficiency syndrome, non-thyroid malignancy, autoimmune rheumatologic or hematologic disease, advanced liver or kidney failure, dysregulated diabetes mellitus, systemic infiltrative diseases (sarcoidiosis, hemochromatosis etc.) history of head-and-neck radiation, thyroid surgery or primary thyroid disease, pregnancy, or the use of medications that could potentially alter complete blood count parameters.

An automated hematology analyzer, Mindray-BC6800, was used to measure the hemogram parameters. The cytology results and laboratory data of eligible patients were retrieved from the medical information system. NLR was calculated with the formules: neutrophil count/lymphocyte count (9). SII was calculated with the formula: neutrophil count X platelet count/lymphocyte count (7). Patients were

grouped according to their Bethesda classification of thyroid nodules, and SII, NLR, and other parameters were evaluated for each group[4]. This classification reports the results as non-diagnostic (Bethesda Category 1), benign (Bethesda Category 2), atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda Category 3), follicular neoplasm or suspicious for a follicular neoplasm (Bethesda Category 4), suspicious for malignancy (Bethesda Category 5) or malignant (Bethesda Category 6).

The parameters of patients with benign cytology (Bethesda 2) and malignant cytology (Bethesda 6) were compared. In addition, the correlation between inflammatory parameters and the Bethesda classification was examined.

Statistical analysis

IBM Corporation Statistical Package for the Social Sciences, version 23.0, was used for all data analyses. The normal distribution of the data between groups was assessed using the Kolmogorov–Smirnov test. Descriptive statistics, including percentages and either mean ± standard deviation or median interquartile range, were used to summarize the data based on the normality of the distribution. The statistical analysis involved comparing the distributions of continuous variables between two independent groups using the Mann–Whitney U test, while the Chi-square test was used for qualitative data. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. The receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of neutrophil, lymphocyte, and SII for malignant thyroid nodules and to determine their optimal cutoff values, sensitivity, and specificity. The statistical significance level was established at a $p < 0.05$.

Results

The total number of patients enrolled in the study was 991. Seven hundred and ninety-six of them were female and 195 were male. The median age of the patients was 53 years. Among the 991 patients, the distribution according to the Bethesda classification was as follows: 126 (12.7%) were classified as Bethesda 1, 573 (57.8%) as Bethesda 2, 202 (20.4%) as Bethesda 3, 28 (2.8%) as Bethesda 4, 28 (2.8%) as Bethesda 5, and 34 (3.4%) as Bethesda 6. The distribution of patients according to FNAB cytology results and inflammatory parameters is presented in table 1. In a retrospective analysis of patients, it was found that all individuals classified as Bethesda 5 and 6 underwent thyroidectomy. Among the 28 patients with Bethesda 5, 24 (85%) had a histopathological diagnosis of differentiated thyroid carcinoma, and similarly, all Bethesda 6 patients had a histopathological diagnosis of differentiated thyroid carcinoma.

The details of the comparison between malignant and benign groups are summarized in table 2. Lymphocyte levels were found to be significantly higher in the benign group compared to the malignant group ($p < 0.001$). Neutrophil, NLR, and SII values were significantly higher in the malignant group compared to the benign group ($p < 0.001$). In addition, the pairwise comparison of the Bethesda groups based on SII and NLR are shown in table 3. Significant differences were observed between 1 and 3, 1 and 5, 1 and 6, 2 and 3, 2 and 5, 3 and 6, and 4 and 6.

The area under the curve (AUC) in the ROC curve drawn for the SII variable of patients with malignant thyroid nodules is 0.822 and its standard error is 0.34. The area under the ROC curve was statistically significant ($p < 0.001$). The cutoff value for SII was found to be $489.86 \times 10^3/mm^3$. The sensitivity of this value is 88.2%, and the specificity is 63.7%. The ROC curve analysis for the NLR variable in patients with malignant thyroid nodules showed an AUC of 0.848 with a standard error of 0.41, indicating statistically significant diagnostic accuracy ($p < 0.001$). The optimal cutoff value for NLR was determined to be 2.06 with a sensitivity of 82.4% and specificity of 83.4%, as demonstrated by figure 1.

A statistically significant positive correlation was identified between the Bethesda classification and the values of NLR and SII, as evidenced by correlation coefficients of 0.230 ($p < 0.001$) and 0.207 ($p < 0.001$), respectively. This association was consistently observed across the range of Bethesda categories. Notably, on excluding cases with non-diagnostic cytology (Bethesda 1), a discernible pattern emerged: a consistent rise in NLR and SII values coincided with an increase in the Bethesda classification. This trend is visually elucidated through figure 2, depicting the correlation of NLR values, and figure 3, illustrating the association of SII values with the Bethesda classification.

Table 1. Inflammatory parameters and cytological results of study participants

Total patients (n = 991%)	NLR	SII	p-value
Bethesda 1 (126, 12.7)	1.86 (1.23-2.55)*	450 (325.41-657.13)*	p1 < 0.001† p2 < 0.001†
Bethesda 2 (573, 57.8)	1.72 (1.43-1.94)*	437.81 (350.87-552.87)*	
Bethesda 3 (202, 20.4)	2.22 (1.56-2.46)‡	561.25 (397.51-704.56)*	
Bethesda 4 (28, 2.8)	2.80 (0.88-2.89)*	576.49 (223.95-773.12)*	
Bethesda 5 (28, 2.8)	3.04 (2.30-3.24)*	746.41 (267.32-881.20)*	
Bethesda 6 (34, 3.4)	3.18 (1.90-3.47)*	665.62 (533.25-921.67)*	

*Median (IQR). †Kruskal–Wallis Test. NLR: neutrophil–lymphocyte ratio; SII: systemic immune-inflammation index; p1: NLR comparison between groups; p2: SII comparison between groups.

Table 2. Demographic characteristics and hemogram parameters of study groups

Parameters	Benign nodule group (n = 573)	Malignant nodules group (n = 34)	p-value
Gender (male/female)	117 (95.1%) / 456 (94.2%)	6 (4.9%) / 28 (5.8%)	0.696*
Age (years)	54 (45-62)†	51.29 ± 16.26‡	0.198§
Leukocyte ($\times10^3/mm^3$)	6.99 (5.97-8.12)†	7.26 ± 1.22‡	0.335§
Neutrophil ($\times10^3/mm^3$)	3.94 (3.33-4.74)†	4.91 ± 1.11‡	< 0.001§¶
Lymphocyte ($\times10^3/mm^3$)	2.35 (1.96-2.74)†	1.77 ± 0.54‡	< 0.001§¶
Platelet ($\times10^3/mm^3$)	259 (222.50-300)†	258.67 ± 50.98‡	0.660§
Hemoglobin (gr/dL)	13.30 (12.40-14.20)†	13.30 ± 1.83‡	0.976§
NLR	1.72 (1.43-1.94)†	3.18 (2.07-3.59)†	< 0.001§¶
SII ($\times10^3/mm^3$)	437.81 (350.46-552.87)†	665.62 (533.25-921.67)†	< 0.001§¶
TSH (mIU/L)	1.37 (0.78-2.28)†	1.00 (0.50-2.18)†	0.118§
Free T4 (ng/dL)	1.12 (1.00-1.29)†	1.08 ± 0.20‡	0.207§
Free T3 (ng/L)	3.06 (2.69-3.37)†	2.88 ± 0.46‡	0.125§

*Chi-square test. †Median (IQR).‡Mean±SD. §Mann–Whitney U test. ²p < 0.05. SII: systemic ımmune-ınflammation ındex; NLR: neutrophil–lymphocyte ratio; TSH: thyroid stimulating hormone.

Discussion

To the best of our knowledge, this study is the first to investigate the correlation between Bethesda classification and inflammatory parameters, making it a pioneering study in this field. In addition, it encompasses one of the largest cohorts of patients with thyroid nodules, allowing for a comprehensive analysis of inflammatory parameters and enhancing the robustness and generalizability of the findings. The inclusion of all patients who underwent FNAB provides substantial and reliable data for evaluating the association between these parameters and thyroid nodules, significantly contributing to the current understanding in the field. Our results showed that SII and NLR values were significantly higher in patients with malignant nodules compared to patients with benign nodules and the ROC analysis revealed that they had moderate discriminatory powers in the diagnosis of malignant thyroid nodules. Furthermore, there was a positive correlation between Bethesda classification and SII and NLR.

The current research on the correlation between SII and thyroid nodules is limited. Our results are in line with earlier studies that have found a connection between increased SII levels and the presence of malignant thyroid nodules. Deng et al. conducted

Table 3. Pairwise comparison of Bethesda groups based on SII and NLR

Bethesda groups	P* (NLO)	P* (SIII)
1 and 2	0.182	0.407
1 and 3	0.005†	**0.003†**
1 and 4	0.561	0.613
1 and 5	**0.033†**	**0.045†**
1 and 6	**<0.001†**	**< 0.001†**
2 and 3	**<0.001†**	**<0.001†**
2 and 4	0.126	0.253
2 and 5	**0.003†**	**0.009†**
2 and 6	**<0.001†**	**< 0.001†**
3 and 4	0.166	0.617
3 and 5	**0.019†**	0.142
3 and 6	**< 0.001†**	**0.001†**
4 and 5	0.088	0.174
4 and 6	**0.009†**	0.021†
5 and 6	**0.029†**	0.572

*Mann–Whitney U test. †Those in bold were statistically significant (p < 0.05). SII: systemic immune- inflammation index; NLR: neutrophil–lymphocyte ratio.

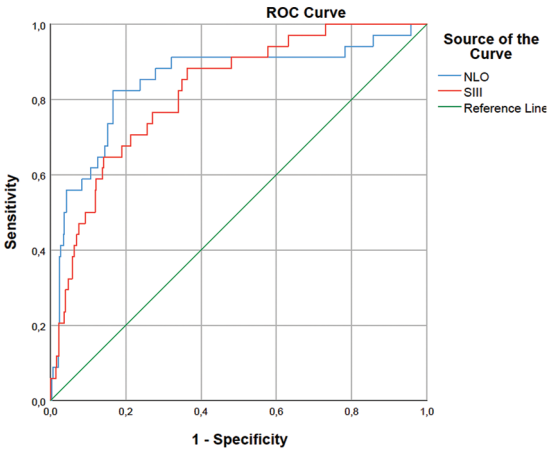

Figure 1. Receiver operating characteristic curve of systemic immune-inflammation index and neutrophil–lymphocyte ratio.

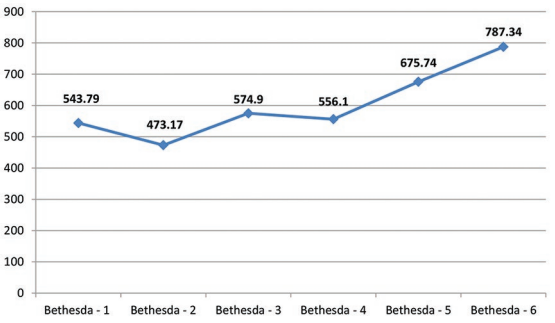

Figure 2. The relationship between Bethesda classification and SII. SII: systemic immune-inflammation index r: 0.207; p < 0.001.

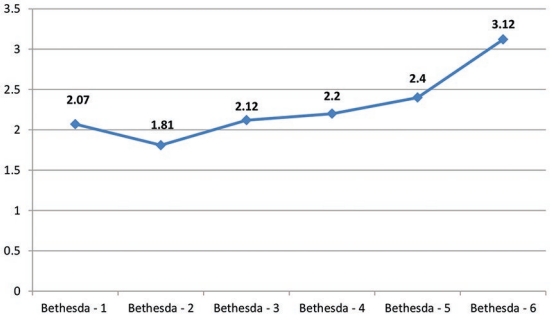

Figure 3: The relationship between Bethesda classification and NLR. NLR: neutrophil–lymphocyte ratio r: 0.230; p < 0.001.

a study on 514 patients classified as TIRADS 3 based on ultrasound evaluation and found that patients with malignant nodules had higher SII values compared to those with benign nodules[13]. In this study, it was found that SII is an independent risk factor for determining malignancy, and a cutoff value of 545.63 × 10^9/L was determined for distinguishing between malignant and benign nodules. In contrast to the previous study, our study included not only patients with TIRADS 3 nodules but all patients who underwent biopsy, resulting in a larger sample size. In another recent study, the SII values of 93 patients with differentiated thyroid carcinoma and 33 control subjects were compared, and the SII values of patients with thyroid cancer were found to be significantly higher[6]. In this study, SII was not found to be associated with histological type, lymphovascular, perineural, or capsule invasion. On the contrary, Zhang et al. found in their study that SII could be an important parameter for determining central lymph node metastasis in differentiated thyroid cancer[8].

The association between NLR and thyroid nodules has been extensively studied. According to a study conducted in Turkey, it has been suggested that preoperative high NLR levels in patients with thyroid nodules could serve as an indicator of possible malignancy[11]. Similarly, in a research by Koçer et al., it was found that NLR values were higher in patients

with thyroid carcinoma compared to those with multinodular goiter. Similar to our study findings, the cutoff value of NLR for distinguishing between malignant and benign nodules was found to be 1.91 with 89% sensitivity and 54.5% specificity in this study[12]. A meta-analysis including nine studies and 3081 patients with differentiated thyroid carcinomas revealed that preoperative NLR is an important biomarker associated with tumor growth, metastasis, and prognosis[10].

The underlying mechanisms linking SII and thyroid malignancy are not fully understood, but conjecture suggests that chronic inflammation might play a role in the initiation and advancement of cancer[14,15]. Inflammation plays a critical role in many pathogenic stages of carcinogenesis, including genomic instability, induction of cell proliferation, suppression of apoptosis, and increase in neovascularization[16]. It has been reported that inflammation is not only a risk factor for tumor formation and development but also that inflammatory cytokines are secreted in tumor tissue[17]. The key cells of inflammation, neutrophils, have been associated with tumor development. Through chemokines and interleukins, neutrophils are recruited and infiltrate the tumor tissue, contributing to tumor proliferation[18]. When the inflammatory cascade is initiated, there is an increase in platelet count and function. Platelets are known to secrete platelet-derived growth factors, which create a favorable microenvironment for tumor development by building extracellular matrix[19]. Lymphocytes play a critical role in fighting tumor cells, especially CD8 T cells, which have cytotoxic effects on malignant cells. Research has established a correlation between cancer incidence and lymphocyte count, with studies indicating that decreased overall survival and progression-free survival are linked to lymphopenia in malignancies[20].

Several limitations should be acknowledged in relation to this study. First, the study focused on a cross-sectional analysis, lacking longitudinal data that would provide insights into the predictive value and stability of the inflammatory parameters over time. Moreover, it was relied on cytological results. Cytology results can occasionally yield false-negative or false-positive outcomes, which could have influenced the accuracy of our findings. In addition, The Bethesda classification system itself is subject to inter-observer and intra-observer variability, which may impact the accuracy of malignancy prediction. Finally, the study primarily focused on a limited set of inflammatory parameters, neglecting other potential markers that could have provided a more comprehensive understanding of their relationship with the Bethesda classification.

Conclusion

Our study demonstrates that SII and NLR can be useful and non-invasive markers in predicting malignancy in thyroid nodules as it provides an easily measurable, inexpensive, and non-invasive method for clinical practice.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the approval of the Ethics Committee for the analysis and publication of clinical data obtained routinely. The informed consent of the patients was not required because it was a retrospective observational study.

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ORIGINAL ARTICLE

Comparing complex decongestive therapy in patients with lymphedema of different causes by measuring: extremity volume, quality of life, and functionality

Comparación de la terapia descongestiva compleja en pacientes con linfedema de diferentes causas mediante la medición del volumen de las extremidades, la calidad de vida y la funcionalidad

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Abstract

Objective: *This study aimed to investigate the effects of complex decongestive therapy (CDT) applied to the lower extremities of patients with lymphedema of different causes on the extremity volume, quality of life (QoL), and functionality.* **Materials and method:** *The study included 90 patients, of whom 28 had primary lymphedema, 30 had secondary lymphedema, 18 had phlebolymphedema, and 14 had lipolymphedema. A total of 137 extremities were treated with CDT. The patients who received CDT for 5 days a week for 3 weeks (15 sessions in total) were included in the sample. Extremity volume was measured using a tape measure. The lymphedema QoL-Leg Questionnaire was used to evaluate QoL, and the lower extremity functional scale (LEFS) was administered to assess lower extremity functionality.* **Results:** *The changes in QoL before and after treatment significantly differed in the primary lymphedema, phlebolymphedema, and lipolymphedema groups ($p < 0.05$). The post-treatment LEFS scores indicated a significant decrease in the phlebolymphedema and lipolymphedema groups compared to the pre-treatment scores ($p < 0.05$).* **Conclusions:** *The difference in appearance, which is one of the sub-parameters of QoL, significantly decreased in the comparisons performed between the groups, whereas the changes in the remaining parameters were not significant.*

Keywords: *Lymphedema. Phlebolymphedema. Lipolymphedema.*

Resumen

Objetivo: *Investigar los efectos de la terapia descongestiva compleja (TDC) aplicada a las extremidades inferiores de pacientes con linfedema de diferentes causas sobre el volumen de la extremidad, la calidad de vida y la funcionalidad.* **Materiales y método:** *Se incluyeron en el estudio 90 pacientes, de los cuales 28 tenían linfedema primario, 30 linfedema secundario, 18 flebolinfedema y 14 lipolinfedema. Un total de 137 extremidades fueron tratadas con TDC. Se incluyeron en la muestra pacientes que recibieron TDC durante 5 días a la semana durante 3 semanas (15 sesiones en total). El volumen de las extremidades se midió con una cinta métrica. Se utilizó el Cuestionario de calidad de vida (QoL) de las piernas para el linfedema para evaluar la calidad de vida, y se administró la Escala funcional de las extremidades inferiores (LEFS) para evaluar la funcionalidad de estas.*

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Resultados: *Los cambios en la calidad de vida antes y después del tratamiento difirieron significativamente en los grupos de linfedema primario, flebolinfedema y lipolinfedema (p < 0.05). Las puntuaciones LEFS posteriores al tratamiento indicaron una disminución significativa en los grupos de flebolinfedema y lipolinfedema en comparación con las puntuaciones previas al tratamiento (p < 0.05).* **Conclusiones:** *La diferencia de apariencia, que es uno de los subparámetros de la calidad de vida, disminuyó significativamente en las comparaciones realizadas entre los grupos, mientras que los cambios en los demás parámetros no fueron significativos.*

Palabras clave: *Linfedema. Flebolinfedema. Lipolinfedema.*

Introduction

Lymphedema is a chronic condition that occurs as a result of the accumulation of protein-rich fluid in the interstitial space[1]. It often appears in the upper and lower extremities. Although upper extremity lymphedema is frequently encountered in lymphedema clinics, lower extremity lymphedema also has a very high density[2,3]. Lower extremity lymphedema may develop due to four causes classified as primary lymphedema (congenital anomalies), secondary lymphedema (secondary to any surgery for any condition, such as cancer in the upper extremity or lower extremity), phlebolymphedema (resulting from venous insufficiency), and lipolymphedema (as a result of damage to the lymphatic system in patients with advanced lipedema)[3]. The lower extremity lymphedema negatively affects patients' functionality, quality of life (QoL), activities of daily living (especially ironing and cleaning), and climbing, sports, and walking activities[4].

Complex decongestive therapy (CDT) is a gold-standard conservative treatment for patients with lymphedema. CDT contains two treatment phases: the first (intensive) phase consists of manual lymph drainage (MLD), skin care, compression bandage, and exercises, and the second (maintenance) phase includes self-drainage, compression stockings, skin care, and exercises[5]. The efficacy of CDT has been shown in studies conducted with patients who developed lymphedema in the lower extremities. There are studies comparing the effects of CDT on QoL and functionality in patients with primary and secondary lymphedema[6-8]. However, studies in the literature are limited to those investigating the efficacy of CDT in patients with primary and secondary lower extremity lymphedema. The purpose of our study was to investigate the effects of CDT on edema, QoL, and functionality in patients who developed different types of lower extremity lymphedema (primary lymphedema, secondary lymphedema, phlebolymphedema, and lipolymphedema).

Materials and methods

Study design and patients

A total of 90 patients who received CDT for 5 days a week for 3 weeks due to lymphedema at the oncological rehabilitation lymphedema laboratory of Ankara City Hospital were divided into primary lymphedema (n = 28), secondary lymphedema (n = 30), phlebolymphedema (n = 18), and lipolymphedema (n = 14) groups, and their data were retrospectively analyzed. Lymphedema was present in 39 extremities of the 28 patients in the primary lymphedema group, 34 extremities of the 30 patients in the secondary lymphedema group, 36 extremities of the 18 patients in the phlebolymphedema group, 28 extremities of the 14 patients in the lipolymphedema group. Before commencing the study, ethical approval was obtained from the Non-Invasive Ethics Committee of Ankara City Hospital (E2-21-906). The patients' demographic (age, weight, length, body mass index [BMI], and gender) and clinical data (lymphedema stage and affected limb) were recorded before treatment, and the data on lower extremity volume, lower extremity functionality, and QoL were recorded both before and after treatment. Lymphedema types were diagnosed by a Physical Medicine and Rehabilitation doctor and the classification of the disease stages of the participants was made according to the International Society of Lymphology[9].

For each group, the criteria for participation in the study were as follows: being aged 18-65 years, not having any orthopedic disease in the lower extremities, not having undergone any surgery due to orthopedic disorder/discomfort, having received CDT treatment for the 1st time, not having a non-regulated chronic disease. The exclusion criteria were as follows: patients with acute infections, uncontrollable heart failure, deep vein thrombosis, orthopedic

disorders that would prevent exercising, mental and cognitive problems, uncooperative patients, not completed chemotherapy/radiotherapy treatments, renal insufficiency, active rheumatic disease, and uncontrolled hypertension were excluded.

Intervention

CDT was applied to the patients for 5 days a week for 3 weeks (15 sessions). The first phase of CDT (MLD, skin care, compression bandage, and exercise) took an average of 45 min for each patient. The CDT technique was applied by the physiotherapist who has a certificate (Foeldi College, Germany).

In primary lymphedema, phlebolymphedema, and lipolymphedema groups, MLD was applied first to the neck and then to the abdominal region. Subsequently, axilla-inguinal anastomoses on the affected side were treated.

MLD treatment was applied to the affected extremity from proximal to distal by stimulating the inguinal lymph node. If edema was present in the contralateral extremity of the patient, axilla-inguinal anastomoses were also treated for the contralateral side, and MLD treatment was applied to the affected leg[5,10].

For the patients with secondary lymphedema, MLD was applied first to the neck and then to the abdominal region. Subsequently, axilla-inguinal anastomoses were treated. MLD was applied to the affected extremity from proximal to distal. If edema was present in the other extremities of the patient, axilla-inguinal anastomoses were treated on the contralateral side, and MLD was applied to the affected leg. The inguinal lymph nodes of these patients were not stimulated by treatment[5,10].

After MLD treatment, skin care was provided with creams with a pH of 5.5, followed by bandaging. First of all, stockinette was put on the patient. The toes were wrapped with elastic finger bandages. The entire lower extremity was wrapped in cotton/sponge to distribute the pressure evenly and avoid damage to the skin. Finally, lower extremity bandaging was performed with bandages with a short tension feature. The treatment was terminated by applying remedial exercises. The patient was asked to keep the bandage for 22 h and recommended to perform remedial exercises during the day[11].

Evaluation

The patient's demographic and clinical data were evaluated before treatment and extremity volume, lower extremity functionality, and QoL both before and after treatment.

Extremity volume

Extremity volume was measured using a tape measure. Measurements were made from the malleol to the groin on the affected extremity at 4-cm intervals. Extremity volume was calculated by entering the measured values into the Frustrum formula: $V = [hx (R1^2 + R1.R2 + R2^2)]/(12 \times \pi)$. The result was recorded in cm^3[3,12].

QoL

The lymphedema QoL (LYMQOL)-leg questionnaire was used to evaluate QoL. The first part of this scale consists of 20 questions under the domains of function, appearance, physical symptoms, and mood. The first 20 questions are graded on a scale of 1-4. Lower scores indicate better QoL. The last question assesses the overall QoL on a scale of 0-10. A higher score on this question indicates better QoL[13].

Lower extremity functionality

Lower extremity functionality was assessed with the lower extremity functional scale (LEFS), which consists of 20 items scored from 0 (extreme difficulty/unable to perform activity) to 4 (no difficulty). The total score is obtained by summing the score of each marked answer for each question. The total score ranges from 0 to 80, with high scores indicating good extremity function[14].

Statistical analysis

Data were analyzed using SPSS version 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.) software package. Continuous variables were expressed as mean ± standard deviation, median (25-75%), and categorical variables as numbers and percentages. The conformity of the data to the normal distribution was examined with the Shapiro–Wilk test. In the examination of independent groups, one-way analysis of variance (*post hoc*: Tukey test) was used when parametric test assumptions were met, and the Kruskal–Wallis analysis of variance (*post hoc*: Mann–Whitney U test with the Bonferroni correction) was used otherwise. To compare the differences between

Table 1. Demographic characteristics of the patients

Variables	Variables	Primary lymphedema	Secondary lymphedema	Phlebolymphedema	Lipolymphedema	p-value
Age (years)	Mean ± SD	49.92 ± 12.46	55.03 ± 8.75	54.75 ± 8.69	59.27 ± 8.78	0.060 (F = 2.577)
Height (cm)	Mean ± SD	165.07 ± 9.79	160.2 ± 6.76	162.58 ± 8.9	160.36 ± 5.2	0.124 (F = 1.978)
Weight (kg)	Median (25-75%)	81 (63.25-96.5)	85.25 (74-92.75)	100 (94.25-129.5)	100 (92-108)	0.0001* (kw = 20.109) (1-3, 1-4, 2-3, 2-4)
BMI (kg/m^2)	Median (25-75%)	28.51 (22.07-34.29)	32.89 (26.96-36.51)	39.41 (34.82-50.05)	41.02 (35.16-44.44)	0.0001* (kw = 20.287) (1-3, 1-4)

*p < 0.05. SD: standard deviation; BMI: body mass index; n: number of participants, F: one-way analysis of variance statistic; kw: Kruskal–Wallis test statistic.

Table 2. Clinical characteristic of the patients

Variables	Primary lymphedema (n = 28) (%)	Secondary lymphedema (n = 30) (%)	Phlebolymphedema (n = 18) (%)	Lipolymphedema (n = 14) (%)	Total (%)	p-value
Gender, n (%)						
Female	21 (75)	28 (93.3)	12 (66.7)	1 (100)	75 (83.3%)	0.019*
Male	7 (25)	2 (6.7)	6 (33.3)	0 (0)	15 (16.7)	(x^2 = 9.960)
Lymphedema stage, n (%)						
1	5 (17.9)	1 (3.3)	0 (0)	0 (0)	6 (6.7)	0.001
2	19 (67.9)	25 (83.3)	9 (50)	6 (42.9)	59 (65.6)	(x^2 = 22.761)
3	4 (14.3)	4 (13.3)	9 (50)	8 (57.1)	25 (27.8)	
Affected limb, n (%)						
Left	9 (32.1)	18 (60)	3 (16.7)	0 (0)	30 (33.3)	0.0001*
Right	8 (28.6)	8 (26.7)	0 (0)	0 (0)	16 (17.8)	(x^2 = 41.570)
Bilateral	11 (39.3)	4 (13.3)	15 (83.3)	14 (100)	44 (48.9)	

*p < 0.05. n: number of participants; x2: Chi-square test statistic.

the measurements, the t-test for dependent groups was used when parametric test assumptions were met, and the Wilcoxon paired-sample test was used otherwise. Differences between categorical variables were analyzed using the Chi-square test. $p < 0.05$ was considered significant in all the analyses.

Results

BMI significantly differed between the groups ($p < 0.05$). The characteristics of the patients are summarized in table 1.

There was a significant difference between the groups in terms of gender, lymphedema stage, and affected limb ($p < 0.05$). The clinical characteristics of the patients are shown in table 2.

Before treatment, there was a significant difference in extremity volume between the groups. The pre-treatment extremity volume value of the primary lymphedema group was significantly lower than that of the lipolymphedema group ($p < 0.05$). Similarly, there was a significant difference in the volume of examinations performed after treatment. The post-treatment extremity volume of the primary lymphedema group was significantly lower than that of the lipolymphedema group ($p < 0.05$). The extremity volume was also observed to significantly change within each group after treatment compared to the pre-treatment evaluation ($p < 0.05$). The inter-group and intra-group comparisons of the extremity volume are shown in table 3.

There was a significant difference in the pre-treatment function subscale scores of the LYMQOL questionnaire between the groups ($p < 0.05$). The pre-treatment function score of the primary lymphedema group was significantly lower than that of the lipolymphedema group ($p < 0.05$). However, there was no significant difference in the post-treatment function scores of the groups. The function subscale scores significantly decreased after treatment

in the primary and phlebolymphedema groups compared to the pre-treatment evaluation ($p < 0.05$).

The pre-treatment appearance subscale scores of the LYMQOL questionnaire significantly differed between the groups ($p < 0.05$), with the pre-treatment appearance score of the secondary group being significantly lower than that of the lipolymphedema group. There was no significant difference between the groups in relation to the post-treatment appearance scores. The analysis of changes in appearance scores from pre-treatment to post-treatment periods revealed a significant decrease in the primary lymphedema, phlebolymphedema, and lipolymphedema groups ($p < 0.05$).

No significant difference was observed in the symptom subscale scores of the LYMQOL questionnaire between the groups before or after treatment. There was a significant decrease in the post-treatment symptom scores in the secondary lymphedema and lipolymphedema groups compared to the pre-treatment evaluation ($p < 0.05$).

The mood subscale scores of the LYMQOL questionnaire did not significantly differ between the groups before or after treatment. The post-treatment mood subscale score significantly decreased in the lipolymphedema group compared to the pre-treatment value ($p < 0.05$).

No significant difference was observed in the overall QoL scores of the groups before or after treatment. The post-treatment overall QoL score indicated a significant decrease in the phlebolymphedema group compared to the pre-treatment value ($p < 0.05$).

Finally, there was no significant difference in the pre-treatment and post-treatment LEFS scores of the groups. The analysis of the changes in the LEFS scores from pre-treatment to post-treatment revealed a significant decrease in the phlebolymphedema and lipolymphedema groups ($p < 0.05$) (Table 4).

Discussion

In this study, we found that the body weight and extremity volumes were the highest in the lipolymphedema group and lowest in the primary lymphedema group. All types of lymphedema most commonly affect the female gender. The patients with stage 2 lymphedema most frequently presented to the clinic, and limb involvement was mostly bilateral in all the lymphedema groups except secondary lymphedema. The results showed that CDT reduced lymphedema volume in each group. The amount of drained lymphedema was the highest in the lipolymphedema group. Among the sub-parameters of QoL, appearance scores

Table 3. Comparison of the extremity volume

Variables	Variables	Primary lymphedema	Secondary lymphedema	Phlebolymphedema	Lipolymphedema	p-value
Before (mL)	Median (25-75%)	9.410 (7.805-12.765)	10.604.85 (8.322.75-13.030.75)	10.349.5 (8.556.25-12.402.83)	12.101.05 (10.662.75-15.208.75)	0.019* (kw = 9.908) (1-4)
After (mL)	Median (25-75%)	9.117 (6.689-11.591)	9.946.5 (8.237-11.801.25)	9.644 (7.667.75-11.780.48)	10.659.5 (9.817.45-13.559.5)	0.034* (kw = 8.674) (1-4)
Within groups	Mean ± SD	0.0001* (z = –5.387)	0.0001* (z = –4.467)	0.0001* (z = –3.823)	0.0001* (z = –3.921)	-
Dif	Median (25-75%)	1.301.48 ± 2.185.97	894.32 ± 1.283.27	1.026.91 ± 1.082.45	1.316.14 ± 1.321.53	0.416 (kw = 2.644)

*p < 0.05. SD: standard deviation; mL: milliliter; dif: difference; kw: Kruskal–Wallis test statistic; t: paired-samples t-test statistic; z: Wilcoxon signed-rank test statistic.

Table 4. Comparison of the quality of life and functionality

Variables	Variables	Primary lymphedema	Secondary lymphedema	Phlebolymphedema	Lipolymphedema	p-value
Function-BT	Median (25-75%)	2 (1.61-2.68)	2.06 (1.5-2.76)	2.23 (1.73-3.59)	3.25 (2.3-4)	0.042* (kw = 8.19) (1-4)
Function-AT	Median (25-75%)	1.8 (1.5-2.12)	1.9 (1.24-2.32)	2 (1.11-2.68)	2.5 (1.25-3.13)	0.534 (kw = 2.192)
Intra-group p		0.025* (z = −2.248)	0.124 (t = 1.583)	0.036* (t = 2.382)	0.114 (t = 1.732)	
Dif	Median (25-75%)	0.12 (−0.04-0.69)	0.11 (−0.08-0.91)	0.38 (0.02-0.97)	0.25 (0-1.9)	0.703 (kw = 1.411)
Appearance-BT	Median (25-75%)	2.85 (2.11-3.63)	2.17 (1.42-2.7)	2.9 (1.99-3.65)	3.4 (1.7-3.8)	0.01* (kw = 11.287) (2-4)
Appearance-AT	Median (25-75%)	2.39 (1.73-3.15)	1.83 (1.28-2.7)	1.93 (1-2.9)	2 (1.7-2.7)	0.187 (kw = 4.795)
Intra-group p		0.038* (z = −2.072)	0.495 (z = −0.682)	0.004* (t = 3.568)	0.002* (t = 4.240)	
Dif	Median (25-75%)	0.13 (−0.08-0.58)	0 (−0.3-0.4)	0.71 (0.21-1.72)	1.1 (0.28-2)	0.003* (kw = 13.371) (2-3, 2-4)
Symptom-BT	Mean ± SD	2.36 ± 0.87	2.21 ± 0.83	2.33 ± 0.68	2.76 ± 0.76	0.297 (F = 1.251)
Symptom-AT	Median (25-75%)	1.9 (1.3-2.8)	1.8 (1.15-2.2)	1.7 (1.2-2.2)	1.8 (1.4-2.6)	0.576 (kw = 1.981)
Intra-group p		0.25 (t = 1.177)	0.001* (z = −3.367)	0.122 (t = 1.673)	0.026* (t = 2.616)	
Dif	Median (25-75%)	0.2 (−0.35-0.6)	0.2 (0-0.8)	0.4 (−0.25-1.25)	0.6 (0-1)	0.291 (kw = 3.742)
Mood-BT	Median (25-75%)	2.35 (1.7-3.15)	1.8 (1.3-2.27)	2.05 (1.27-2.5)	2.3 (1.66-3.3)	0.105 (kw = 6.139)
Mood-AT	Median (25-75%)	1.82 (1.35-3)	1.73 (1.16-2.3)	1.17 (1-2.41)	1.8 (1-2.6)	0.229 (kw = 4.324)
Intra-group p		0.17 (t = 1.411)	0.174 (z = −1.358)	0.097 (t = 1.814)	0.012* (z = −2.521)	
Dif	Median (25-75%)	0.14 (−0.34-0.69)	0.05 (−0.12-0.38)	0.47 (0-0.83)	0.2 (0-1.06)	0.329 (kw = 3.434)
Overall-BT	Mean ± SD	6.07 ± 2.12	5.93 ± 1.87	6.08 ± 1.73	5.27 ± 1.49	0.675 (F = 0.513)
Overall-AT	Median (25-75%)	6 (6-7)	6 (5-8)	7.5 (6.25-8.75)	6 (5-7)	0.279 (kw = 3.844)
Intra-group p		0.347 (z = −0.941)	0.462 (z = −0.735)	0.003* (t = −3.767)	0.068 (z = −1.826)	
Dif	Median (25-75%)	0 (−1-0)	0 (−1-0.25)	−1 [−1.75-(−1)]	0 (−2-0)	0.061 (kw = 7.355)
LEFS-BT	Median (25-75%)	48 (26.35-67)	46 (29.75-58)	43.7 (6.5-58.6)	18 (8-46)	0.109 (kw = 6.055)
LEFT-AT	Median (25-75%)	56.5 (34.1-69.5)	51.2 (31.25-63.5)	48.8 (25.5-59.5)	23 (12-72)	0.236 (kw = 4.252)
Intra-group p		0.056 (z = −1.912)	0.056 (t = −1.987)	0.05* (t = −2.178)	0.046* (z = −1.994)	
Dif	Median (25-75%)	−4 (−11-2.85)	−4.2 (−11-3.28)	−13.1 (−20.5-1.6)	−3 (−15-0)	0.383 (kw = 3.057)

*p < 0.05. BT: before treatment; AT: after treatment; dif: difference; SD: standard deviation; F: one-way analysis of variance statistic; kw: Kruskal–Wallis test statistic; t: paired-samples t-test statistic; z: Wilcoxon signed-rank test statistic. LEFS: lower extremity functional scale

significantly decreased in the evaluation performed between the groups, whereas changes in the remaining sub-parameters were not statistically significant. Improvement in function was significant only in the phlebolymphedema and lipolymphedema groups.

Although CDT is the gold standard in primary and secondary lymphedema, there is no standardized guideline or consensus for lipolymphedema and phlebolymphedema. CDT is a conservative treatment method recommended for these types of lymphedema. The success of CDT in clinical practice is parallel to improvement in not only edema but also other clinical findings[15]. Researchers agree that compression will reduce venous reflux and increase venous pump function in patients with chronic venous insufficiency. This information supports the idea that CDT can control the volume of edema in patients with phlebolymphedema in the lower extremity[16]. Földi and Idiazabal, reporting their clinical experience, suggested that surgical treatment of veins in patients with the coexistence of lipedema and lymphedema would worsen their clinical state in the long term, and surgery was unnecessary unless there was an absolute indication for this treatment (ascending phlebitis and/or bleeding). In line with this argument, the QoL of patients with lipolymphedema can only be optimized with CDT and physiotherapy[17]. The use of CDT in the treatment of lipedema reduces not only leg volume but also hematoma due to increased capillary resistance and altered capillary fragility in this condition[18].

As we predicted, differential diagnoses in lymphedema types do not change the necessity of CDT in treatment. When we examined the effect of CDT in these different types of lymphedema, we observed that edema reduction and improvement in extremity volume reached clinically significant levels. Contrary to our study, in the literature, some studies examining the effects of CDT in primary and secondary lymphedema reported that the change in leg volume was significant in intra-group evaluations but did not significantly differ between groups. Improvement in QoL in secondary lymphedema is considerably greater than in primary lymphedema[7,8]. Weiss and Spray reported that CDT improved both leg volume and QoL in patients with primary lymphedema, secondary lymphedema, deep vein thrombosis, and peripheral edema caused by orthopedic operations and venous insufficiency[19]. There are many studies showing that CDT increases QoL and improves extremity volume, especially in cases of secondary lymphedema due to cancer[20,21]. However, there are not a sufficient number of studies revealing the efficacy of this treatment in phlebolymphedema and lipolymphedema. German professionals recommend that the decongestive phase of CDT should be added to the treatment guidelines for phlebolymphedema to keep the venous lymphostatic status stable, while continuation with phase II should be decided according to clinical findings[22].

In light of the results of our study, we consider that CDT should be added to the treatment of not only primary and secondary lymphedema but also other lymphedema types. In particular, in lipolymphedema with a course and treatment that is very open to interpretation, the treatment we applied provided the most reduction in changes in leg volume compared to other lymphedema types. Although the treatment had a similar effect in primary and secondary lymphedema, the amount of drained edema in phlebolymphedema was very high, and the decrease in extremity volume was significant. As a result of the decrease in edema, appearance also significantly improved according to the inter-group evaluation, emphasizing the effect of CDT on all lymphedema types.

Researchers examining the effect of CDT on chronic venous insufficiency have reported significant improvement in extremity volume and function[23]. When we evaluated the effect of CDT on the function of phlebolymphedema caused by venous insufficiency, we determined that improvement was very significant. There are studies suggesting that a similar effect can be achieved with pneumatic intermittent compression for phlebolymphedema[24]. However, to our knowledge, there is no study comparing the effects of the two methods. In our study, the increase in functional status was evident in the phlebolymphedema and lipolymphedema groups. In the remaining lymphedema groups, there was improvement but not at a significant level.

Conclusion

CDT is an effective treatment modality for primary lymphedema, secondary lymphedema, phlebolymphedema, and lipolymphedema. According to our clinical experience, it would be appropriate to standardize CDT for phlebolymphedema and lipolymphedema. The decreased extremity volume and increased function of the patients also had a positive effect on their QoL.

Limitations

This study only presented the short-term outcomes of the patients. Long-term results are needed to prove the efficacy of CDT in different types of lymphedema.

In the literature, studies investigating conservative methods in the treatment of lipolymphedema and phlebolymphedema are limited. Therefore, our results are open to development and discussion. There was not a sufficient number of patients presenting to the clinic with different lymphedema diagnoses, which affected the equal distribution of sample size among the groups. This is a retrospective study. For these reasons, the number of participants in the groups is different. Prospective studies investigating the effectiveness of CDT in different groups are needed.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ARTÍCULO ORIGINAL

Estimulación cerebral profunda para enfermedad de Parkinson: experiencia, beneficios y limitaciones en un centro en Latinoamérica

Deep brain stimulation for Parkinson's disease: experience, benefits and limitations in a center in Latin America

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Resumen

Antecedentes: *La enfermedad de Parkinson está poco estudiada en Colombia. Es de manejo farmacológico, pero para casos refractarios la cirugía es una opción terapéutica que impacta positivamente en la calidad de vida.* **Objetivo:** *Determinar el impacto de la estimulación cerebral profunda como manejo en el control de la progresión en pacientes con enfermedad de Parkinson atendidos nuestra institución entre los años 2014 a 2020.* **Método:** *Estudio descriptivo de corte retrospectivo con pacientes recolectados entre los años 2014 y 2020 sometidos a cirugía de estimulación cerebral profunda. Se aplicó la MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale) en el pre- y el posoperatorio, y se compararon los resultados.* **Resultados:** *Se incluyeron 21 pacientes y se les aplicó la MDS-UPDRS, encontrando una disminución en las puntuaciones en el posoperatorio. Un paciente presentó infección del sitio operatorio.* **Conclusiones:** *Hubo mejoría en la puntuación de la MDS-UPDRS, con baja tasa de complicaciones. El tiempo de realización del procedimiento fue prolongado desde la valoración preoperatoria. La estimulación cerebral profunda es el manejo de elección para la enfermedad de Parkinson refractaria. Los pacientes de esta serie mostraron mejoría en sus síntomas. Desafortunadamente, existen limitaciones para la realización de este procedimiento en Colombia, como el retraso en la autorización del procedimiento.*

***Palabras clave*:** *Enfermedad de Parkinson. Estimulación cerebral profunda. Temblor.*

Abstract

Background: *Parkinson's disease is poorly studied in Colombia. It is pharmacologically managed, but for refractory cases, surgery is a therapeutic option, positively impacting on quality of life.* **Objective:** *To determine the impact of deep brain stimulation as management in the control of progression in patients with Parkinson's disease attended our institution between the years 2014 to 2020.* **Method:** *Descriptive retrospective study, with patients collected between 2014 and 2020 undergoing deep brain stimulation surgery. The MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale) was applied in the pre- and postoperative period, and the results were compared.*

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Results: *21 patients were included and the UPDRS was applied, finding a decrease in scores in the postoperative period. One patient had an operative site infection.* **Conclusions:** *There was an improvement in the MDS-UPDRS score, with a low rate of complications. The procedure time was prolonged from the preoperative evaluation. Deep brain stimulation is the management of choice for refractory Parkinson's disease. The patients in this series showed improvement in their symptoms. Unfortunately, there are limitations to perform this procedure in Colombia, such as the delay in the authorization of the procedure.*

Keywords: *Parkinson Disease. Deep brain stimulation. Tremor.*

Introducción

La enfermedad de Parkinson (EP) fue descrita por primera vez en el año 1817 por James Parkinson[1]. Constituye la segunda enfermedad neurodegenerativa más frecuente en todo el mundo, con una prevalencia de 150 casos por cada 100,000 habitantes[2,3]. La prevalencia en los países europeos varía entre 65.6 y 12.500 casos por cada 100,000 habitantes[3]. En Colombia, el estudio EPINEURO realizado en el año 2003 reportó una prevalencia de 4.4 casos por cada 100.000 habitantes[4], y en otro estudio realizado en la región de Antioquia en el año 2004 se reportó de 30.7 casos por cada 100,000 habitantes[5]. Fisiológicamente, en la EP se produce una disfunción de los ganglios de la base secundaria a la depleción de dopamina[6]. En este circuito, los principales núcleos involucrados son el núcleo estriado (caudado y putamen), el núcleo subtalámico (NST), el globo pálido externo (GPe), el globo pálido interno (GPi) y la sustancia *nigra*[7] (Fig. 1). A su vez, las vías están segregadas en cinco grandes vías: 1) el motor, el cual tiene posición dorsolateral con proyecciones hacia la corteza motora primaria y el área motora suplementaria; 2) el asa oculomotora, que tiene como centro el núcleo caudado, conectando con los campos oculares frontales; 3) el asa prefrontal dorsolateral, que conecta también el caudado con la corteza prefrontal dorsolateral y parietal posterior; 4) el asa orbitofrontal, la cual genera conexión principalmente del caudado con la corteza orbitofrontal, y 5) el asa límbica, que conecta con el cíngulo anterior, el lóbulo temporal y la corteza orbitofrontal con los ganglios basales[8].

Adicionalmente, dentro de los ganglios basales se conocen clásicamente tres grandes vías: la directa, que se encarga principalmente de la estimulación del movimiento, y las vías indirecta e hiperdirecta, que contrario a la directa se encargan de inhibir el movimiento[8]. En la EP, la falta de dopamina se traduce en hiperactividad del NST y del complejo GPi/sustancia *nigra* reticular, lo que conlleva la inhibición talamocortical y un disbalance entre las vías directa, hiperdirecta e indirecta[9,10], traduciéndose clínicamente en bradicinesia, rigidez muscular, temblor en reposo e inestabilidad postural, entre otras manifestaciones.

Si bien hoy en día el tratamiento farmacológico de la EP continúa siendo el estándar, existe un número de casos no despreciable en los cuales se presenta refractariedad al mismo durante la primera y la segunda décadas de la enfermedad, lo que ha llevado a desarrollar nuevas técnicas terapéuticas como la estimulación cerebral profunda (ECP, *deep brain stimulation*). La ECP es un procedimiento que consiste en la estimulación de una de las tres dianas terapéuticas: el núcleo ventral intermedio, el GPi o el NST[7,11]. Por su parte, la ECP ha demostrado producir mejoría tanto en el control del movimiento como en la espasticidad[12], mejorando la calidad de vida del paciente y de su familia.

En Colombia, al igual que en muchos países de bajos y medianos ingresos, existen múltiples limitaciones, principalmente asociadas al costo elevado que implica realizar esta cirugía. En Colombia, el sistema de salud está compuesto por dos regímenes: privado contributivo y público subsidiado. A su vez, existen diferentes empresas prestadoras de salud (EPS) que se encargan de administrar las diferentes instituciones prestadoras de salud con el fin de brindar todos los servicios de salud. Para poder realizar una ECP en Colombia se requiere una autorización por parte de la EPS, lo cual en muchos escenarios puede retrasar la realización del procedimiento.

Por todo lo anterior, el objetivo de este estudio fue determinar el impacto que tiene la ECP en el control de la progresión de los síntomas en una serie de pacientes con EP atendidos en nuestra institución, así como describir las limitaciones para poder realizar este procedimiento en una institución en Colombia.

Método

Se realizó un estudio de tipo descriptivo de corte retrospectivo. Los criterios de inclusión fueron: pacientes mayores de 18 años con EP, con refractariedad al tratamiento médico, sin presencia de síndrome demencial asociado, en los que no se hubiera realizado

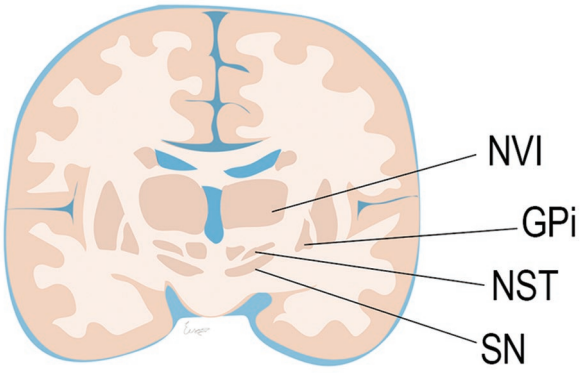

Figura 1. *Dianas para la estimulación cerebral en la enfermedad de Parkinson. GPi: globo pálido interno; NST: núcleo subtalámico; NVI: núcleo ventral intermedio; SN: sustancia nigra.*

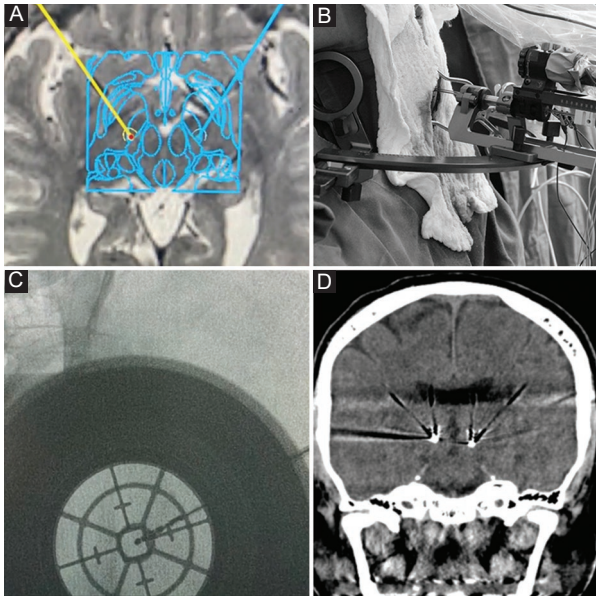

Figura 2. *Imágenes pre-, intra- y posoperatorias de estimulación cerebral profunda para enfermedad de Parkinson.* **A:** *planeamiento para la localización del núcleo subtalámico de forma bilateral.* **B:** *fotografía intraoperatoria con el montaje del arco de estereotaxia de Leksell para el macro- y microrregistro.* **C:** *confirmación radiológica intraoperatoria de localización estereotáctica de la punta de los electrodos.* **D:** *tomografía posoperatoria para evaluar las correctas trayectoria y localización de los electrodos.*

previamente tratamiento quirúrgico con ECP y que se les hubiera realizado ECP de forma unilateral o bilateral en nuestra institución entre los años 2014 y 2020. Todos los procedimientos fueron realizados por un neurocirujano funcional (OZ) y llevados a estimulación con macro- y microrregistro (Fig. 2).

El procedimiento fue realizado en dos tiempos. Primero, la estimulación con registro, en la cual se utiliza un marco de Leksell, guiada por imágenes preoperatorias de tomografía computarizada y resonancia magnética, ambas con protocolo de cortes finos para cirugía de Parkinson; se hace el registro y se llega a la diana terapéutica en cuestión. Posteriormente se procede a la colocación del generador, que de acuerdo a la experiencia del cirujano puede ser recargable o no recargable.

Se excluyeron los pacientes que tuvieron ECP extrainstitucional previa y aquellos con otros trastornos del movimiento. A los pacientes, mediante la revisión de historias clínicas vía electrónica, se les realizó la recolección de datos demográficos tales como sexo, edad, lateralidad, características de la presentación clínica de la patología y si hubo complicaciones quirúrgicas o no quirúrgicas. Para el seguimiento objetivo de la sintomatología se utilizaron la MDS-UPDRS *(Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale)* y la escala de Hoem y Yarh, dejando registrados cada uno de sus ítems en tres momentos: preoperatorio, a los 30 días del posoperatorio y a los 60 días del posoperatorio.

Toda la información se depositó en una tabla en Excel, con espacio y codificación para cada una de las variables para su posterior análisis estadístico en Stata 17.0. Dicho análisis constó de dos partes: 1) inicialmente, para las variables de tipo cuantitativo se emplearon media e intervalos de confianza, y para el análisis de las cualitativas, frecuencia y porcentaje con sus respectivos intervalos de confianza, y 2) se obtuvieron las medias de los puntajes de la escala MDS-UPDRS en el momento preoperatorio, a 30 días y a 60 días de posoperatorio, y se compararon para evaluar si hubo disminución en dichos puntajes (mediante la prueba t pareada).

Resultados

Se incluyeron 21 pacientes con una edad media de 53.71 ± 9.93 años, siendo la mayoría de sexo masculino (61.9%). Todos los pacientes pertenecían al régimen contributivo dentro del sistema de salud, provenientes de EPS privadas. El 100% de los pacientes presentaba en el estadio preoperatorio una evolución del cuadro clínico de la enfermedad con una media de 10 ± 3.47 años (rango: 6-20). De los 21 pacientes, se realizó la cirugía utilizando generador recargable en el 47.6% y no recargable en el 52.4%, de acuerdo con la preferencia del cirujano. Cabe aclarar que en la cirugía de ECP se utiliza un generador

de pulsos que es el que envía la energía a la diana terapéutica, y este puede ser recargable, el cual tiene una duración más larga (aproximadamente 9 años) respecto al no recargable, que dura normalmente entre 3 y 5 años antes de tener que realizar el cambio. Además, dentro de las variables evaluadas se incluyeron el uso de medicamentos en el preoperatorio y el posoperatorio, y no se observó disminución en el uso de levodopa y carbidopa, pero sí se evidenció una tendencia a la disminución en el uso del resto de los fármacos evaluados (amantadina, biperideno, entacapone, pramipexol, rotigotina y rasagilina), pero sin significancia estadística ($p > 0.05$). También se documentó una tendencia a la disminución en la cantidad de medicamentos utilizados por los pacientes al comparar el estado pre- y posoperatorio, sin ser estadísticamente significativa ($p > 0.05$).

Adicionalmente se evaluaron los aspectos clínicos del paciente: el temblor, la rigidez y la bradicinesia. Los tres síntomas se encontraban en el 100% de los pacientes en el estado preoperatorio. Se observó mejoría en los pacientes, con una disminución del 71.4% para el temblor, del 57.1% para la rigidez y del 71.4% para la bradicinesia ($p = 0.0010$) (Tabla 1).

También se realizó un análisis de los datos obtenidos al aplicar la MDS-UPDRS en los pacientes en los tres distintos momentos evaluados (preoperatorio, 30 días y 60 días del postoperatorio), y se aplicaron la prueba t pareada y la prueba de Wilcoxon para comparar: 1) el estado preoperatorio con el estado a los 30 días de posoperatorio, 2) el estrado preoperatorio con el estado a los 60 días de posoperatorio y 3) los dos estados posoperatorios. Al comparar el estado preoperatorio con el estado a los 30 días se observó una diferencia con disminución en las medias de los pacientes en la MDS-UPDRS: 58.8 ± 21.2 vs. 45.9 ± 11.2. Al comparar con el estado a los 60 días también se evidenció una disminución en la escala de 58.8 ± 21.2 a 34.0 ± 12.7. Finalmente, al comparar los dos estadios postoperatorios se encontró una disminución entre ellos de 45 ± 11.2 a 34.04 ± 12.7. Dentro de la MDS-UPDRS, los hallazgos que más generaron cambios en estas cifras fueron los aspectos relacionados tanto con sintomatología como con exploración física del aspecto motor, principalmente en las partes de temblor, rigidez y bradicinesia, que corresponden a los tres síntomas principales de la enfermedad. Todos estos resultados se hallaron con un valor de $p < 0.005$ (Tabla 2).

Por último, cabe señalar que de los 21 pacientes evaluados en el estudio, durante todo el seguimiento que se realizó hasta los 60 días, solo uno presentó una complicación (4.8%), que correspondió a una infección del sitio operatorio. También, de los 21 pacientes evaluados, al 100% se les realizó ECP de manera bilateral en los NST, logrando así la estimulación en las dianas terapéuticas.

Tabla 1. Comparación de resultados para temblor, rigidez y bradicinesia en los pacientes entre el estado preoperatorio y el posoperatorio

Aspecto clínico	Preoperatorio	Posoperatorio	p
Temblor			0.0001
Proximal	-	1 (5%)	
Distal	21 (100%)	5 (24%)	
Sin temblor	-	15 (71%)	
Rigidez			0.0001
Sí	21 (100)	9 (43%)	
No	-	12 (57%)	
Bradicinesia			
Sí	21 (100)	6 (29%)	0.0001
No	-	15 (71%)	

Tabla 2. Resultados de las medias de los puntajes en la escala MDS-UPDRS aplicada en el preoperatorio y a los 30 y 60 días de posoperatorio

Variable	Pacientes	Media	DE	IC95%
Preoperatorio vs. 30 días				
Preoperatorio	21	58.8	21.2	49.15-68.46
30 días	21	45	11.2	40.83-51.06
Diferencia	21	13.8	12.5	7.16-18.54
Preoperatorio vs. 60 días				
Preoperatorio	21	58.8	21.2	49.15-68.46
60 días	21	34	12.7	28.22-39.86
Diferencia	21	24.7	22.3	14.61-34.91
30 vs. 60 días				
30 días	21	45.9	11.2	40.83-51.06
60 días	21	34.	12.7	28.22-39.86
Diferencia	21	11.9	1.5	6.11-17.69

DE: desviación estándar; IC95%: intervalo de confianza del 95%.

Discusión

En el presente estudio se encontró que la edad de presentación promedio fue por encima de los 50 años (53.7 años), con ligera predilección por el sexo masculino. Por su parte, en el estudio EPINEURO se documentó la EP en personas mayores de 60 años, principalmente del noroccidente de Colombia, con una predilección por los hombres con respecto a las mujeres[4]. Sin embargo, al observar el número de

pacientes documentados en ambos trabajos se debe aclarar que aún no se pueden sacar conclusiones frente a la condición de la población colombiana, la cual se encuentra sesgada por su localización geográfica y el estado de la enfermedad. Por otra parte, en todo el mundo, se conoce que esta patología afecta aproximadamente a una o dos personas por cada 1000 habitantes y que compromete al 1-3% de la población por encima de los 60 años[13]. Para el presente estudio se encontró que en primer lugar comprendió pacientes quirúrgicos que fueron referidos a nuestra institución basados en el contrato con su EPS. Este estudio también evaluó el tiempo transcurrido entre la primera atención por parte del grupo de neurocirugía funcional en la que se indicó el procedimiento y el momento en que este se realizó, y se encontró que en promedio el tiempo de espera de los pacientes en la institución fue de 6.2 meses. Adicionalmente, es importante mencionar que algunos de los pacientes que no se incluyeron en el estudio no lograron la autorización o tuvieron que ser referidos a otra institución.

Por otra parte, los pacientes de nuestro estudio presentaron mejoría clínica (71.4% para el temblor, 57.1% para la rigidez y 71.4% para la bradicinesia; p = 0.001) y tuvieron una disminución en el uso de medicamentos posterior a la cirugía, lo cual implica una mayor calidad de vida para el paciente, que además se reflejó en una mejor adherencia al tratamiento farmacológico y una disminución de los efectos adversos derivados de esta terapia, tales como náuseas, hipotensión, cefalea y edema de miembros inferiores, entre otros.

Con respecto a la evaluación con la MDS-UPDRS, un metaanálisis de 16 estudios mostró que existe eficacia estadísticamente significativa, con disminución de 4 puntos en la escala después de realizar ECP en el GPi o en el NST[14]. En nuestro estudio no se evidenció ningún cambio para el componente emocional (depresión y ansiedad), ya que ninguno de los pacientes presentó síntomas de este tipo en el preoperatorio ni en el posoperatorio. Sin embargo, en la literatura mundial se sabe que la ECP, principalmente aquella en la que se estimula el GPi, se relaciona con una mejoría de las alteraciones del ánimo y del comportamiento[15]. En cuanto a la condición clínica del paciente evaluada con la MDS-UPDRS, encontramos que sí hay mejoría estadísticamente significativa tanto en los síntomas como en la calidad de vida. De igual manera, el metaanálisis publicado por Bratsos et al.[16] encontró una mejoría general del puntaje MDS-UPDRS en los pacientes que se sometieron a ECP, en comparación con aquellos bajo terapia médica óptima. Sin embargo, vale la pena aclarar que, si bien este tipo de manejo ofrece mejoría sintomática, no influye en la evolución natural ni en el desarrollo de la enfermedad; por ende, no tiene una intención curativa[17].

Por otro lado, se ha visto que en términos generales la cirugía es un procedimiento seguro. La complicación más frecuente es la sobreestimulación del tejido cerebral circundante (50%), seguida por la hemorragia cerebral y la infección, que son muy infrecuentes[13]. En nuestro estudio no se evidenció ningún tipo de complicación vascular ni por sobreestimulación; únicamente hubo un caso de infección del sitio operatorio, lo cual es esperable en nuestra serie y es comparable con lo reportado en otros estudios.

Por último, es importante recordar que la cirugía de ECP es un tratamiento de tipo paliativo, es decir, que sirve para mejorar la calidad de vida y los síntomas de los pacientes, pero no modifica la evolución de la enfermedad. Al final, esta condición continuará de manera irremediable su progresión, y por eso es menester aclarar que en el presente estudio se hace seguimiento hasta 60 días, tiempo durante el cual sí se observó mejoría, pero en caso de realizar un estudio a más largo plazo se observaría el desarrollo de la enfermedad que se manifestaría con el deterioro de los pacientes.

ECP en Colombia y América latina

Existen distintos equipos de neurocirugía funcional en la región, destacando los grupos de México[18,19], Argentina[20] y Chile[21,22], entre otros. El desarrollo de grupos multidisciplinarios, incluyendo neurólogos, psiquiatras y neurocirujanos, ha permitido el progreso de la subespecialidad. A pesar de que la incidencia y la prevalencia de la enfermedad no son tan altas, y el número de pacientes que requieren manejo quirúrgico tampoco es tan alto, otros trastornos del movimiento diferentes de la EP, así como el desarrollo de la cirugía de la epilepsia y de la cirugía para el dolor, han generado un aumento en la realización de procedimientos como la ECP y la cirugía de epilepsia en Latinoamérica.

Actualmente, la cirugía de ECP se realiza en diferentes lugares del país, como Barranquilla[23], Bucaramanga[24], Medellín, Pereira, Cali y Bogotá[25]. A pesar de que el procedimiento se realiza de manera amplia en todas las ciudades grandes del país, el acceso a través del sistema de salud es bajo debido a los altos costos

del procedimiento. Cada cirugía puede costar alrededor de 30,000 USD, que comparativamente representa más de 100 veces el salario mínimo en Colombia. A pesar de estos costos, una revisión sistemática mostró que diferentes estudios han evidenciado que la cirugía de ECP es costo-efectiva en comparación con el mejor tratamiento médico[26]. Por este motivo, debe seguirse considerando la cirugía de ECP como la mejor alternativa a pesar de todas las limitaciones que se encuentren en países de bajos y medianos ingresos, como Colombia.

Limitaciones para realizar la ECP en un país de medianos ingresos

En primer lugar, se debe mencionar que una de las primeras limitantes que se encuentran para realizar este procedimiento en un país de medianos ingresos es la falta de equipos multidisciplinarios para llevar a cabo todo el abordaje y manejo del paciente con esta condición. Dado que este es un procedimiento de alto nivel de especialización, son pocos los centros que cuentan con el personal y los recursos necesarios para poder realizar la cirugía y el seguimiento adecuado. En segundo lugar, es importante recalcar que la ECP es un procedimiento de alto costo, pues solo el estimulador puede llegar a costar hasta 20.000 USD, lo que implicando dificultades en las autorizaciones para el procedimiento. Por último, este procedimiento normalmente requiere controles periódicos para el seguimiento adecuado del paciente, y en varias ocasiones se encuentra el problema de que los controles son llevados a cabo en instituciones diferentes de aquella donde se hizo la cirugía, o los pacientes regresan a su sitio de origen, que puede ser en regiones rurales, lo que conlleva no solo una dificultad para el manejo posoperatorio integral del paciente, sino también una pérdida de este a la adherencia al seguimiento. Esto resulta en un entorpecimiento de la continuidad clínica y epidemiológica de los pacientes.

Limitaciones del estudio

La primera limitación de este estudio es que la información recolectada fue tomada de manera retrospectiva y es posible que algunos de los datos no se encontraran de manera completa para poder realizar el análisis adecuado de todas las variables. La segunda es que, debido a múltiples factores, muchos de los pacientes se pierden durante el seguimiento y no es posible realizar controles a plazos más largos, lo que permitiría hacer un análisis más extenso y riguroso hacia el futuro. Aún falta la realización de estudios adicionales en nuestro país que no solo sean descriptivos, sino que también tengan el componente de seguimiento a más largo plazo y con mayor cantidad de pacientes, con el fin de poder establecer cifras estandarizadas adaptadas a nuestro contexto nacional y regional. A pesar de dichas limitaciones, consideramos que este estudio representa la caracterización y la evaluación de muchos obstáculos que se presentan en los países latinoamericanos para realizar ECP en pacientes con EP.

Conclusiones

La experiencia de nuestro centro demuestra que la ECP es una opción viable y eficiente para la mejoría de los síntomas y a su vez de la calidad de vida de los pacientes con EP. A pesar del retraso en la realización del procedimiento debido a las autorizaciones por las EPS, los pacientes presentaron una mejoría clínica estadísticamente significativa y una tendencia a disminuir la cantidad de fármacos posterior a la intervención. A futuro se necesitan estudios multicéntricos regionales que permitan evidenciar todas las limitaciones que existen para realizar ECP en los países de Latinoamérica.

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Los autores declaran no tener ningún conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido la aprobación del Comité de Ética para el análisis y publicación de datos clínicos obtenidos de forma rutinaria. El consentimiento informado de los pacientes no fue requerido por tratarse de un estudio observacional retrospectivo.

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ARTÍCULO ORIGINAL

Adaptación transcultural y validación de la versión mexicana del cuestionario DASH en individuos sanos y pacientes con trastornos neurogénicos del miembro superior

Transcultural adaptation and validation of the DASH questionnaire in Mexican healthy volunteers and patients with neurogenic disorders of the upper extremity

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Resumen

Objetivo: *Realizar la adaptación cultural y validación del cuestionario DASH para conocer la perspectiva de pacientes con trastornos neurogénicos del miembro superior respecto al impacto en su calidad de vida.* **Método:** *Se realizó una adaptación al vocabulario mexicano de la versión española del cuestionario DASH y se aplicó en 478 voluntarios. Se estimaron el efecto techo, el efecto suelo, la correlación ítem-total, las medidas de tendencia central de ítems y el puntaje total, la consistencia interna, la precisión y la validez transversal y longitudinal mediante la comparación de individuos sanos y enfermos con diferente nivel de discapacidad.* **Resultados:** *Nuestra versión del cuestionario DASH resultó equivalente a las previamente aprobadas y mostró homogeneidad de los ítems respecto al valor total del cuestionario (alfa de Cronbach > 0.96). Además, tuvo una precisión de 7.25 puntos y se documentó la validez transversal y longitudinal con diferencias significativas entre grupos y subgrupos con diferente nivel de discapacidad.* **Conclusiones:** *El cuestionario DASH puede ser empleado con un nivel de confianza alto en la población mexicana.*

***Palabras clave*:** *Cuestionario DASH. Discapacidad del miembro superior. Adaptación cultural. Validación de cuestionarios.*

Abstract

Objective: *To conduct a cultural adaptation and validation of the DASH questionnaire to evaluate the perspective of patients with neurogenic disorders of the upper extremity regarding the impact on their quality of life.* **Method:** *We performed an adaptation of the Spanish version of the DASH questionnaire to the Mexican vocabulary and applied it to 478 volunteers. Ceiling effect, floor effect, item-total correlation, descriptive statistics of items and total score, internal consistency, precision, cross-sectional and longitudinal validity were estimated by comparing healthy controls and affected individuals with different disability levels.*

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Results: *Our DASH questionnaire version was equivalent to those previously approved and showed homogeneity of the items with respect to the total value of the questionnaire (Cronbach's alpha > 0.96). In addition, it showed an accuracy of 7.25 points and the cross-sectional and longitudinal validity was documented with significant differences between groups and subgroups with distinct disability levels.* **Conclusions:** *The DASH questionnaire can be used with a high level of confidence in the Mexican population.*

Keywords: *DASH questionnaire. Upper limb disability. Cultural adaptation. Questionnaire validation.*

Introducción

Diversos trastornos de origen neurológico afectan al miembro superior, entre los que destacan las alteraciones degenerativas de la columna cervical con compromiso de componentes nerviosos (radiculopatía/mielopatía)[1], así como las neuropatías periféricas de etiología variada, incluyendo, por su importancia clínica y funcional, el síndrome de salida torácica (TOS, *thoracic outlet syndrome*), el síndrome del túnel carpiano y las neuropatías traumáticas[2].

En la actualidad, la valoración del impacto funcional de estos padecimientos se evalúa mediante escalas validadas para uso médico, como la escala de la Asociación Ortopédica Japonesa modificada (mJOA)[3] o el índice de discapacidad cervical (NDI, *Neck Disability Index*)[4], por mencionar algunas. Sin embargo, estas herramientas requieren conocimientos anatómicos, funcionales y clínicos que permitan una determinación objetiva del grado de compromiso del miembro. Además, se han empleado para alteraciones con una etiología específica generalmente de carácter ortopédico y no consideran al miembro superior como un ente funcional completo. Así mismo, existen pocas herramientas validadas que permitan conocer la perspectiva de los pacientes respecto a la función de sus miembros superiores y el impacto de diferentes trastornos neurogénicos en su calidad de vida y sus actividades de la vida diaria.

El cuestionario de discapacidad de brazo, hombro y mano (DASH, *Disabilities of the Arm, Shoulder and Hand*) es un instrumento clínico-métrico creado por la American Academy of Orthopedic Surgeons en 1996 para la medición del impacto de patologías del miembro superior en la calidad de vida de las personas, enfocándose en sus síntomas, estado físico y dificultad para realizar diferentes actividades de la vida diaria[5]. Esta herramienta autoaplicable consta de 30 ítems que gradúan el compromiso para diferentes actividades en una escala del 1 al 5, obteniéndose un puntaje final que se convierte en una escala a través de la fórmula descrita en su versión original[5,6]. El resultado final de este cuestionario expresa en términos cuantitativos el grado de discapacidad general del miembro superior percibido por el paciente.

El cuestionario DASH ha sido traducido y adaptado culturalmente a unos 54 idiomas, incluyendo su versión original en inglés[7], así como versiones en francés[8], alemán[9], italiano[10], portugués[11], ruso[12], japonés[13] y español[14,15], entre otras, y en diferentes países de habla hispana, incluyendo México, todas ellas aprobadas por el Institute for Work and Health[16]. Sin embargo, además de la traducción y la adaptación cultural se deben comprobar las propiedades métricas de dicha herramienta en la población para la cual ha sido readecuada. En este sentido, el uso del cuestionario DASH para conocer el grado de discapacidad del miembro superior aún debe ser validado en el contexto mexicano. Además, la capacidad de esta herramienta para identificar individuos con disfunción del miembro superior secundaria a diversas etiologías neurológicas no ha sido analizada formalmente en México.

El objetivo del presente estudio fue comprobar la utilidad de la versión mexicana del cuestionario DASH previamente traducida por el Institute for Work and Health[16], lo anterior a través de una readaptación cultural a partir de su versión española[15], así como una validación de su utilidad para conocer la percepción y el grado de discapacidad del miembro superior en la población general de México. Como segundo objetivo, se propuso evaluar esta herramienta en un grupo de individuos con trastornos conocidos del miembro superior de origen neurológico.

Método

Traducción y adaptación cultural

Dado que el cuestionario DASH ha sido previamente traducido al español por el Institute for Work and Health[16], se realizó una comprobación de dicha adaptación cultural a partir de la versión española validada por Hervás et al.[15] en 2006. Para dicho propósito, un profesional en filosofía y letras, así como un especialista en neurología, realizaron un análisis lingüístico de dicha herramienta y una adaptación al

vocabulario popular de la población mexicana. Los cambios realizados consistieron en adaptaciones en algunos términos cuyo uso es más coloquial en el contexto sociocultural de México respecto al de España, siguiendo las buenas prácticas de traducción y adaptación cultural previamente establecidas[17-19]. Al concluir dicho proceso, se compararon la versión resultante de este trabajo y la propuesta por el Institute for Work and Health.

Población de estudio

Para validar la versión mexicana del cuestionario DASH resultante del proceso de adaptación cultural se hizo un estudio piloto en el servicio de consulta externa de un centro de atención a padecimientos neurológicos y neuroquirúrgicos al norte de la Ciudad de México, mediante invitación abierta a pacientes regulares de dicho centro y sus familiares o acompañantes, incluyéndose en el análisis todos los individuos que aceptaron de forma voluntaria contestar el cuestionario en un periodo de 6 meses. Se excluyeron del estudio las personas iletradas o con trastornos del movimiento, así como con alteraciones que comprometieran las funciones mentales superiores, incluyendo enfermedades vasculares cerebrales, oncológicas y autoinmunitarias, deterioro cognitivo leve y demencia de causas diversas, entre otras, debido al diseño autoaplicable de la herramienta evaluada.

De esta forma, el cuestionario fue aplicado en un grupo piloto de 478 voluntarios sanos e individuos con trastornos neurogénicos del miembro superior, incluyendo pacientes con radiculopatía cervical diagnosticada mediante criterios clínicos y resonancia magnética de la columna cervical, así como sujetos con neuropatía periférica del miembro superior secundaria a TOS, síndrome del túnel carpiano o neuropatía traumática evaluados mediante interrogatorio clínico, exploración física, resonancia magnética del miembro superior y electromiografía.

Todos los participantes dieron su consentimiento informado por escrito para su inclusión en el estudio. El estudio fue revisado por un comité científico interno y excusado de aprobación por un comité de ética debido a su carácter de investigación sin intervención ni riesgo. Los datos fueron procesados y resguardados de acuerdo con las leyes nacionales de protección de datos personales, y el estudio fue conducido de acuerdo con la Norma Oficial Mexicana NOM-012-SSA3-2012, que establece los criterios para la ejecución de proyectos de investigación para la salud en seres humanos.

Propiedades métricas y validación del cuestionario

Para evaluar las propiedades métricas del cuestionario DASH en su versión mexicana se estimaron el efecto techo, el efecto suelo y la correlación ítem-total, así como las medidas de tendencia central de cada ítem y del puntaje total en dicha herramienta en todos los participantes y en los grupos de estudio. La consistencia interna de la escala, es decir, la homogeneidad de los ítems respecto a la herramienta entera, fue evaluada mediante el cálculo del alfa de Cronbach[20], aplicada en el total de la muestra y en los diferentes grupos de esta. La precisión del cuestionario se determinó tanto por el error estándar de la medición (EEM) como por el intervalo de confianza del 95% del EEM (EEM_{95}), ambos estimados como fue previamente descrito por otros autores[19]. Con el fin de determinar la validez del uso del cuestionario para evaluar la discapacidad del miembro superior secundaria a trastornos neurogénicos se compararon las puntuaciones de pacientes sanos respecto a individuos con algún padecimiento, así como entre casos agrupados de acuerdo con el trastorno específico del miembro superior (TOS vs. neuropatía periférica). Así mismo, se realizaron comparaciones en todos los participantes del estudio categorizados por edad, sexo, nivel de estudios y presencia de comorbilidad. La validez longitudinal del cuestionario respecto a su capacidad de estimar la respuesta al cambio se analizó mediante la comparación de las puntuaciones basales y postratamiento en un subgrupo de individuos con TOS operados mediante escalenotomía anterior.

Análisis estadístico

Se utilizó estadística descriptiva con medidas de tendencia central para la caracterización de la población del estudio. Las variables categóricas se analizaron con frecuencias absolutas y frecuencias relativas (porcentajes). Las variables continuas se analizaron mediante la prueba de Kolmogórov-Smirnov para determinar la normalidad de su distribución. Las variables cuantitativas con distribución normal se describen en términos de medias con desviación estándar o rango, y mediana con rango intercuartílico para los datos con distribución no normal. Las diferencias entre dos grupos fueron estimadas con la prueba exacta de Fisher o la prueba χ^2 para las

variables cualitativas, mientras que para las variables cuantitativas se usaron las pruebas U de Mann-Whitney, Kruskal-Wallis con prueba de Dunn, o Wilcoxon, según fuese apropiado. Todos los análisis se llevaron a cabo con el *software* GraphPad Prism versión 8 (La Joya, CA, USA). Algunas pruebas estadísticas específicas también se mencionan en los pies de tabla. Se consideraron valores de $p < 0.05$ de dos colas como estadísticamente significativos.

Resultados

Población de estudio

Un total de 478 sujetos se consideraron en la cohorte de validación y contestaron la versión mexicana del cuestionario DASH. De estos, el 35.7% eran hombres y el 64.2% eran mujeres, con una mediana de edad de 37 años y un rango de 15-91 años. La mayoría de los participantes fueron de raza mestiza, con un 96.23%. Esta población fue divida en 442 voluntarios considerados como controles para la validación del uso de la herramienta en la población general mexicana debido a la ausencia de un trastorno neurogénico del miembro superior diagnosticado de forma objetiva, siendo estos el 36.65% hombres y el 63.34% mujeres, con una mediana de edad de 35 años y un rango de 15-91 años. Por otro lado, el segundo grupo estuvo conformado por 36 individuos que fueron considerados casos debido a algún padecimiento demostrado del miembro superior de origen neurológico. Este grupo fue conformado por un 25% de hombres y un 75% de mujeres, con una mediana de edad de 55 años y un rango de 23 a 78 años. En ambos grupos, el nivel de educación de mayor predominio en nuestra población fue universitario en el 42.40%, seguido de preparatoria en el 37.34%. El primer lugar de procedencia fue la Ciudad de México, en el 53.97%, y en segundo lugar el Estado de México, en el 23.64%. En cuanto a la comorbilidad de los participantes, predominó el alcoholismo en el 44.56%, seguido de la ansiedad en el 35.84% y la depresión en el 34.10%. Los datos antropométricos y otras características demográficas de la población de estudio se resumen en la tabla 1. Cabe mencionar que se encontraron diferencias estadísticamente significativas en la edad, la talla, el índice de masa corporal y la proporción de individuos con hipotiroidismo primario entre los grupos de estudio, mientras que el resto de sus características demográficas y antropométricas fueron similares.

Propiedades métricas y validez de la versión mexicana del cuestionario DASH

La adaptación cultural a partir de la versión española del cuestionario DASH a la población mexicana resultó ser equivalente a la previamente aprobada por el Institute for Work and Health para el español de México (https://dash.iwh.on.ca/sites/dash/public/translations/DASH_Spanish_Mexico_2018.pdf). Sin embargo, pese a su previa aprobación y uso en algunas series de casos pequeñas de pacientes mexicanos con trastornos reumatológicos de la mano[21], las propiedades métricas y la validez de esta versión no habían sido formalmente evaluadas en un estudio clínico con un tamaño de muestra amplio. Como puede observarse en la tabla 2, la aplicación del cuestionario adaptado a nuestra población de estudio total demostró propiedades métricas aceptables, con un 100% de datos computables, lo que significa que ningún paciente elegible omitió o se rehusó a contestar el cuestionario. Así mismo, el efecto techo y el efecto suelo estuvieron dentro de los parámetros óptimos en la muestra total y en los grupos de esta. Respecto a la consistencia interna, el resultado del alfa de Cronbach fue determinado en un valor > 0.96 en el total de individuos incluidos en el estudio, siendo este parámetro de 0.95 en los controles y 0.96 en los casos; ambos valores traduciendo una homogeneidad de los ítems respecto al valor total del puntaje del cuestionario y siendo similar a la consistencia de la versión original[5]. Lo anterior significa que la versión aplicada a nuestra población es equivalente tanto en la población general como en sujetos con diagnóstico previo de alteración neurogénica, esto a pesar del número limitado de casos incluidos en el estudio.

La media, la mediana y las medidas de tendencia central del puntaje del cuestionario en la muestra total mostraron un nivel bajo de discapacidad del miembro superior. Sin embargo, como era de esperar, los puntajes fueron mayores en los casos que en los controles. Las tablas 3 y 4 muestran las estadísticas descriptivas de cada ítem en la población total del estudio y en los casos con alteraciones neurogénicas del miembro superior, respectivamente. Finalmente, la precisión en términos de EEM_{95} fue de 7.25 puntos en general, lo que significa que, para una aplicación del cuestionario determinada en un momento dado, el valor real se puede encontrar 7.25 puntos por arriba o por debajo del valor obtenido, con una confianza del 95%.

Tabla 1. Características de la cohorte de validación

Características	Total	Controles	Casos	p
Edad, años (rango)	37 (15-91)	35 (15-91)	55.5 (23-78)	< 0.0001
Sexo, n (%)				
Masculino	171 (35.77)	162 (36.65)	9 (25)	0.20
Femenino	307 (64.22)	280 (63.34)	27 (75)	
Raza, n (%)				
Blanca	17 (3.55)	16 (3.61)	1 (2.77)	> 0.99
Mestiza	460 (96.23)	425 (96.15)	35 (97.22)	
Negra	0	0	0	
Indígena	0	0	0	
Asiática	0	0	0	
Nivel de educación, n (%)				
Iletrado	11 (2.32)	11 (2.51)	0	0.99
Primaria	30 (6.32)	27 (6.16)	3 (8.33)	0.48
Secundaria	41 (8.64)	34 (7.76)	7 (19.44)	0.02
Preparatoria	177 (37.34)	165 (37.67)	12 (33.33)	0.72
Universidad	201 (42.40)	188 (42.92)	13 (36.11)	0.48
Posgrado	14 (2.95)	13 (2.96)	1 (2.77)	> 0.99
Procedencia, n (%)				
Ciudad de México	258 (53.97)	236 (53.39)	22 (61.11)	0.39
Estado de México	113 (23.64)	104 (23.52)	9 (25)	0.83
Puebla	11 (2.30)	10 (2.26)	1 (2.77)	0.58
Oaxaca	53 (11.08)	51 (11.53)	2 (5.55)	0.40
Nuevo León	3 (0.62)	3 (0.67)	0	> 0.99
Hidalgo	6 (1.25)	6 (1.35)	0	> 0.99
Chiapas	21 (4.39)	19 (4.29)	2 (5.55)	0.66
Jalisco	2 (0.41)	2 (0.45)	0	> 0.99
Veracruz	2 (0.41)	2 (0.45)	0	> 0.99
Querétaro	2 (0.41)	2 (0.45)	0	> 0.99
San Luis Potosí	1 (0.20)	1 (0.22)	0	> 0.99
Morelos	1 (0.20)	1 (0.22)	0	> 0.99
Tlaxcala	1 (0.20)	1 (0.22)	0	> 0.99
Yucatán	1 (0.20)	1 (0.22)	0	> 0.99
Guanajuato	1 (0.20)	1 (0.22)	0	> 0.99
Sinaloa	1 (0.20)	1 (0.22)	0	> 0.99
Antropométricos				
Talla, m (rango)	1.62 (1.56-1.71)	1.62 (1.56-1.71)	1.56 (1.50-1.64)	0.003
Peso, kg (rango)	68.5 (61-80)	68.5 (60.55-80.0)	68.50 (62.78-76.75)	0.95
IMC, kg/m^2 (rango)	26 (23.3-28.8)	25.9 (23.26-28.72)	27.41 (25.04-30.51)	0.01
Comorbilidad, n (%)				
Ansiedad	171 (35.84)	162 (36.73)	9 (25)	0.20
Depresión	163 (34.10)	153 (34.61)	10 (27.77)	0.46
Hipertensión	39 (8.17)	34 (7.70)	5 (13.88)	0.20
Diabetes	25 (5.2)	25 (5.65)	0	0.24
SAHOS	1 (0.20)	1 (0.22)	0	>0.99
Hipotiroidismo	7 (1.46)	4 (0.90)	3 (8.33)	0.01
Alcoholismo	213 (44.56)	199 (45.02)	14 (38.88)	0.49
Tabaquismo	100 (20.92)	89 (20.13)	11 (30.55)	0.14

IMC: índice de masa corporal; SAHOS: síndrome de apnea/hipopnea obstructiva del sueño.
Las diferencias entre grupos fueron estimadas mediante las pruebas exacta de Fisher para variables categóricas y U de Mann-Whitney para variables cuantitativas.

En la tabla 5 se muestra la correlación entre las características demográficas de los participantes del estudio y sus puntajes en el cuestionario aplicado. Como puede observarse, el puntaje presentó diferencias significativas entre sexos, algunos grupos de edad y segmentos de la población con diferente grado de escolaridad. Por último, la tabla 6 ilustra los resultados de la evaluación de la validez del cuestionario. Se documentaron diferencias significativas en el puntaje de controles y casos, así como entre casos agrupados de

Tabla 2. Propiedades métricas del cuestionario DASH versión en español de México

Características	Total	Controles	Casos
Datos computables	100%	100%	100%
Media	42.88	40.07	77.39
Desviación estándar	18.59	14.7	25.8
Mediana	35	34	74
Rango intercuartílico	31-46	31-43	56-95
Efecto techo	5 (1.05)	0	5 (13.88)
Efecto suelo	94 (19.66)	94 (21.26)	0
Alfa de Cronbach	0.9602	0.9512	0.9692
EEM	3.70	3.24	4.52
Precisión transversal (EEM_{95})	7.25	5.20	8.87

EEM: error estándar de la medición; EEM_{95}: intervalo de confianza del 95% del EEM.

Tabla 3. Correlación ítem-total, puntuación media, puntuación mediana y rango por ítem

Ítem	Correlación ítem-total	Media (DE)	Mediana (RIC)	Rango
Q1	0.67	1.6 (1.0)	1 (1-2)	1-5
Q2	0.57	1.2 (0.6)	1 (1-1)	1-5
Q3	0.65	1.2 (0.6)	1 (1-1)	1-5
Q4	0.65	1.2 (0.7)	1 (1-1)	1-5
Q5	0.74	1.5 (0.9)	1 (1-2)	1-5
Q6	0.79	1.4 (0.9)	1 (1-2)	1-5
Q7	0.80	1.5 (0.9)	1 (1-2)	1-5
Q8	0.55	1.2 (0.6)	1 (1-1)	1-5
Q9	0.72	1.2 (0.6)	1 (1-1)	1-5
Q10	0.76	1.4 (0.8)	1 (1-2)	1-5
Q11	0.76	1.7 (1.1)	1 (1-2)	1-5
Q12	0.78	1.5 (1.0)	1 (1-2)	1-5
Q13	0.68	1.2 (0.6)	1 (1-1)	1-5
Q14	0.73	1.4 (0.9)	1 (1-2)	1-5
Q15	0.70	1.1 (0.6)	1 (1-1)	1-5
Q16	0.72	1.1 (0.6)	1 (1-1)	1-5
Q17	0.57	1.1 (0.5)	1 (1-1)	1-5
Q18	0.71	1.5 (0.9)	1 (1-2)	1-5
Q19	0.78	1.5 (0.9)	1 (1-2)	1-5
Q20	0.71	1.2 (0.7)	1 (1-1)	1-5
Q21	0.66	1.2 (0.7)	1 (1-1)	1-5
Q22	0.71	1.3 (0.8)	1 (1-1)	1-5
Q23	0.75	1.3 (0.8)	1 (1-1)	1-5
Q24	0.66	1.6 (0.9)	1 (1-2)	1-5
Q25	0.64	1.6 (0.9)	1 (1-2)	1-5
Q26	0.46	1.6 (0.9)	1 (1-2)	1-5
Q27	0.62	1.4 (0.9)	1 (1-2)	1-5
Q28	0.56	1.3 (0.7)	1 (1-1)	1-5
Q29	0.62	1.3 (0.8)	1 (1-1)	1-5
Q30	0.77	1.4 (0.8)	1 (1-1)	1-5

DE: desviación estándar; RIC: rango intercuartílico.

acuerdo con la etiología específica de su padecimiento. Además, se observó una disminución significativa del puntaje del cuestionario aplicado después del tratamiento quirúrgico de un grupo de pacientes con TOS respecto a su nivel basal. En conjunto, estos resultados proveen datos preliminares sobre la utilidad del cuestionario DASH adaptado a la población mexicana como herramienta sensible para detectar cambios en la gravedad y la respuesta al tratamiento de trastornos neurogénicos que afectan la función del miembro superior, esto evaluado desde la perspectiva del paciente.

Discusión

Diversos trastornos cuya etiología es de carácter neurogénico causan signos y síntomas que afectan directamente la función del miembro superior. Por ejemplo, en individuos con alteraciones estructurales secundarias a procesos traumáticos, degenerativos o idiopáticos de la columna cervical que condicionan radiculopatía o mielopatía se presentan manifestaciones neurológicas importantes, como dolor radicular, alteraciones sensitivas como parestesias y disestesias, pérdida de la fuerza muscular y atrofia, los cuales pueden afectar porciones proximales y distales de los miembros torácicos. De igual manera, las alteraciones compresivas o traumáticas de los nervios periféricos que inervan los miembros superiores pueden ocasionar un espectro de manifestaciones similares, pero de gravedad variable dependiendo del mecanismo de daño al paquete neurovascular, la cronicidad de la enfermedad y el nivel afectado[1,2]. De forma importante, algunos de estos trastornos son susceptibles de mejoría si reciben tratamiento médico y rehabilitación física de manera oportuna, o bien tratamiento definitivo mediante descompresión quirúrgica.

Tabla 4. Correlación ítem-total, puntuación media, puntuación mediana y rango por ítem en individuos con trastornos del miembro superior

Ítem	Correlación ítem-total	Media (DE)	Mediana (RIC)	Rango
Q1	0.56	3.2 (0.8)	3 (3-4)	1-5
Q2	0.74	1.8 (1.2)	1 (1-3)	1-5
Q3	0.55	2.1 (1.2)	2 (1-3)	1-5
Q4	0.85	2.0 (1.4)	1 (1-3)	1-5
Q5	0.66	2.6 (1.4)	3 (1-4)	1-5
Q6	0.80	2.5 (1.5)	3 (1-4)	1-5
Q7	0.80	3.0 (1.4)	3 (2-4)	1-5
Q8	0.76	1.9 (1.3)	1 (1-3)	1-5
Q9	0.82	2.2 (1.2)	2 (1-3)	1-5
Q10	0.79	2.5 (1.4)	3 (1-3)	1-5
Q11	0.67	3.0 (1.2)	3 (2-4)	1-5
Q12	0.89	2.2 (1.5)	1 (1-3)	1-5
Q13	0.76	2.2 (1.4)	1 (1-3)	1-5
Q14	0.76	2.3 (1.5)	1 (1-4)	1-5
Q15	0.92	1.9 (1.3)	1 (1-3)	1-5
Q16	0.91	2.0 (1.4)	1 (1-3)	1-5
Q17	0.82	1.7 (1.3)	1 (1-2)	1-5
Q18	0.81	2.7 (1.5)	3 (1-4)	1-5
Q19	0.77	2.7 (1.5)	3 (1-4)	1-5
Q20	0.82	2.1 (1.3)	1 (1-3)	1-5
Q21	0.88	2.1 (1.5)	1 (1-3)	1-5
Q22	0.84	2.0 (1.2)	1 (1-3)	1-5
Q23	0.77	2.2 (1.4)	2 (1-3)	1-5
Q24	0.30	2.8 (1.2)	3 (1-4)	1-5
Q25	0.44	2.6 (1.3)	3 (1-4)	1-5
Q26	0.26	2.3 (1.2)	2 (1-3)	1-5
Q27	0.43	2.2 (1.3)	2 (1-3)	1-5
Q28	0.44	2.1 (1.3)	1 (1-3)	1-5
Q29	0.80	2.5 (1.5)	2 (1-4)	1-5
Q30	0.88	2.5 (1.4)	2 (1-4)	1-5

DE: desviación estándar; RIC: rango intercuartílico.

Tabla 5. Correlación entre las características de los participantes y el puntaje en la escala DASH en español de México

Características	DASH	p
Edad (años)		
< 20	36 (31-47)	0.0001*
20-30	34 (31-41)	
30-40	33 (30-37)	
40-50	34 (31-56)	
50-60	35 (31-51)	
> 60	43 (32-60)	
Sexo		
Hombre	33 (30-39)	< 0.0001
Mujer	37 (32-49)	
Nivel de estudios		
Iletrado	39 (33-43)	0.0003†
Primaria	54 (37-78)	
Secundaria	36 (31-68)	
Preparatoria	34 (31-44)	
Universidad	34 (31-44)	
Posgrado	34 (31-45)	
Comorbilidad		
No	36 (31-45)	0.46
Sí	35 (31-46)	

*Se observaron diferencias significativas entre los grupos de 20-30 años vs. > 60 años (p = 0.0004) y 30-40 años vs. > 60 años (p = 0.0001).
†Se observaron diferencias entre los grupos primaria vs. preparatoria (p = 0.0001) y primaria vs. universidad (p = 0.0001)
Las diferencias entre grupos fueron estimadas con la prueba U de Mann-Whitney y la prueba de Kruskal-Wallis/Dunn según fuese apropiado.

La capacidad de medir objetivamente la gravedad de la afectación de los miembros superiores por los padecimientos mencionados, así como la posibilidad de determinar el beneficio aportado por intervenciones terapéuticas, es crucial en la toma de decisiones y tiene el potencial de impactar en el resultado funcional de los pacientes con trastornos del miembro superior. Sin embargo, hoy en día existe un auge por mejorar la calidad de la atención a la salud en términos de la influencia que tienen las intervenciones en la restauración de la calidad de vida y la reincorporación a las actividades cotidianas de los pacientes.

A pesar de ello, cuando se trata de los trastornos neurogénicos del miembro superior, y en particular durante su evaluación y tratamiento por el área de neurocirugía, existe una gran variedad de métodos objetivos como escalas clínicas, estudios de imagen y estudios de neurofisiología que permiten evaluar en una primera instancia la complejidad clínica y posteriormente la eficacia y la resolución de cada una desde el punto de vista del médico tratante, pero que omiten la perspectiva del paciente respecto a su propia enfermedad. Por lo tanto, es ideal considerar tanto la perspectiva médica como la experiencia subjetiva del paciente respecto a la repercusión de la enfermedad en su vida diaria, ya que esta consideración integral también puede ser determinante en el abordaje y el manejo

Tabla 6. Validez de la escala DASH en español de México

Criterio de validez	DASH	Diferencia	d de Cohen	Tamaño del efecto	p
Validez por gravedad					
Controles	34 (31-43)	40	-	-	< 0.0001
Casos	74 (56-94)				
Validez por gravedad					
Radiculopatía	57 (47-89)	34	-	-	0.04
TOS	91 (69-97)				
Validez longitudinal*					
Pretratamiento	93 (73-97)	60	4.32	0.9	< 0.0001
Postratamiento	32 (30-34)				

TOS: síndrome de salida torácica.
*Evaluada en pacientes con TOS sometidos a tratamiento quirúrgico.
Las diferencias entre grupos se estimaron con la prueba U de Mann-Whitney. Las diferencias entre las puntuaciones pre- y postratamiento se estimaron con la prueba de Wilcoxon.

médico/quirúrgico, puesto que permite evaluar de manera global todos los aspectos que influyen en el pronóstico del paciente. En particular, esto se vuelve aún más importante ya que no siempre existe correlación y equivalencia entre los hallazgos objetivos clínico-radiológicos y su impacto real en el desempeño funcional de los individuos afectados[22].

Desafortunadamente, siguen siendo pocas las herramientas válidas para conocer la visión de los pacientes respecto a los trastornos neurogénicos del miembro superior que les afectan. De hecho, muchas de las herramientas conocidas están dirigidas a evaluar solo algunos segmentos anatómicos de las extremidades torácicas y generalmente se utilizan en otras especialidades, en particular en cirugía ortopédica[3,4]. Una de dichas herramientas es el cuestionario DASH, que tiene la particularidad de ser adaptable a diferentes circunstancias ya que evalúa la discapacidad del miembro superior considerándolo como un ente funcional único[7]. Este cuestionario fue originalmente validado en idioma inglés, y pese a que existen versiones en español, su uso en un contexto sociocultural diferente requiere una nueva adaptación lingüística, incluso tratándose del mismo idioma[19], primeramente en la población general, lo que permite evaluar la aceptación de las adecuaciones textuales en el contexto sociocultural al que se dirige la readaptación, y después en individuos con trastornos comprobados del miembro superior. Por lo tanto, en este estudio aplicamos una versión adecuada a la población mexicana y validamos su uso como herramienta útil para conocer, en primera instancia, la equivalencia lingüística de esta herramienta para uso en la población mexicana, y en segundo lugar la validez para estimar la repercusión de trastornos neurogénicos (como radiculopatía cervical, TOS, síndrome del túnel carpiano y neuropatía periférica traumática) en la calidad de vida.

Al aplicar el cuestionario DASH identificamos que algunos conceptos no eran aptos para nuestra población mexicana, por lo que se realizó una adaptación de conceptos a palabras más comunes en el contexto de nuestro país. Para dicho propósito nos aseguramos de que las palabras que se cambiaron no afectaran el concepto de la pregunta de la versión ya existente del DASH en español, utilizando sinónimos adecuados a nuestra cultura, de manera que los ítems fueran equivalentes[19]. Esto permite evitar el sesgo del lenguaje, facilitando su aplicación, haciendo más confiables los resultados de esta herramienta y colocando al cuestionario DASH como una valiosa opción para la valoración de la discapacidad del miembro superior desde la perspectiva del paciente en el área de neurocirugía.

Los resultados indican una equivalencia de la versión resultante de nuestro estudio con la previamente propuesta[16], que al ser aplicada a nuestra población tiene propiedades similares con respecto a la versión española y la versión original en inglés[5,14,15], esto sustentado en las mediciones de las propiedades métricas del cuestionario, incluyendo las determinaciones de correlación ítem-total, efecto suelo, efecto techo, precisión transversal y consistencia interna entre sus ítems y el puntaje total. Por lo tanto, nuestras observaciones indican que este cuestionario puede ser empleado de forma autoaplicable con un nivel de confianza alto en la población mexicana. Es interesante que, al comparar los puntajes del cuestionario en la totalidad de nuestra cohorte de validación, encontramos diferencias significativas entre ambos sexos, siendo el grado de discapacidad basal mayor

en las mujeres que en los hombres. Lo anterior ya había sido observado previamente en estudios observacionales[23], aunque también puede deberse a una mayor proporción de mujeres con TOS en el grupo de casos en nuestro estudio.

Igualmente pudimos identificar diferencias entre personas de diferentes grupos de edad, siendo los de mayor grado de discapacidad basal aquellos por arriba de los 60 años, lo cual también ya había sido documentado en un estudio de discapacidad del brazo en trabajadores alemanes[24]. Finalmente, observamos un mayor grado de discapacidad en personas con escolaridad primaria respecto a aquellas con niveles de preparatoria y universidad, lo cual pudiera estar relacionado con los diferentes trabajos que desempeñan las personas con distintos grados de estudios. Cabe mencionar que nuestro estudio incluye un amplio rango de grupos de edad, escolaridad y comorbilidad, por lo que algunos parámetros observados en nuestra investigación podrían tener una aplicación epidemiológica.

Por último, pudimos validar el uso del cuestionario para detectar cambios en la gravedad de la discapacidad del miembro superior desde la perspectiva del paciente. De esta forma, demostramos que la versión mexicana del cuestionario DASH es útil para identificar un cambio en la gravedad de la discapacidad entre individuos sanos y sujetos con alteraciones neurogénicas del miembro superior, así como entre grupos con distintas etiologías de la discapacidad. Por último, la versión validada en este estudio demostró ser sensible para detectar un cambio en la perspectiva del paciente con TOS al comparar los puntajes obtenidos antes y después del tratamiento quirúrgico de dicho padecimiento, corroborando lo que nuestro grupo había documentado previamente[25]. Sin embargo, cabe mencionar que una limitación importante del estudio es el número limitado de individuos con alteraciones probadas del miembro superior, lo cual debe considerarse al interpretar los resultados. Pese a ello, nuestros resultados no deben ser descartados ya que constituyen evidencia preliminar útil para estudios futuros, además de que se demuestra una consistencia interna más que aceptable en casos y controles, los cuales mostraron valores comparables de alfa de Cronbach. Por lo tanto, el presente estudio sienta un antecedente para realizar más estudios dirigidos a conocer el grado de discapacidad específicamente en individuos mexicanos con diversos trastornos del miembro superior.

Conclusiones

Se realizaron una adaptación cultural y una validación de la versión española del cuestionario DASH para la población mexicana. Nuestros resultados muestran que esta herramienta puede ser empleada con un nivel de confianza alto, comprobando su utilidad en la evaluación de diversos trastornos neurogénicos del miembro superior y su influencia e impacto en la calidad de vida desde la perspectiva de los pacientes. Por lo tanto, el cuestionario DASH se debe considerar entre la batería de herramientas clínico-métricas útiles en estudios de investigación dirigidos a evaluar el impacto de dichos trastornos en la calidad de vida, así como en su vigilancia y seguimiento postratamiento.

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Conflicto de intereses

Los autores declaran que no tienen ningún tipo de relación académica, profesional o comercial con entidades públicas o privadas que puedan constituir un conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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ORIGINAL ARTICLE

Prediction of short-term results after laparoscopic right hemicolectomy. Is sarcopenia superior to other methods?

Predicción de resultados a corto plazo tras hemicolectomía derecha laparoscópica. ¿Es la sarcopenia superior a otros métodos?

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Abstract

Objective: *We aimed to determine the factors that predict early mortality and morbidity in patients who underwent laparoscopic right hemicolectomy and their superiority over each other.* **Method:** *Demographic data, age-adjusted Charlson Comorbidity Index, American Society of Anesthesiologists Score, body mass index, modified-Glasgow Prognostic Score (mGPS), stage of disease, and sarcopenia were evaluated in patients who underwent right hemicolectomy between 2010-2022. Their superiority in predicting short-term outcomes was compared.* **Results:** *78 patients were included in the study. The complication rate was higher in sarcopenic patients (p = 0.002). A high mGPS score was associated with increased mortality risk (p = 0.012). Other methods were not found to be related to short-term results.* **Conclusions:** *Sarcopenia is useful for the prediction of complications, and the mortality rate can be estimated by the mGPS score. These are superior to the other short-term results prediction methods. However, randomized controlled studies are needed.*

Keywords: *Sarcopenia. Glasgow prognostic score. Short-term results.*

Resumen

Objetivo: *Determinar los factores que predicen la mortalidad y la morbilidad precoces en pacientes sometidos a hemicolectomía derecha laparoscópica y su superioridad entre ellos.* **Método:** *Se evaluaron datos demográficos, el índice de comorbilidad de Charlson ajustado por edad, el puntaje de la American Society of Anesthesiologists, el índice de masa corporal, el puntaje de pronóstico de Glasgow modificado (mGPS), el estadio de la enfermedad y la sarcopenia en pacientes que se sometieron a hemicolectomía derecha entre 2010 y 2022. Se comparó su superioridad en la predicción de resultados a corto plazo.* **Resultados:** *Se incluyeron en el estudio 78 pacientes. La tasa de complicaciones fue mayor en los pacientes sarcopénicos (p = 0.002). Una puntuación mGPS alta se asoció con un mayor riesgo de mortalidad (p = 0.012). No se encontró que otros métodos estuvieran relacionados con los resultados a corto plazo.* **Conclusiones:** *La sarcopenia es útil para la predicción de complicaciones y la tasa de mortalidad puede estimarse mediante la puntuación mGPS. Estos son superiores a los otros métodos de predicción de resultados a corto plazo. Sin embargo, se necesitan estudios controlados aleatorizados.*

Palabras clave: *Sarcopenia. Puntuación de pronóstico de Glasgow. Resultados a corto plazo.*

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Introduction

Even though the incidence of colorectal cancer has been increasing over the last few years, the mortality rates have been decreasing gradually[1]. Advances in diagnosis, treatment methods, and screening programs have affected survival outcomes positively[2]. One of the most important factors affecting survival is the early diagnosis and treatment of complications. Many methods have been identified in predicting mortality and complications of colorectal cancer patients in the post-operative period[3-11]. Biochemical parameters such as C-reactive protein (CRP), albumin levels, platelet count, neutrophil-lymphocyte ratios; pre-operative body mass index (BMI), stage of cancer, modified Glasgow Prognostic Score (mGPS); The American Society of Anesthesiologists (ASA) Score, and the age-adjusted Charlson comorbidity index (ACCI) which evaluate comorbidities, and sarcopenia scores, which assesses muscle quality, are the most used methods for the evaluation of mortality and morbidity. With the prediction and early diagnosis of complications, their treatment can be carried out in a shorter time. Thus, patients can be referred to adjuvant therapy right on time. And as a result, overall survival gets positively affected.

Sarcopenia is a syndrome that can lead to negative consequences such as physical disability, poor quality of life, and mortality due to the progressive loss of skeletal muscle mass and strength. It was first described by Rosenberg[12], and is usually prominent in the elderly and cancer patients. The easiest way to detect sarcopenia is through radiological methods. For this, the most frequently used muscle groups are the psoas muscle and abdominal wall muscles such as transversus abdominis, internal and external oblique muscles, and rectus abdominis. Skeletal muscle area in single-section images correlates well with total muscle volume, and an idea of the whole muscle mass can be obtained from these measurements[13]. In recent years, this method has been used more than others in evaluating morbidity, especially in cancer patients.

In our study, we aimed to determine the factors that predict early mortality and morbidity in patients who underwent laparoscopic right hemicolectomy and their superiority over each other. We aimed to evaluate stage of disease, obesity status, ASA score, ACCI, mGPS, and sarcopenia as predictive variables. Our primary outcome is to evaluate the relationship between our variables and complications and mortality. Our secondary outcome, on the other hand, is the analysis of our variables and other short-term results such as length of stay, operation time, and estimated blood loss.

Materials and methods

Our study was planned retrospectively in our institute's surgical oncology department. The data of the patients were searched using the electronic patient file system of the hospital. Approval was obtained from our university's ethics committee. Stages I, II, and III patients who underwent elective laparoscopic right hemicolectomy due to colon cancer between March 2010 and September 2022 were included in the study. Patients whose data could not be accessed and who underwent an additional surgical procedure and palliative surgery were excluded from the study. A total of 78 patients were included in the study after screening (Fig. 1).

Demographic data of the patients such as age, gender, height, and weight, operative information such as tumor localization, type of surgery, operation time, estimated blood loss, and pathological results such as tumor diameter, tumor type, tumor progressions, lymph node involvement were evaluated in the study. CRP and albumin levels from biochemical data, as well as the comorbidity status of the patients, were recorded to be analyzed in our study. During the follow-up period, length of stay, complications, and mortality were assessed. The formula of dividing the weight (kg) by the square of the height (m^2) was used when calculating the BMI of the patients. Obese patients were identified according to the obesity classification of the World Health Organization[14]. Stages were determined by the TNM staging specified in the eighth edition of the American Joint Committee on Cancer (AJCC)[15]. Stage I cancers were included in early-stage cancers, and Stages II and III cancers were included in advanced cancers. Comorbidities were scored according to ACCI[16]. The total score is the sum of the weighted scores for all variables. ACCI was assessed for all patients at baseline and patients were divided into three groups according to ACCI: 0-2, 3-4, and $\geq$ 5. One of the pre-operative indicators of systemic inflammation of the patients, mGPS, a measurement based on pre-operative serum albumin and CRP levels, was recorded. The calculation was made with the data in the last month before the operation. Patients with a CRP level of 10 mg/dl or less were determined as mGPS 0, those with a CRP level above 10 were determined as mGPS 1, and those with an albumin level above 35 g/L were determined as mGPS

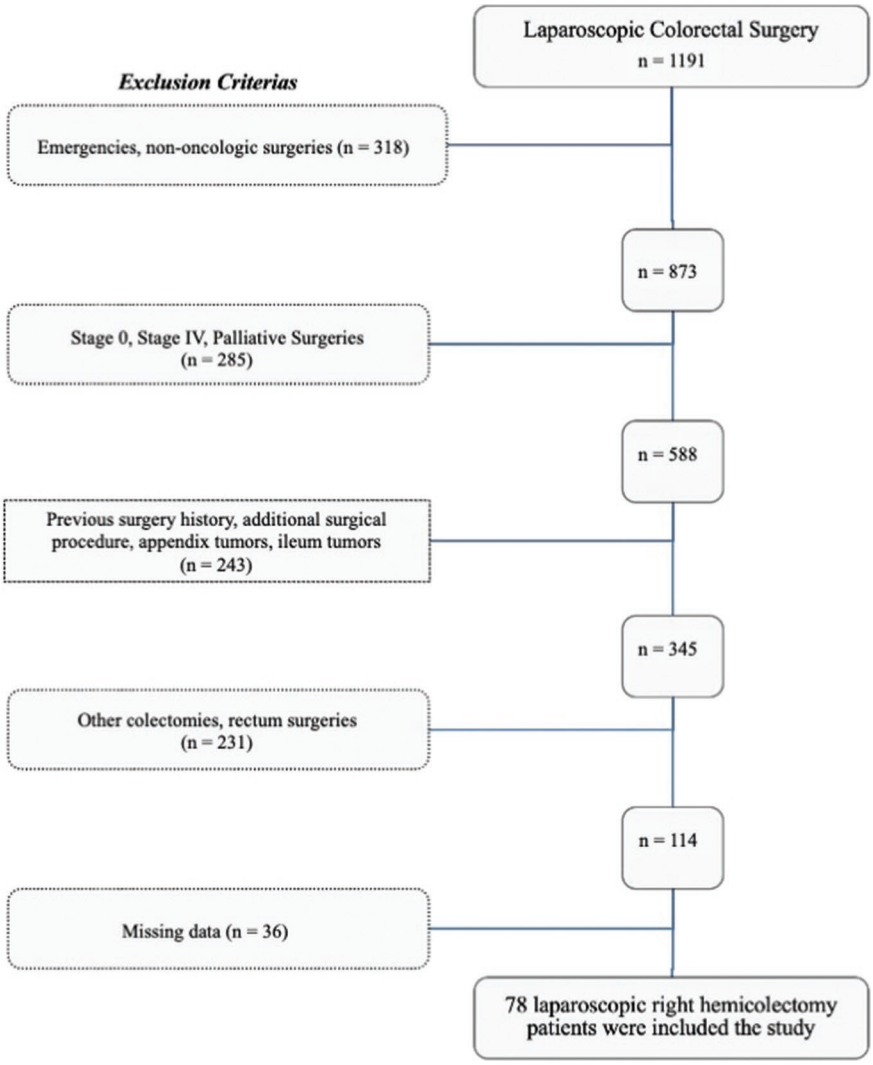

Figure 1. *Flow diagram of exclusion criteria.*

2. mGPS 0 is low score and shows good prognosis, mGPS 1 is moderate and shows moderate prognosis, and mGPS 2 shows poor prognosis[17]. Complications were classified according to the Clavien-Dindo Classification[18]. Clavien-Dindo ≥ 3 was considered a major complication. Others were included in the mild complication category.

For the assessment of sarcopenia, the previously described scoring over psoas muscle volume was calculated[19]. If the patient had a contrast-enhanced computed tomography (CT) taken within the last month, it was included in the study. Sarcopenia calculations were made by a specialist radiologist using the picture archiving and communication system. No information was given to the radiologist about the patients. L3 vertebrae were detected in the axial section, and the right and left psoas muscle areas were measured from the upper border of the vertebrae in square centimeters (cm^2) by freehand drawing method (Fig. 2). The first of these methods is the total psoas index (TPI). The total psoas area is used as a representation of total body muscle mass in the calculation[20]. The TPA values obtained by the sum of the right psoas area and the left psoas area were divided by the square meter (m^2) of the patient's height and normalized according to the patients, and TPI was obtained. Another method is the Hounsfield Unit average calculation (HUAC). This method also measures the Hounsfield Unit (HU) values of the areas and the muscle density and in a way gives an idea about the quality of the muscle. While this value is low in muscles with more adipose tissue, HU values are higher

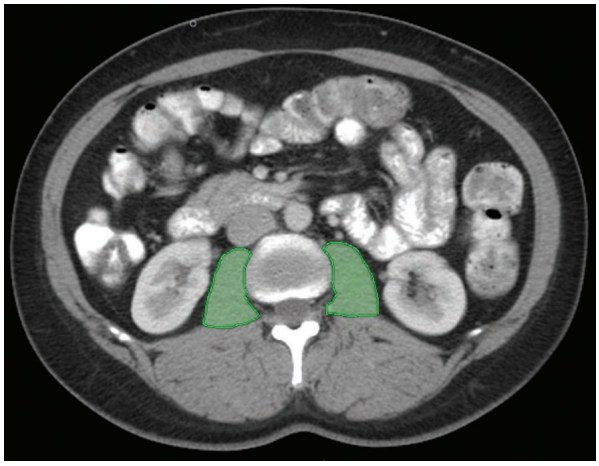

Figure 2. *Psoas area calculation by freehand drawing method.*

in psoas muscles that are richer than muscle[21]. {[(Right psoas mean HU * Right psoas area)/TPA] + [(Left psoas mean HU * Left psoas area)/TPA]}/2 formula is used in the calculation[22]. For both genders, patients in the last quartile of calculated TPI and HUAC values were considered sarcopenic. Patients who were considered sarcopenic at either TPI or HUAC were considered sarcopenic in total.

Perioperative care

In our institution, bowel preparation with two 135 mL rectal enemas and an oral laxative solution is performed one day before the operation as standard for all patients who are scheduled for colorectal surgery and who do not have an obstructive lesion. A nasogastric catheter and urinary catheter are inserted before the operation. Antibiotic prophylaxis is administered with 1 g ceftriaxone and 500 mg metronidazole before anesthesia induction. At least two general surgery specialists are involved in the operations.

All patients included in the study were operated with the laparoscopic method, while intra-abdominal pressure was maintained at an average of 12-15 mm/Hg. Anastomoses were performed side-by-side using a linear stapler with the extracorporeal method from the incision where the piece was removed. A suction drain was placed in the right paracolic area during the operations. All patients were admitted to the intensive care unit after the operation. Patients with good general conditions and stable hemodynamics were taken to their rooms. Urinary and nasogastric catheters were terminated on the first postoperative day as standard procedure. Routine mobilization and respiratory physiotherapy recommendations were made until discharge. The patients were followed up for at least 1 month after discharge.

Statistical analysis

The data were evaluated with the IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. package program. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were given as frequency (%) and continuous variables as median (interquartile range [IQR]). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Numerical variables were compared using either the Mann-Whitney U or Kruskal-Wallis test, as appropriate. Logistic regression analysis was used to determine the odds ratio for complication in sarcopenic patients. The logistic regression model was developed by adjusting for age, gender, ACCI, stage of disease, and mGPS.

Results

78 patients were included in the study. The median age was 63. 37 (47.4%) of the patients were female. The demographic features of the patients are summarized in table 1. The median TPI value was 4.37 (3.24-5.11) in women and 4.84 (3.75-5.50) in men. The median HUAC value was 23.45 (20.94-27.23) in women and 25.01 (22.22-27.71) in men. No significant difference was found between the two genders for both parameters (p = 0.123, p = 403, respectively). According to TPI or HUAC, 35 (44.9%) patients were defined as sarcopenic. The patient outcomes are listed in table 2 based on sarcopenia status.

Complication and mortality rates

A total of 13 (16.7%) complications were observed in patients: Grade 1 in two (2.6%) patients, Grade 2 in four (5.1%) patients, Grade 3a in two (2.6%) patients, Grade 4a in two (2.6%) patients, and Grade 5 in three (3.8%) patients. No statistically significant correlation was found between stage of disease, obesity status, ACCI, ASA score, and mGPS and complication rates (p = 0.605, 0.443, p = 0.267, p = 0.391, 0.797, respectively). The complication rate

Table 1. Baseline characteristics

Variable	Total (n = 78)	Non-sarcopenic (n = 43)	Sarcopenic (n = 35)	p-value
Age (years)*	63 (56-71)	63 (54-71)	63 (56-73)	0.381†
Sex				0.856‡
Female	37 (47.4%)	20 (46.5%)	17 (48.6%)	
Male	41 (52.6%)	23 (53.5%)	18 (51.4%)	
Localization				-
Caecum	44 (56.4%)	25 (58.1%)	19 (54.3%)	
Ascending colon	17 (21.8%)	10 (23.3%)	7 (20.0%)	
Hepatic flexure	15 (19.2%)	6 (14.0%)	9 (25.7%)	
Transverse colon	2 (2.6%)	2 (4.7%)	0 (0.0%)	
Operation				0.504§
Right Hemicolectomy	69 (88.5%)	37 (86.0%)	32 (91.4%)	
Extended Right Hemicolectomy	9 (11.5%)	6 (14.0%)	3 (8.6%)	
Tumor Size (cm)*	4.8 (3.0-6.0)	4.5 (3.4-6.0)	5.0 (3.0-6.5)	0.625†
Tumor Type				-
Adenocarcinoma	59 (75.6%)	33 (76.7%)	26 (74.3%)	
Medullary Carcinoma	2 (2.6%)	0 (0.0%)	2 (5.7%)	
Mucinous Adenocarcinoma	16 (20.5%)	10 (23.3%)	6 (17.1%)	
Neuroendocrine Carcinoma	1 (1.3%)	0 (0.0%)	1 (2.9%)	
T Stage				-
T1	12 (15.4%)	5 (11.6%)	7 (20.0%)	
T2	5 (6.4%)	5 (11.6%)	0 (0.0%)	
T3	43 (55.1%)	24 (55.8%)	19 (54.3%)	
T4a	14 (17.9%)	7 (16.3%)	7 (20.0%)	
T4b	4 (5.1%)	2 (4.7%)	2 (5.7%)	
Resected LN*	20 (15-26)	20 (14-25)	21 (16-27)	0.418†
Positive LN*	0 (0-2)	0 (0-2)	0 (0-2)	0.320†
N Stage				-
N0	47 (60.3%)	29 (67.4%)	18 (51.4%)	
N1a	7 (9.0%)	1 (2.3%)	6 (17.1%)	
N1b	11 (14.1%)	5 (11.6%)	6 (17.1%)	
N1c	3 (3.8%)	2 (4.7%)	1 (2.9%)	
N2a	5 (6.4%)	2 (4.7%)	3 (8.6%)	
N2b	5 (6.4%)	4 (9.3%)	1 (2.9%)	
Stage				0.151‡
Early	47 (69.3%)	29 (67.4%)	18 (51.4%)	
Advanced	31 (39.7%)	14 (32.6%)	17 (48.6%)	
BMI (kg/m^2)*	26.29 (23.34-28.93)	26.22 (23.74-29.11)	26.35 (22.97-28.81)	0.501†
BMI categorized				0.447‡
< 30	64 (82.1%)	34 (79.1%)	30 (85.7%)	
≥ 30	14 (17.9%)	9 (20.9%)	5 (14.3%)	
ACCI				-
0-2	9 (11.5%)	5 (11.6%)	4 (11.4%)	
3-4	31 (39.7%)	18 (41.9%)	13 (37.1%)	
≥ 5	38 (48.7%)	20 (46.5%)	18 (51.4%)	
ASA				-
ASA I	30 (38.5%)	19 (44.2%)	11 (31.4%)	
ASA II	40 (51.3%)	18 (41.9%)	22 (62.9%)	
ASA III	7 (9.0%)	5 (11.6%)	2 (5.7%)	
ASA IV	1 (1.3%)	1 (2.3%)	0 (0.0%)	
mGPS*	0.20 (0.10-0.44)	0.17 (0.09-0.34)	0.24 (0.12-0.59)	0.310†

*Reported as median (IQR).
†Mann-Whitney U test,
‡Chi-square test.
§Fisher's exact test.

Table 2. Outcomes of patients according to sarcopenia status

Variable	Total (n = 78)	Non-sarcopenic (n = 43)	Sarcopenic (n = 35)	p-value
Complication	13 (16.7%)	2 (4.7%)	11 (31.4%)	**0.002**‡
Major complication	7 (9.0%)	1 (2.3%)	6 (17.1%)	**0.041**§
Mortality	3 (3.8%)	0 (0.0%)	3 (8.6%)	0.086§
Length of stay (days)*	6 (6-7)	6 (6-7)	7 (6-9)	0.099†
Operation time (min.)*	158 (120-190)	155 (123-195)	160 (123-188)	0.948†
Estimated blood loss (mL)*	100 (60-140)	100 (50-150)	90 (60-120)	0.522†

*Reported as median (IQR).
†Mann-Whitney U test.
‡Chi-square test.
§Fisher's exact test.
In bold: values when a patient is sarcopenic, which increases the likelihood of experiencing all types of complications, including those classified as Clavien-Dindo grade I-II, not just major complications.

was higher in sarcopenic patients (31.4% vs. 4.7%, p = 0.002). In addition, the rate of major complications (≥ grade 3) was also found to be higher in sarcopenic patients (17.1% vs. 2.3%, p = 0.041). After adjusting for age, gender, ACCI, stage of disease and mGPS, sarcopenia was associated with an increased risk of complications (adjusted OR: 10.56, 95% CI: 1.91-58.34, p = 0.007). However, this increased risk was not statistically significant in the risk of major complications (adjusted OR: 7.22, 95% CI: 0.74-70.18, p = 0.088).

High mGPS was found to be associated with increased mortality risk. While no mortality was observed in 39 patients with low risk according to mGPS, mortality was observed in one (3.2%) of 31 patients with medium risk and two (25.0%) of 8 patients with high risk (p = 0.012). In addition, mortality was not observed in non-sarcopenic patients, whereas mortality was observed in three (8.6%) patients with sarcopenic, but the difference was not statistically significant (p = 0.086).

Length of stay

The median length of stay was 6 (6-7) days. No correlation was found between stage of disease, obesity status, ACCI and ASA scores, and length of stay (p = 0.867, p = 0.322, p = 0.549, p = 0.467, respectively). Patients with a low mGPS had a shorter hospital stay than those with a moderate or high score [6 (5-7) days vs. 7 (6-8) days, p = 0.011]. The hospital stay was longer in sarcopenic patients, but the difference was not statistically significant [7 (6-9) days vs. 6 (6-7) days, p = 0.099].

Operation time and estimated blood loss

The median operative time was 158 (120-190) min. No statistically significant correlation was found between the duration of the operation and the stage of disease, obesity status, ACCI, ASA score, mGPS, and sarcopenia (p > 0.05). The median estimated blood loss was 100 (60-140) mL. No statistically significant correlation was found between the estimated blood loss and disease stage, obesity status, ACCI, ASA, mGPS, and sarcopenia (p > 0.05).

Discussion

Colorectal cancer-related mortality rates are gradually decreasing in the United States and many western countries[23]. Early detection of the disease with screening programs, improved surgical techniques, and neoadjuvant and adjuvant treatments have significantly increased the survival time. However, mortality rates continue to increase, especially in Eastern Europe, and central and South American countries[24]. Surgical resection is the only known curative treatment for colorectal cancer, which is still a major problem all over the world. Surgical resection, on the other hand, is not innocent. Mortality and complications may develop after colorectal cancer surgery, as in any surgery. While morbidity rates can reach up to 35% in colorectal cancer surgery, mortality rates have been reported between 1% and 16.4%[25]. Predicting who may

develop complications and recognizing and treating them earlier may positively affect survival outcomes.

Sarcopenia differs from cachexia, which is characterized by decreased BMI and weight loss in cancer patients and indicates muscle mass loss[26]. It is an early diagnostic component and an indicator of nutritional status[27]. Sarcopenia can also be observed in obese patients, as it is an indicator of muscle mass loss, not weight loss. Sarcopenia is very common in gastrointestinal system malignancies, as in many cancer types[28]. The relationship between sarcopenia and oncological and clinical outcomes has been demonstrated in the previous studies[29-32]. As reported, sarcopenia is associated with a prolonged length of stay, increased mortality, and complication rates[33]. There are many studies that include negative medical results between colorectal cancers and sarcopenia[34-36].

Another parameter used prognostically like sarcopenia is mGPS. It was first used by Forrest et al. to predict the prognosis of inoperable lung cancer[37]. Although the ratio was used in the beginning, it was later modified and grouped[17]. Among the hemogram parameters, lymphocytes, monocytes, neutrophils, platelets, and red cell distribution width (RDW) and their ratios to each other are generally related to increased inflammatory processes. However, increased levels of CRP, which is itself an inflammatory marker, in the pre-operative period reflects an ongoing inflammatory reaction. It plays a role in the impairment of immune functions. Hypoalbuminemia is the indicator of impaired nutritional status and susceptibility to infection due to cancer. mGPS, calculated by the ratio of CRP and albumin level, is mostly preferred to predict long-term oncological outcomes and overall survival. However, in recent years, it has been reported that it may be associated with poor prognosis in the early post-operative period after colorectal cancer surgery[38].

In our analysis, we observed that sarcopenia, which we obtained from the measurements we made on the psoas muscle, was associated with complications. Early general complications are more common in sarcopenic patients. In addition, major complications were observed to be more frequent in sarcopenic patients. There was also an increased overall complication rate in sarcopenic patients in the multivariate analysis performed after adjusting for age, gender, ACCI, stage of disease, and mGPS. Therefore, care should be taken in terms of complications in laparoscopic right hemicolectomy operations to be performed in sarcopenic patients. However, sarcopenia has not been shown to influence predicting mortality. Instead of sarcopenia, mGPS should be used to evaluate mortality. mGPS is statistically significant in predicting mortality. There is an increased risk of mortality in patients with a high mGPS. While sarcopenia was superior in predicting complications, mGPS was found to be superior in predicting mortality.

No statistically significant relationship could be found between the stage of disease, obesity status, ACCI and ASA score, and complication and mortality, among the methods used in the literature for the evaluation of short and long-term outcomes. As is known, TNM staging is calculated by the extent of the tumor in the colon wall and lymph node, and the distant metastasis status. It is known that the long-term results of the disease are directly related to overall survival. We included Stages I, II, and III patients in our study. We found that staging was not associated with 30-day complications and mortality in our analysis. Another variable that we evaluated was obesity. In a study evaluating the relationship between long-term outcomes of colorectal cancer and BMI, no significant relationship was found between oncologic outcomes and BMI[3]. Since we know that cancer patients can be sarcopenic without being cachectic, we wanted to evaluate the obesity status in our study. However, we have seen that there is no relationship between short-term results and obesity status. Two of the calculations made with the comorbidities of the patients are the ASA score and ACCI. The ASA score is basically a scoring system used by anesthesiologists to determine surgical risk. ACCI, on the other hand, is a frequently used index in the literature to identify and classify comorbidities. Anemia, type 2 diabetes, hyperlipidemia, coronary artery disease, asthma, and chronic obstructive pulmonary diseases constituted most of the comorbidities in the patients included in the study. Wound healing could be impaired due to these diseases, and anastomotic leakage could increase. As a result, we would expect higher complication and mortality rates in those patients. However, we did not observe a relationship between ASA score and ACCI, which indicate comorbidity, and short-term results. We think that this is due to the fact that ASA score and ACCI are used for different purposes. Grouping and evaluating comorbidities as comorbidities that impair wound healing and those that do not impair wound healing, perhaps, would have enabled us to achieve more meaningful results. But this time, we would have evaluated the postoperative complications only on the basis of wound healing. Not evaluating cardiac, pulmonary, and all other complications would have been biased.

The secondary outcome of our study was to analyze our variables in terms of short-term outcomes other than complication and mortality. Cancer stage, obesity status, ASA score, and ACCI cannot be used predictively in the estimation of complications and mortality, as well as in the estimation of hospitalization time, operation time, and estimated blood loss. The relationship between sarcopenia, which is statistically significant in predicting complications, and mGPS, which we used to predict mortality, was first evaluated. Patients with a low mGPS and good prognosis have shorter hospital stays. In the study conducted by Xu et al., it was reported that mGPS could be used to predict long-term outcomes in colorectal cancers[39]. We aimed to evaluate short-term outcomes in colorectal malignancies. We have demonstrated that mGPS can be used to predict mortality and hospital stay. Again, in the literature, it has been shown that mGPS is associated with the length of stay of colorectal cancer patients[40]. When the relationship between sarcopenia and length of stay was evaluated, we observed that although it was not statistically significant, sarcopenic patients had a longer hospital stay.

As far as we know, it has not been evaluated before in the literature whether muscle loss, nutrition and inflammatory conditions of colorectal cancer patients will affect the operation time and intraoperative blood loss. Although van Wijk et al. previously reported that prolonged operation time is a risk factor for the development of sarcopenia[41], we aimed to evaluate the opposite of this situation in our study. However, we did not show both the sarcopenia status and the statistical relationship of mGPS with the operation time. Likewise, there was no correlation between estimated blood loss and mGPS and sarcopenia status.

There were some limitations of our study. Firstly, our study is a single-centered retrospective study. For better results, multicentric, randomized controlled trials could be preferred. In our study, only mGPS, which contains CRP, was evaluated among the inflammatory parameters. CRP alone and other parameters used in the hemogram were not included in our study. We aimed to evaluate different parameters since there were many studies of this kind in the literature before. Another shortcoming is that only laparoscopic right hemicolectomy patients were included in the study. Our study does not provide any information about other colon and rectal cancer patients. In determining our patient group in this way, we aimed to include patients who were treated more homogeneously and with standard treatment. However, this resulted in a low number of patients, and we may have caused selection bias. In addition, 36 patients who underwent laparoscopic right hemicolectomy and met other inclusion criteria, but whose data could not be reached, were excluded from the study. In this context, further studies with larger volumes will be needed. Finally, only short-term results were discussed in our study. Since the majority of our patients consist of surgeries we have performed in recent years, long-term results can be evaluated in the later stages as long-term follow-up is completed.

Our study is illuminating in terms of predicting short-term outcomes after laparoscopic surgery in right colon cancers. It is a study in which multiple different variables such as stage of disease, obesity status, sarcopenia status, mGPS, ASA score, and ACCI are evaluated together, and short-term results are investigated. In this respect, it appears in the literature as a pioneering study. Our study has shown that the mGPS and sarcopenia can be used to estimate complications and mortality. Again, to the best of our knowledge, this is a rare study that evaluates the estimation of operative time and estimated blood loss from short-term outcomes for colon cancers. We believe that it will contribute positively to the literature with these aspects. These are the positive aspects of our work.

Conclusion

Sarcopenia status and mGPS are superior to other methods in predicting early outcomes. Sarcopenia can be used in the development of complications, and the mGPS can be used to predict mortality. While increased complications are observed in sarcopenic patients, mortality is higher in patients with high mGPS. However, randomized controlled studies are needed to obtain more reliable results and to eliminate the question marks.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Application of colon leakage score in the left-sided colorectal surgery

Aplicación de la puntuación de fuga del colon en la cirugía colorrectal del lado izquierdo

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Abstract

Objective: *The study aims to apply the CLS in patients undergoing left-sided colorectal surgery.* **Method:** *Retrospective study in patients with the left-sided colorectal surgery and primary anastomosis without diverting stoma. CLS was calculated in patients, who were classified in AL and NO-AL groups. Predictive value of CLS was evaluated by receiver operator characteristic. Correlation between CLS and AL was determined. 208 patients (55% male, mean age 59 years) were included in the study.* **Results:** *Overall, AL was 7.2%. Mean CLS of all patients was 7.2 ± 3.2 (0-17). Patients with AL had a higher CLS (11.8 ± 2.3) than NO-AL patients (6.8 ± 3) (p = 0.0001). The area under the curve for the prediction of AL by CLS was 0.898 ([CI] 0.829-0.968, p = 0.0001). A CLS of 8.5 had 93% sensitivity and 72% specificity. There was a statistically significant odds ratio for CLS and AL (0.58: [CI] 0.46-0.73, p = 0.0001).* **Conclusions:** *CLS is a useful tool to predict AL in the left-sided colorectal surgery.*

Keywords: *Colorectal surgery. Anastomosis leak. Colon leakage score. Outcomes. Risk prediction.*

Resumen

Objetivo: *Este estudio tiene el objetivo de aplicar el CLS en pacientes con cirugía colorrectal de lado izquierdo.* **Método:** *Estudio retrospectivo en pacientes con cirugía colorrectal izquierda y anastomosis primaria sin estoma de derivación. Se calculó el CLS en los pacientes, los cuales fueron clasificados en los grupos con AL y sin AL.* **Resultados:** *La media del CLS de todos los pacientes fue de 7.2 ± 3.2 (0-17). Los pacientes con AL tenían un CLS más alto (11.8 ± 2.3) que los pacientes sin AL (6.8 ± 3) (p = 0.0001). El área bajo la curva para la predicción de la AL mediante el CLS fue de 0.898 (intervalo de confianza (CI) 0.829-0.968; p = 0.0001). Un CLS de 8.5 tuvo una sensibilidad del 93% y una especificidad del 72%. Además, se obtuvo un Odds Ratio con una diferencia estadísticamente significativa para el CLS y AL (0.58; CI 0.46-0.73; p = 0.0001).* **Conclusiones:** *La CLS es una herramienta útil para predecir la AL en la cirugía colorrectal del lado izquierdo.*

***Palabras clave*:** *Cirugía colorrectal. Fuga de anastomosis. Puntuación de fuga de colon. Resultados. Predicción de riesgo.*

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Introduction

Anastomotic leak (AL) is one of the most detrimental complications following colorectal surgery[1]. The incidence rate of AL has been widely reported from 3% to 27% in different series[2-5]. Risk factors for AL have been categorized as preoperative (patient/disease-specific) and intraoperative[6-8]. Significant pre-operative risk factors related to AL are male sex, high American Society of Anesthesiologists (ASA) grades, renal disease, comorbidity, smoking history, obesity, poor nutrition, and radiotherapy. Disease-specific factors may include site, size, metastatic disease, and emergency surgery. Intraoperative factors associated with AL include significant blood loss, surgery duration (> 4 h), adequate blood supply for the remaining bowel, and a tension-free anastomosis[6-8].

Despite all published data on AL risk factors and the general acceptance of these by the surgical community, accurate prediction of AL is still a difficult task[9,10]. Clinical risk assessment for AL by the operating surgeon might have a low predictive value and underestimate leakage rate[11]. In addition, the surgeon has to decide to perform a protective stoma to counteract the problem of AL. Even though a diversion stoma cannot diminish AL incidence, it can reduce the severity of AL-related morbidity[6,12,13]. Despite this, a diverting stoma can cause morbidity, discomfort, and increased health costs which cannot be ignored. Therefore, the decision to create a protective stoma should be judiciously evaluated.

The colon leakage score (CLS), was developed by Dekker in 2011, specifically for the assessment, and risk prediction of AL in the left-sided colorectal surgery[14]. The CLS is composed of 11 weighted patient and operative parameters and was calculated as a numeric score ranging from 0 to 43 (Table 1). A score of 11 of 43 was associated with a 3% risk of AL, which was the authors´ cutoff for a low- *versus* high-risk anastomosis[14]. Few studies have validated the efficacy of the CLS[15-18], thus, the clinical use of the CLS has been limited. This present study aims to apply the CLS in patients undergoing left-sided colorectal surgery to evaluate the use of the CLS for predicting AL in a third-level reference social security hospital in Mexico.

Material and methods

Study design and participants

A single-center retrospective study was designed and conducted, previous IRB approval (R-2020-3001-079), in patients who underwent left-sided colorectal surgery with primary anastomosis and no diverting stoma from January 2017 to July 2020. Left-sided colorectal surgery was defined if the patient underwent left colectomy, sigmoid resection, or rectal resection, and they were considered as a single group. Exclusion criteria were: recurrent disease (cancer), abdominoperineal resection, patients with sepsis caused by ITU that could have been counted as an AL, and incomplete data.

Patient data and outcome parameters

The CLS was calculated from data obtained from the medical record of each patient. AL was defined as a leak of luminal contents from a surgical join between 2 hollow viscera diagnosed by any of the following when clinical signs and symptoms (fever, pain, and sepsis) were present: Radiologically (radiographic enema or computed tomography with presence of leakage or collection adjacent to the anastomosis); clinically (evidence of bowel content or gas through a drain or wound); and intraoperatively in a second surgery. AL was classified as grade A: (no intervention), grade B: (active radiological intervention without surgical intervention), and grade C: (surgical reintervention) (7). Patients were classified into two groups: AL (patients who developed AL) and NO-AL (patients who did not develop AL).

Statistical analysis

Groups (AL and NO-AL) were compared using Student's t-test (continuous variables) and using Chi-square and Fisher's exact (categorical variables). The predictive value of CLS was evaluated by receiver operator characteristic (ROC) curve. The predicting ability of the ROC curve was determined by the area under the curve (AUC). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the CLS were also evaluated by ROC to calculate the statistical optimal cutoff value. An AUC of 0.5-0.7 indicates a lower predictive value, 0.7-0.9 indicates moderate predictive value and 0.9 indicates a high predictive value. Binary logistic regression analysis was performed to determine the correlation between CLS and AL with Hosmer-Lemeshow goodness of fit. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS version 25.0.

Results

A total of 248 patients who underwent left-sided colorectal surgery were identified. Forty patients were

Table 1. Colon leakage score system

Item	Score
Age	
< 60	0
60-69	1
70-79	2
≥ 80	4
Gender	
Female	0
Male	1
American Society of Anesthesiologists	
I	0
II	1
III	3
IV	6
Body Mass Index	
19-24	0
25-30	1
> 30 / < 19 or weight loss (> 5 kg/6 mo)	3
Intoxication	
None	0
Smoking	1
Alcohol (> 3 units/d)	1
Steroids (present use excluding inhalers)	4
Neoadjuvant therapy	0
None	1
Radiotherapy	2
Chemoradiation	
Emergency surgery	
None	0
Bleeding	2
Obstruction	3
Perforation	4
Distance between anastomosis and anal verge (cm)	
> 10	0
05-10 cm	3
< 5	6
Additional Procedures	
No	0
Yes	1
Blood loss (mL) and blood transfusion	
< 500	0
500-1000	1
1001-2000	3
> 2000	6
Duration of operation (h: min)	
< 2:00	0
2:00-2:59	1
3:00-3:59	2
≥ 4:00	4

excluded from the study (10 recurrent disease, 10 abdominoperineal resection, and 10 incomplete data) leaving 208 patients (138 colons and 70 rectums) who were identified and included in the study. Baseline patient characteristics, treatment, and outcomes are shown in table 2. The mean age of all patients was 59.02 ± 14.1 years with male predominance (55%). ASA II was the most common (53.8%) pre-operative anesthetic classification. Eighty patients (38.5%) had either tobacco or alcohol intake history and 42 (20.2%) had both (alcohol and tobacco) intake history. In terms of neoadjuvant therapy, 20.2% (n = 42) patients received radiotherapy, 8.2% (n = 17) chemotherapy and 9 patients (4.3%) received radiotherapy and chemotherapy. Only one patient (0.5%) underwent emergency surgery (obstruction). Most of the anastomosis (67.3%) were 10 cm above the anal verge, and the majority of the anastomosis were stapled (88%). Eighty-seven percent (n = 182) of the surgery were performed under 3 h.

The overall AL was 7.2% (n = 15) with 86.7% (n = 5) being grade C, 6.7% (n = 1) grade B, and 6.7% (n = 1) grade A. AL patients were older (68 years) than NO-AL patients (58.3 years) and had higher ASA grades (III and IV), and these differences were statistically significant (Table 2). No other statistically significant differences in any patient characteristics were noted between AL and NO-AL patients.

The Mean CLS of all patients was 7.2 ± 3.2 (0-17). Patients with AL had a statistically significantly higher CLS (11.8 ± 2.3) than NO-AL patients (6.8 ± 3) (p = 0.0001 by Student´s t-test). CLS values and AL data for all patients are shown in figure 1. The AUC (ROC analysis) for the prediction of AL by CLS was 0.898 (95% Confidence Interval [CI] 0.829-0.968, p = 0.0001). A CLS of 8.5 had a 93.3% sensitivity and 72% specificity. The PPV of the CLS was 20.5% (95% CI: 16.6-25.2%) and the NPV of the CLS was 99.2% (95% CI: 95.4-99.8%). A CLS of 11 (original cutoff) had a 53% sensitivity and 93% specificity. Binary logistic regression showed that the odds ratio for AL prediction by the CLS was 0.58 (CI: 0.46-0.73) (p = 0.0001). The Hosmer-Lemeshow goodness of fit for the regression analysis was 2.54 (Chi-square) (p = 0.9).

Discussion

Herein, we demonstrate that the CLS has a good discrimination capability in predicting AL in the left-sided colorectal surgery, where a CLS of 8.5 had 93% sensitivity and 72% specificity. A CLS of 8.5 had 99.2% NPV for AL appearance. Moreover, there was also a well-adjusted statistically significant odds ratio for CLS and AL.

Table 2. Patient, treatment, characteristics, and outcome

Item	Value (n = 208)	AL (n = 15)	NO-AL (n = 193)	p-value
Age (years) (mean ± SD)	59.02 ± 14.1	68 ± 11.9	58.3 ± 14.1	0.01*
Gender				
Female (n), %	(92) 44.2	(6) 40	(86) 44.6	0.7
Male (n), %	(116) 55.8	(9) 60	(107) 55.4	
ASA (n), %				
ASA I	(39) 18.8	(0) 0	(39) 20.2	0.0001†
ASA II	(112) 53.8	(5) 33.3	(107) 55.4	
ASA III	(51) 24.5	(6) 40	(45) 23.2	
ASA IV	(6) 2.9	(4) 26.7	(2) 1.2	
BMI (kg/m^2) (mean ± SD)	25.6 ± 4.05	27.2 ± 6.7	25.4 ± 3.7	0.3
Intoxication (n), %				
No	(86) 41.3	(3) 20	(83) 43	0.08
Yes	(122) 58.7	(12) 80	(110) 57	
Anatomic Site (n), %				
Colon	(138) 66.3	(9) 60	(129) 66.8	0.5
Rectum	(70) 33.7	(6) 40	(64) 33.2	
Etiology (n), %				
Cancer	(172) 82.7	(12) 80	(160) 82.9	0.7
Benign	(36) 17.3	(3) 20	(33) 17.1	
Neoadjuvant therapy (n), %				
No	(140) 67.3	(8) 53.3	(132) 68.4	0.2
Yes	(68) 32.7	(7) 46.7	(61) 31.6	
Emergency Surgery (n), %				
No	(207) 99.5	(14) 93.3	(193) 100	0.07‡
Yes	(1) 0.5	(1) 6.7	(0) 0	
Distance of anastomosis				
to anal verge (cm) (n), %				
> 10 cm	(140) 67.3	(9) 60	(131) 67.9	0.4
5-10 cm	(58) 27.9	(6) 40	(52) 26.9	
< 5 cm	(10) 4.8	(0) 0	(10) 5.2	
Additional procedures (n), %				
No	(180) 86.5	(12) 80	(168) 87	0.4
Yes	(28) 13.5	(3) 20	(25) 13	
Anastomosis type (n), %				
Hand-sewn	(25) 12	(3) 20	(22) 11.4	0.3
Stapled	(188) 88	(12) 80	(171) 88.6	
Blood loss (cc) (n), %				
< 500 cc	(185) 88.9	(11) 73.3	(174) 90.2	0.06‡
500-1000 cc	(23) 11.1	(4) 26.7	(19) 9.8	
Duration of operation (h: Min) (n), %				
< 2:00	(95) 45.7	(8) 53.3	(87) 45.1	
2:00-2:59	(87) 41.8	(5) 33.3	(82) 42.5	
3:00-3:59	(24) 11.5	(1) 6.7	(23) 11.9	
≥ 4:00	(2) 1	(1) 6.7	(1) 0.5	0.09
Colon Leakage Score (mean ± SD)	7.2 ± 3.2	11.8 ± 2.3	6.8 ± 3.03	0.0001*

*Statistically significant by student t test.
†Statistically significant by Chi-square.
‡Fisher's exact.
AL: anastomotic leak; ASA: American Society of Anesthesiologists; BMI: body mass index.

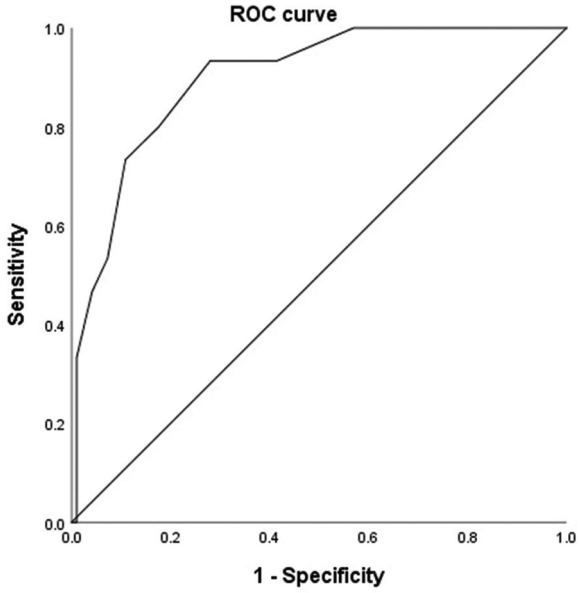

Figure 1. *Receiver operator characteristic curve for colon leakage score.*

The CLS comprises 11 variables with different weighted points. According to the score; higher ASA classification, high blood loss, and shorter anastomosis distance to the anal verge confer the most points per variable (from 0 to 6). In this sense, Dekker et al.[14] reported statistically significant differences of mean CLS and AUC when AL and NO-AL groups were compared, and an odds ratio of 1.74 (95% CI = 1.32-2.28). An in-depth examination of the results of our study reveals that the significant differences and subsequent points are given by the variables were the ASA classification and blood loss (variables with high score points) followed by age. We also had a significant difference in AL CLS versus NO-AL CLS (12 vs. 7 points) and a good AUC (close to 0.9) which was slightly lower than the results obtained in the original publication.

The purpose of a score is patient stratification. In particular, CLS might help the surgeon to define a low versus a high-risk colorectal anastomosis. This decision is critical regarding whether to perform a diverting stoma. Even though diversion stoma can reduce the severity of AL-related morbidity[6,12,13], it has been associated with perioperative mortality and longer hospitalization of patients[1,2]. Surgeons' clinical risk assessment for AL appeared to have a low predictive value in gastrointestinal surgery (< 60% both sensitivity and specificity)[11]. Therefore, it is necessary to identify an objective and accurate system that can be easily used to determine when to perform a diverting stoma. One interesting feature of the ROC analysis is the ability to choose a cutoff point, depending on the emphasis on sensitivity and specificity. The majority of the studies of CLS validation[5,14,17] have determined a cutoff value of 11 in the CLS. In this study, this cutoff (11 points) had very good specificity (> 95%) but poor sensitivity (around 50%). Our study evidences a lower cutoff value (8.5), with better sensitivity and specificity than 11 points, which might be useful to minimize the risk of AL. In addition, when regression analysis is performed, it is possible to determine risks, such as AL in this setting. Here, the odds ratio of 0.58/CLS value was statistically significant. Interestingly, the regression model had goodness of fit by Hosmer-Lemeshow test as well.

As previously stated, few studies have validated the CLS[15-18]. These studies are detailed in table 3. Several aspects should be considered when examining all these results. First; all the studies included only colorectal cancer patients but this study and Dekker's CLS study. In this study, 82% of our patients underwent surgery for cancer; thus, we decided to include patients with a benign etiology of the disease to broaden the predicting capability of the score similarly to Dekker et al.[14]. In addition; there was not enough information in the studies about patients who underwent a non-diverting stoma in addition to the colorectal surgery. It was our belief that not including patients with a non-diverting stoma, created a more homogenous study population. Another aspect is that the AL rates in all the studies (including the present one) were acceptable (< 10%), which might also work as a surrogate marker for good study outcomes. Differences in scores between AL and NO-AL patients were similar (5-6 points between studies)[15-17]. Finally, it is important to notice that the results of our study had a lower cutoff value (8.5) with one of the highest sensitivity and specificity of all studies, with a good predicting capability (AUC).

Early detection of leakage at the anastomotic site helps in the early detection, treatment, and prevention of post-operative complications, sepsis, and mortality. There are different strategies for identifying AL using different markers, including C-reactive protein (CRP), white cell count (WCC), and procalcitonin (PCT)[19-21]. CRP is being studied as a specific early protein marker for postoperative complications. Acute phase reactants are produced by hepatocytes in response to inflammatory cytokines[20]. The tendency for CRP usually increases 48 h after surgery. A steady trend showing

Table 3. Studies validating the colon leakage score

Author (year) Ref	(n)	Inclusion criteria	AL rate (%)	Mean CLS		AUC (95% CI)	Sensitivity (%)	Specificity (%)	Cut-off value
				AL	NO-AL				
Dekker et al. 2011[14]	121	Left-sided colorectal surgery	8.3	15.7	7.6°	0.95 (0.89-1.000)	n/d	n/d	11
Yu et al. 2016[15]	304	Left-sided colorectal cancer	6.9	13.8	7.75°	0.96 (091-1.00)	84.6	87.2	11
Sammour et al. 2017[16]	626	Binational Colorectal Cancer Audit database	7.2	13	8	0.8 (0.61-0.98)	n/d	n/d	n/d
Muñoz et al. 2018[17]	180	Left-sided colorectal cancer	6.6	11.5	6.9°	0.82 (0.69-0.96)	67	89	11
Yang, et al; 2019[18]	566	Left-sided colorectal cancer	4.1	12.5	9.6°	0.7 (0.61-0.78)	91.3	43.3	8.5
Present study, 2021	208	Left-sided colorectal surgery	7.2	11.8	6.8°	0.89 (0.82-0.96)	93.3	72	8.5

AL: anastomotic leak, AUC: area under curve, CLS: colon leakage score, n/d: not disclose, Ref: reference.

increased inflammatory markers, such as CRP, WCC, and PCT would suggest looking out for an AL with the clinical features[19-21]. Their levels between post-operative days 3 and 7 are carefully taken into consideration as they could be the predictor of the leak[21]. The post-operative trajectories of these inflammatory markers are very useful tools to predict AL after colorectal surgery[21]. Nevertheless; despite the usefulness of these inflammatory markers, they are postoperatively determined, as opposed to the CLS items, in which most of them are pre-operative registered and the rest of them are measured during surgery.

This study has limitations that we have to acknowledge: First, the study is a retrospective single-center with a moderate sample size for prediction, and patients were operated on by different surgical departments (colorectal surgery and surgical oncology) which might bias the procedure. In addition, due to the retrospective nature of the study, there is always the possibility that the AL rate may be underestimated (localized abscesses in a computed tomography caused by a small leak may not be counted as AL). This underestimation might have created a confusing AL low prevalence, which might have influenced the low PPV (20%). However, the NPV was superior to 99%, which means that a low CLS had a very good probability of AL absence. Although the studies on CLS have been retrospective, they have confirmed that CLS is a tool to accurately identify patients at risk for AL preoperatively, assisting surgeons in the surgical procedure through a simple score calculation from 0 to 43. Thus, optimizing this score with an adaptation of standard operating procedures could change pre-operative decision-making regarding preventive measures for a favorable postoperative outcome. Finally, a prospective comparison study between pre-operative leakage scores and post-operative inflammatory markers (CRP and PCT) could enhance AL prediction and subsequent management.

Conclusion

CLS is a useful tool to predict AL in the left-sided colorectal surgery. Further larger prospective multicenter series will continue to validate this score in our institution and other hospitals.

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Conflicts of interest

The authors declare no conflicts of interest and have no relationships relevant to the contents of this paper to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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Síndrome de *cocoon* (peritonitis esclerosante encapsulante) como causa de oclusión intestinal en un paciente con *bypass* gástrico

Abdominal cocoon syndrome (sclerosing encapsulated peritonitis) causing small bowel occlusion in a patient with gastric bypass

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Resumen

La peritonitis esclerosante encapsulada es una condición rara caracterizada por una membrana fibrótica que se genera sobre las asas intestinales causando cuadros de oclusión intestinal. Se presenta el caso de un paciente varón de 56 años con antecedente de derivación gastroyeyunal por laparoscopia que presenta oclusión intestinal. Se realizó tomografía computada que evidenció sitio de transición previo al sitio de anastomosis. Se realizó de anastomosis extensa y toma de biopsias. Histológicamente se observó engrosamiento de la membrana peritoneal, células fusiformes (D2-40 positivo en inmunohistoquímica) similares a fibroblastos con láminas de colágeno peritoneal denso. La peritonitis esclerosante encapsulada es una patología de prevalencia desconocida. El cuadro clínico es inespecífico y el diagnóstico definitivo es por patología con biopsia peritoneal.

Palabras clave: *Peritonitis encapsulante esclerosante. Laparotomía. Adherenciólisis. Cirugía de bypass gástrico.*

Abstract

A rare condition, sclerosing encapsulating peritonitis, is characterized by a fibrotic membrane forming over the bowels, leading to intestinal obstruction. In this case of a 56-year-old male patient with a history of laparoscopic gastric bypass, a computed tomography scan showed findings indicative of the condition. Extensive adhesiolysis was performed, and biopsies confirmed the presence of fusiform cells (D2-40 positive on immunochemistry) resembling fibroblasts, within dense collagenous peritoneal tissue sheets, typical of sclerosing encapsulating peritonitis. The prevalence of this condition is uncertain, and diagnosis typically requires a peritoneal biopsy due to the nonspecific clinical presentation.

Keywords: *Sclerosing encapsulating peritonitis. Laparotomy. Adhesiolysis. Gastric bypass surgery.*

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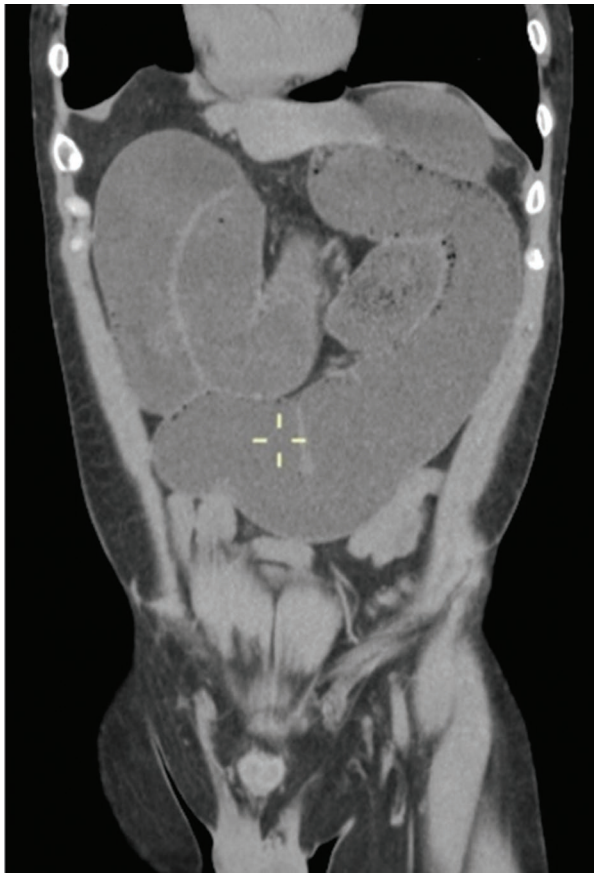

Figura 1. *Tomografía computada abdominal simple, corte coronal, que muestra dilatación importante de asas de intestino delgado sin edema de pared. Las paredes con reforzamiento a pesar de ser un estudio no contrastado.*

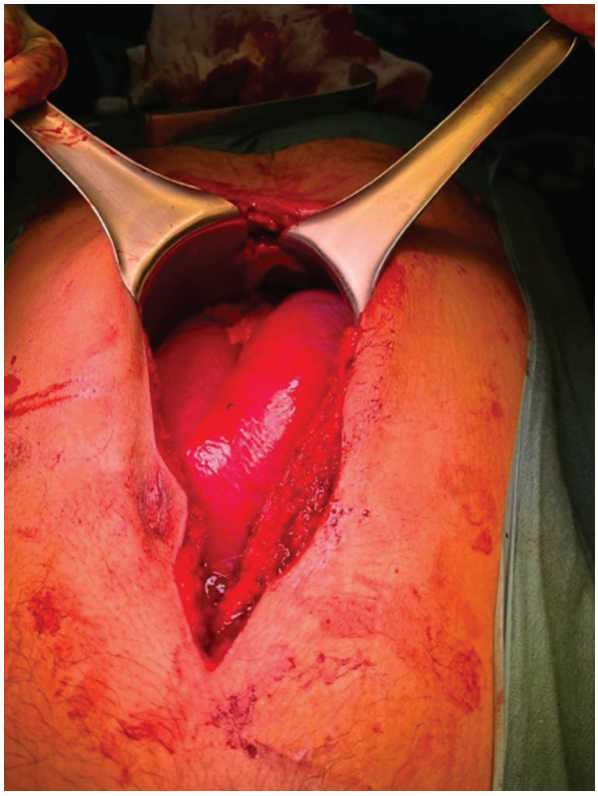

Figura 2. *Laparotomía supra- e infraabdominal en la que se observan asas encapsuladas en bloque, fijas y dilatadas. Todo esto recubierto de peritoneo visceral engrosado y adherido.*

Introducción

La peritonitis esclerosante encapsulada es una condición rara caracterizada por una membrana fibrótica que se genera sobre las asas intestinales causando cuadros de oclusión intestinal. Su prevalencia es desconocida, pero se ha reportado que en los pacientes con diálisis peritoneal es del 1.4% al 7.3%[1].

Caso clínico

Varón de 56 años, con único antecedente de obesidad mórbida y derivación gastroyeyunal por laparoscopia 2 años previos, con posterior abdominoplastia. Inició su padecimiento con dolor abdominal súbito epigástrico posterior a la ingesta de alimento, acompañado de intolerancia a la vía oral, náusea y vómito de 2 días de evolución, por lo que acudió al servicio de urgencias. Se realizaron estudios que solo destacaron proteína C reactiva de 10.3.

La tomografía computarizada simple evidenció dilatación de esófago distal, reservorio gástrico y asas de yeyuno proximal (calibre de hasta 60 mm), asociado a sitio de transición previo al sitio de anastomosis, y engrosamiento de pared (Fig. 1). Se sospechó una hernia interna y fue sometido a laparotomía, donde se encontraron asas intestinales fijas, dilatadas y rodeadas de una membrana peritoneal engrosada, provocando adherencias firmes entre asas y a la pared abdominal, involucrando solo las asas del *bypass* en Y-de-Roux (Fig. 2). Se realizó adherenciólisis extensa y toma de biopsias. El paciente presentó una adecuada evolución posquirúrgica y fue dado de alta 4 días después.

Histológicamente se observó engrosamiento de la membrana peritoneal conformado por matriz fibrosa, con células similares a fibroblastos, y abundantes vasos sanguíneos con variación en el grosor de su pared y congestivos. La capa de células mesoteliales era discontinua. Todos los fragmentos se encontraron recubiertos por material de aspecto fibrinoso. Las células fusiformes resultaron positivas para D2-40. Hallazgos microscópicos compatibles con esclerosis peritoneal encapsulante (Fig. 3).

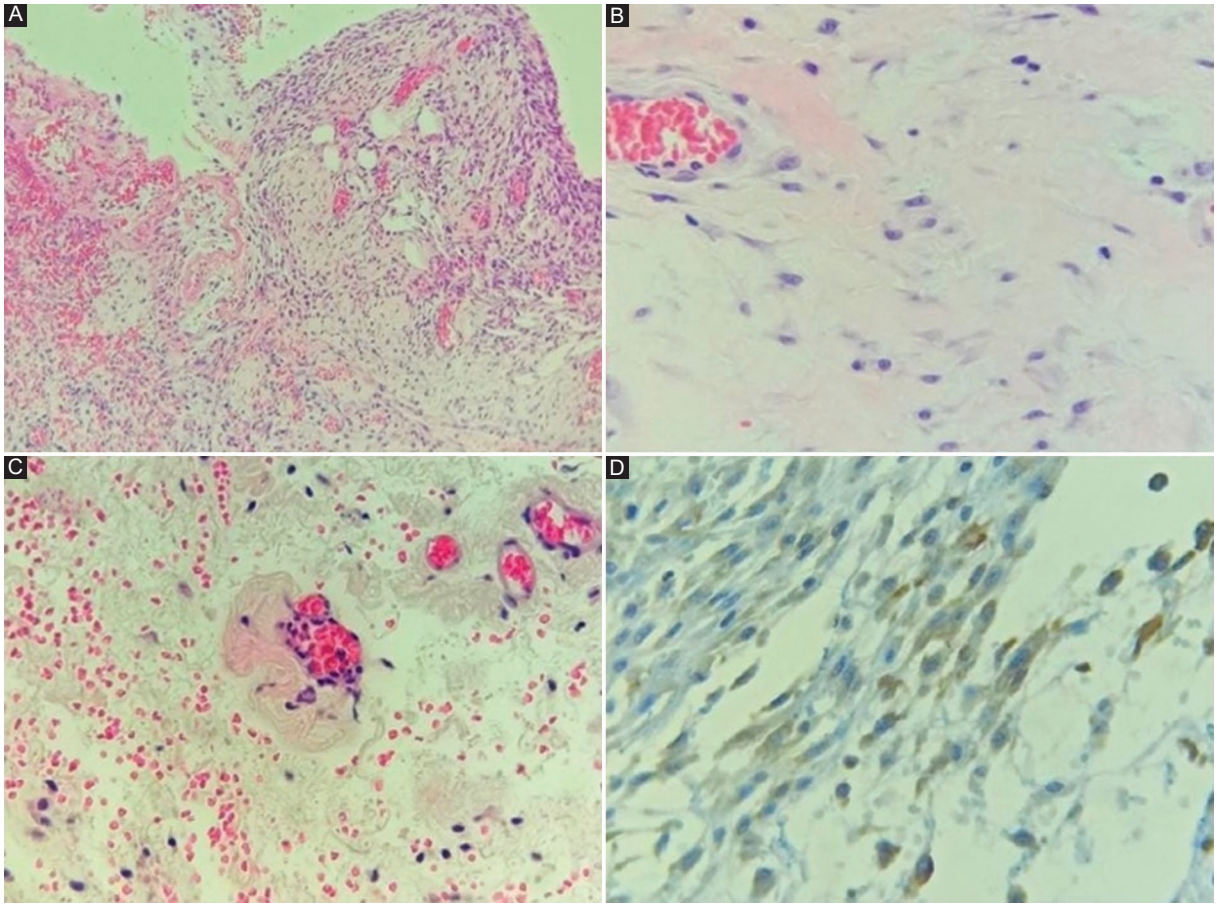

Figura 3. A: *tinción de hematoxilina y eosina, 10×. Cubierta mesotelial discontinua y de grosor variable. En la izquierda de la imagen se observa recubrimiento por material fibrinoso.* **B:** *tinción de hematoxilina y eosina, 40×. Células fusiformes similares a fibroblastos. Los núcleos con cromatina granular fina y hasta tres nucléolos pequeños.* **C:** *tinción de hematoxilina y eosina, 40×. Las paredes de los capilares con acentuada variación en su grosor.* **D:** *tinción de inmunohistoquímica para D2-40, 40×. Células fusiformes positivas.*

Discusión

Las primeras descripciones de la peritonitis esclerosante se realizaron en la década de 1970, incluido un reporte de 10 mujeres jóvenes con cuadro de oclusión intestinal agudo en las que se mostró asociación con menstruación retrógrada[2]. Se clasifica como primaria o idiopática, la cual es menos frecuente, y se postula que está relacionada con procesos virales y reacciones inmunitarias, como en los casos de menstruación retrógrada, y la secundaria con procesos crónicos irritativos en la cavidad abdominal, como diálisis peritoneal, tuberculosis, válvulas ventriculoperitoneales, peritonitis, sarcoidosis o trauma abdominal[3]. Según la extensión puede ser de tipo I con encapsulamiento parcial de asas, de tipo II con encapsulamiento completo o de tipo III con afección de asas intestinales y órganos adyacentes[4]. El cuadro clínico es inespecífico, de inicio insidioso y frecuentemente agudo, aunque también se han reportado casos de cuadros subagudos y crónicos; se acompaña de síntomas como anorexia, náusea o vómito, distensión y dolor abdominal difuso[5], lo cual en nuestro caso nos hizo pensar en causas más comunes de oclusión intestinal tras cirugía bariátrica. Los estudios de imagen utilizados, como la radiografía de abdomen, suelen arrojar resultados compatibles con oclusión intestinal, o ser normales. La tomografía computada es altamente sensible y puede mostrar engrosamiento peritoneal, aglutinación de asas intestinales y dilatación de la segunda y la tercera porciones del duodeno[6]. Si bien dichos estudios son útiles, el diagnóstico definitivo se realiza por histopatología, que puede encontrar áreas de celularidad aumentada compuesta por fibroblastos, una matriz de tejido fibroconectivo, infiltrado de células inflamatorias, mononucleares, fibrina y congestión vascular[3,7].

Braun et al.[8] propusieron las siguientes características histológicas para diagnosticar esclerosis peritoneal encapsulante histológicamente: presencia de células similares a fibroblastos, presencia de exudado, denudación de células mesoteliales, zonas acelulares, densidad de los vasos sanguíneos, variación de la pared de los vasos sanguíneos, presencia de infiltrado inflamatorio agudo y crónico, depósitos de fibrina, depósitos de hierro y expresión de podoplanina (D2-40) en células vasculares y no vasculares. De estas, la presencia de células similares a fibroblastos, la denudación de células mesoteliales y la expresión de podoplanina son las más frecuentes en los pacientes con esclerosis peritoneal encapsulante.

El manejo agudo es quirúrgico y el hallazgo transoperatorio que más se ha descrito es dilatación de asas intestinales que se encuentran recubiertas de una membrana fibrocartilaginosa con adherencias firmes entre asas, limitando el manejo a la resección de la membrana y la liberación de adherencias, así como la resección de segmentos intestinales que se encuentren con datos de isquemia o necrosis.

La tasa de recurrencia se desconoce; sin embargo, la mortalidad asociada puede llegar a ser del 35.4%, y se relaciona con complicaciones posquirúrgicas en un 7.7%[9]. Las complicaciones asociadas con la persistencia de la peritonitis esclerosante se reportan en el 18.2%[9].

En cuanto al manejo médico, se sugiere el tratamiento de la causa (cuando aplique), como el cambio de diálisis peritoneal a hemodiálisis, o el manejo de la tuberculosis en caso de que el paciente cuente con esta comorbilidad[3]. El tratamiento inmunosupresor se ha estudiado como resultado de pacientes receptores de trasplantes renales en quienes se observó mejoría del cuadro clínico. Fármacos como los corticosteroides, la colchicina, la azatioprina, la ciclosporina, el micofenolato y los inhibidores de la rapamicina se han utilizado para el manejo de esta patología, pero con resultados no concluyentes[9].

Financiamiento

Los autores declaran no haber recibido financiamiento.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido la aprobación del Comité de Ética para el análisis y publicación de datos clínicos obtenidos de forma rutinaria. El consentimiento informado de los pacientes no fue requerido por tratarse de un caso clínico.

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Shock hemorrágico secundario a pseudoaneurisma roto de arteria hipogástrica. Una complicación infrecuente de la fuga de anastomosis colorrectal

Hemorrhagic shock secondary to ruptured hypogastric artery pseudoaneurysm. A rare complication of colorectal anastomotic leakage

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Resumen

La hemorragia masiva por rotura de un pseudoaneurisma de la arteria hipogástrica es una complicación muy rara de la fuga anastomótica colorrectal. Mujer de 41 años con antecedentes de cirugía por cáncer de recto, que debutó con un cuadro de rectorragias masivo y shock hipovolémico secundario a la rotura de un pseudoaneurisma de la arteria hipogástrica como complicación tardía de una fuga de la anastomosis colorrectal. La rotura de un pseudoaneurisma de la arteria hipogástrica se debe tener presente en el diagnostico diferencial de pacientes con rectorragia masiva y antecedentes de dehiscencia de anastomosis colorrectal. La embolización endovascular es actualmente el tratamiento de elección.

Palabras clave: *Pseudoaneurisma de arteria hipogástrica. Shock hemorrágico. Fuga de anastomosis colorrectal.*

Abstract

Massive bleeding due to rupture of hypogastric artery pseudoaneurysm is an exceptional complication of colorectal anastomotic leakage. A 41-year-old woman with history of rectal cancer surgery, who debuted with massive rectorrhagia and hypovolemic shock due to rupture of a hypogastric artery pseudoaneurysm as a late complication of a colorectal anastomosis leak. The ruptured hypogastric artery pseudoaneurysm should be taken into account in the differential diagnosis of patients with massive rectorrhagia and history of colorectal anastomosis leak. Endovascular embolization is considered the first-line treatment.

Keywords: *Hypogastric artery pseudoaneurysm. Hemorrhagic shock. Colorectal anastomosis leak.*

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Introducción

Los pseudoaneurismas son lesiones vasculares resultado de la rotura completa de todas las capas de la pared arterial y de la extravasación de sangre en los tejidos circundantes, cuya pared está formada por las estructuras vecinas. Dentro de ellos, los pseudoaneurismas de la arteria hipogástrica son raros y suelen ser secundarios a traumatismos, infecciones o causas iatrogénicas. Reportamos el caso de una paciente que debutó con un cuadro de *shock* hipovolémico por rotura de un pseudoaneurisma de la arteria hipogástrica como complicación tardía de una fuga de anastomosis colorrectal.

Caso clínico

Mujer de 41 años, sin antecedentes médicos de interés, intervenida de resección anterior de recto con anastomosis colorrectal e ileostomía de protección por adenocarcinoma de recto T4N0M0, tras haber recibido quimioterapia y radioterapia neoadyuvante. A los 2 años de seguimiento comenzó con un cuadro de dolor neuropático en la región presacra de difícil control, diagnosticándose, mediante tomografía computarizada (TC) con contraste rectal, de fuga de la anastomosis colorrectal. Se realizó tratamiento quirúrgico con drenaje transanal y antibioticoterapia, con mejoría clínica y resolución de la colección sacra. Tres meses más tarde, la paciente acude a urgencias con un cuadro de rectorragias masivo de 24 horas de evolución. En la exploración física presentaba una presión arterial de 85/50 mmHg y una frecuencia cardiaca de 130 latidos por minuto, y en el tacto rectal se evidenciaron múltiples coágulos en la ampolla rectal. Dada la inestabilidad hemodinámica, se llevó a cabo resucitación con volumen y se realizó una angiotomografía (angio-TC), que informó de una arteria hipogástrica derecha de paredes muy irregulares, sugestivo de pseudoaneurisma, con extravasación de contraste, que se proyectaba medialmente hacia una colección de 37 × 46 × 30 mm (AP × T × CC) a nivel presacro y adyacente a la anastomosis (Fig. 1). Tras estos hallazgos se realizaron una arteriografía (Fig. 2) y una embolización con cianoacrilato desde el origen de la arteria hipogástrica derecha hasta la zona distal del pseudoaneurisma (Fig. 3). Las series de control no mostraron puntos de sangrado activo. La paciente evolucionó de manera favorable y fue dada de alta a los 5 días. No se registraron nuevos episodios de sangrado durante el seguimiento radiológico posterior (Fig. 4).

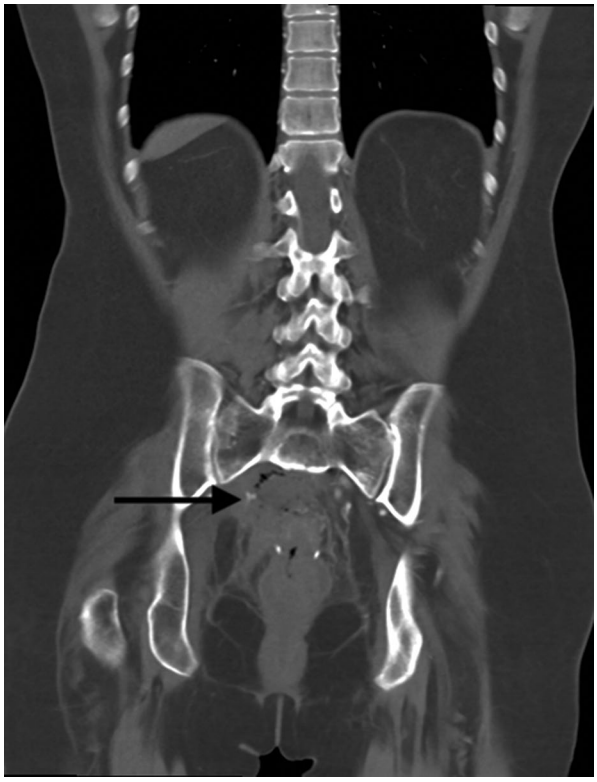

Figura 1. *Pseudoaneurisma con densidad contraste (flecha).*

Discusión

Los pseudoaneurismas de la arteria hipogástrica son muy poco frecuentes, apenas descritos en la literatura y con una incidencia desconocida. El principal mecanismo etiológico son los traumatismos, seguidos de las complicaciones iatrogénicas por procedimientos endovasculares o cirugías pélvicas[1]. Las infecciones crónicas, los trastornos del tejido conectivo, las vasculitis y la erosión secundaria a malignidad también pueden estar implicados en su formación[2]. En nuestro caso, el desarrollo del pseudoaneurisma fue por la erosión de la pared arterial en contacto con la zona de fuga anastomótica.

Los factores de riesgo de dehiscencia de anastomosis tras resección anterior de recto son el sexo masculino, el índice de masa corporal >25 kg/m^2, un riesgo ASA (American Society of Anestesiologist) > 2, la quimioterapia preoperatoria, un tamaño tumoral > 5 cm, un tiempo operatorio más largo, el uso de múltiples líneas de grapado, la transfusión intraoperatoria y la realización de anastomosis bajas. El nivel de estadiaje TNM no se relacionó como factor de riesgo[3].

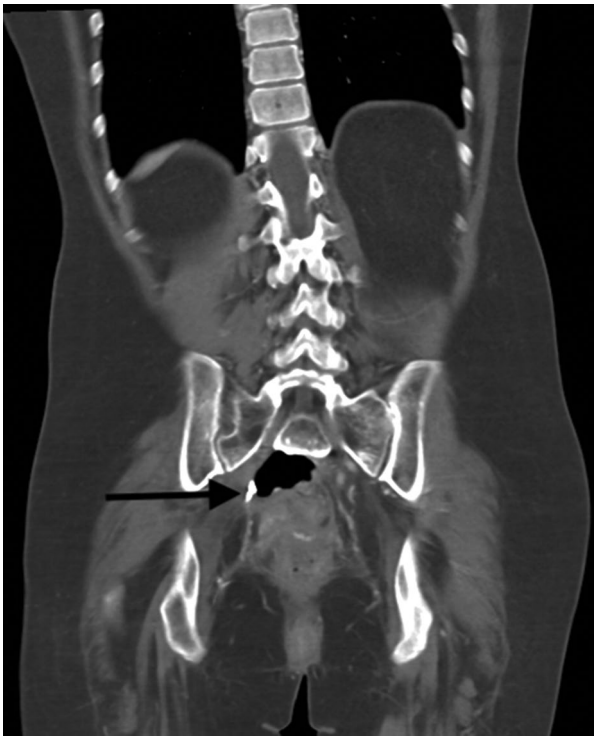

Figura 2. *Ilíaca derecha con densidad pegamento (flecha).*

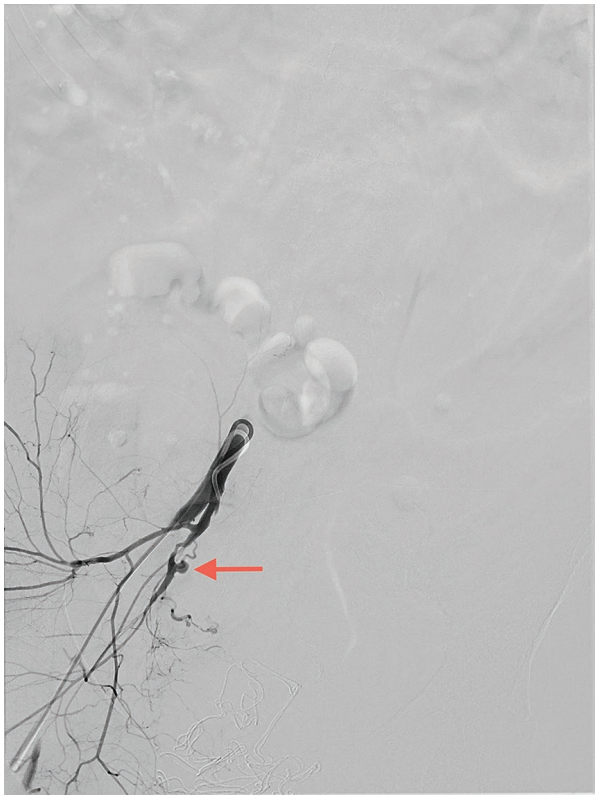

Figura 3. *Arteriografía con pseudoaneurisma de la arteria hipogástrica (flecha).*

La forma de presentación más habitual es el hallazgo incidental sin asociarse a ninguna sintomatología, pero pueden aparecer signos y síntomas derivados de la compresión local hasta en el 43% de los casos[4]. La rotura ocurre en el 33-40% de los casos. Su localización en la pelvis puede dificultar la identificación durante la exploración física. En estos casos, el cuadro clínico se caracteriza por dolor abdominal súbito asociado a hipotensión arterial, y la mortalidad es elevada, entre el 30% y el 50%[5].

El diagnóstico se basa en las técnicas de imagen, entre las que destacan la ecografía Doppler, la angio-TC, la angiorresonancia magnética y la arteriografía[5,6]. La ecografía Doppler es una prueba no invasiva, pero puede presentar limitaciones por la profundidad de las arterias en la pelvis o la interposición de gas intestinal[5]. La angio-TC es el método de referencia, ya que no solo permite confirmar el diagnóstico, sino también valorar las características morfológicas del pseudoaneurisma, que determinarán el tipo de tratamiento a realizar[5,6].

La terapia endovascular es actualmente de primera elección para el tratamiento de los pseudoaneurismas arteriales y se usa como una alternativa al manejo quirúrgico. Chemelli et al.[7], en su serie de tratamiento endovascular de aneurismas aislados de la arteria ilíaca, informaron una tasa de éxito técnico del 90.1%

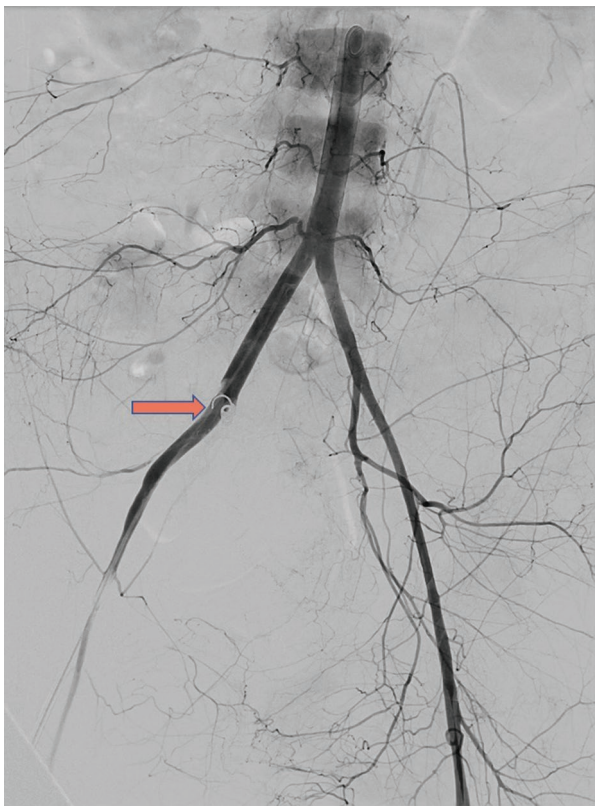

Figura 4. *Pseudoaneurisma hipogástrica derecha excluido (Flecha).*

y una tasa de éxito clínico del 93.4%. Por lo tanto, los buenos resultados intraoperatorios y posoperatorios tempranos, así como los resultados duraderos a medio plazo, confirman que la terapia endovascular es hoy en día el tratamiento de primera línea de los pseudoaneurisma de la arteria hipogástrica[8].

Existe una gran variedad de agentes embolizantes, que se pueden clasificar en función de su tiempo de acción en temporales y permanentes. Dentro de los permanentes, los más usados son los *coils* de platino blando, el cianocrilato y el Onyx®; estos dos últimos son agentes líquidos muy usados en las embolizaciones arteriales distales[9].

Como conclusión, el caso presentado es una complicación muy rara de una fuga de anastomosis colorrectal. Con este, solo son dos los casos reportados en la literatura hasta la fecha actual[10]. No obstante, recomendamos tener un alto grado de sospecha ante pacientes con antecedentes quirúrgicos de dehiscencia de anastomosis y cuadro de rectorragia masivo, ya que la demora en el diagnóstico se asocia a un mal pronóstico y una mayor mortalidad. Afortunadamente, en nuestro caso, el rápido diagnóstico y el oportuno tratamiento condujeron a un buen resultado.

Financiamiento

Los autores declaran no haber recibido financiamiento para este estudio.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de la paciente referida en el artículo. Este documento obra en poder de la autora de correspondencia.

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CLINICAL CASE

Unusual neonatal case of superior mesenteric artery syndrome with Meckel's diverticulum and literature review

Caso inusual neonatal de síndrome de la arteria mesentérica superior con divertículo de Meckel y revisión de la literatura

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Abstract

Superior mesenteric artery syndrome (SMAS) is a rare cause of duodenal obstruction which is characterized by compression of the duodenum due to narrowing of the space between the superior mesenteric artery and aorta. Incomplete duodenal obstruction due to SMAS in neonates is rarely reported in the literature. In this case, it is a full-term 2-day-old male with the complaint of recurrent vomiting starting soon after birth. The patient was diagnosed with SMAS and duodenoduodenostomy was performed. Accompanying Meckel's diverticulum was excised.

Keywords: *Duodenal obstruction. Newborn. Superior mesenteric artery syndrome. Vomiting.*

Resumen

El síndrome de la arteria mesentérica superior (SMAS) es una causa rara de obstrucción duodenal que se caracteriza por la compresión del duodeno debido al estrechamiento del espacio entre la arteria mesentérica superior y la aorta. La obstrucción duodenal incompleta por SMAS en recién nacidos rara vez se informa en la literatura. En este caso se trata de un varón de 2 días nacido a término que presenta vómitos recurrentes desde poco después del nacimiento. El paciente fue diagnosticado de SMAS y se le realizó duodenoduodenostomía. Se extirpó el divertículo de Meckel que lo acompañaba.

Palabras clave: *Obstrucción duodenal. Recién nacido. Síndrome de la arteria mesentérica superior. Vómitos.*

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Introduction

Superior mesenteric artery syndrome (SMAS), also known as aortomesenteric duodenal compression, cast syndrome, chronic duodenal ileus, or Wilkie syndrome, was first described in 1861 based on an autopsy case by Von Rokitansky[1]. David Wilkie published the largest series of 75 patients in 1927, made a detailed clinical and pathophysiological description, and recommended treatment approaches; hence, it is also called Wilkie Syndrome[2]. Cast syndrome was used by Dorph in 1950[3]. Finally, it was named as SMAS by Kaiser et al. in 1960[4].

SMAS is one of the rare causes of upper gastrointestinal tract obstruction. It is characterized by the narrowing of the space between the superior mesenteric artery (SMA) and the abdominal aorta causing compression of the third segment of the duodenum. Although the exact prevalence of the disease is unknown, its incidence is estimated to be between 0.1% and 0.3%. The SMAS occurs in adolescents and mostly young adults between the ages of 10 and 39 years, but can ultimately occur at any age. It is observed 3:2 more frequently in females than in males. An ethnic predisposition has not been described, but familial cases have been reported[5,6]. Patients usually present after orthopedic surgical procedures or acute weight loss due to hyperthyroidism, anorexia nervosa, or gastroenteritis. Symptoms typically consist of chronic intermittent abdominal pain, vomiting (sometimes bilious), nausea, early satiety, and anorexia[7]. In neonates and infants, SMAS is extremely rare and presents as a rare cause of feeding intolerance or incomplete duodenal obstruction. The diagnosis of SMAS is usually confirmed by upper gastrointestinal radiography, but can also be diagnosed by computed tomography or diagnostic laparotomy/laparoscopy.

Ethical approval

Ethical consent was obtained from the patient's family for the publication of the medical case and accompanying images. The ethical consent form was archived by the first author of this article.

Case presentation

A 3065-g male baby was born at 38 + 3 gestational weeks from a healthy 31-year-old mother with gravida 2 and 1 abortion. He was admitted to our hospital on the 2nd postnatal day due to recurrent bilious vomiting soon after delivery. There were no abnormalities on his prenatal follow-up. On physical examination, the abdomen was mildly distended, there was no tenderness, and no mass was noted. Bowel sounds were normoactive. Other systemic examinations were normal. The patient was followed up with an orogastric tube and had 13 cc/h of bilious fluid. All laboratory tests were normal. Antibiotic treatment was started empirically in terms of neonatal sepsis. The abdominal ultrasound was normal. The patient's complaints persisted and therefore an upper gastrointestinal series with contrast was performed. A stenosis in the third part of the duodenum and marked dilatations in the second and first parts of the duodenum were observed (Fig. 1). The late babygram revealed passage of the contrast material to the colon (Fig. 2).

Diagnostic laparotomy was performed since the patient did not improve clinically. The patient was examined for duodenal stricture, and external compression, especially the duodenal web and annular pancreas. It was found that the duodenum was trapped under SMA and this segment was stenotic (Fig. 3). In addition, Meckel's diverticulum was detected incidentally and excised (Fig. 4). The ligament of Treitz was examined and the position was found normal. After meticulous dissection of the duodenum, the stenotic segment was excised and duodenoduodenostomy was performed. A penrose drain was left in place.

Following the operation, the patient was admitted to the neonatal intensive care unit, and total parenteral nutrition and antibiotherapy were redefined. Defecation occurred on the post-operative 2nd day. Minimal enteral feeding was initiated on the 5th post-operative day orally. The patient gained weight and was discharged on the post-operative 14th day.

Discussion

Intestinal obstructions either partial or complete occur approximately one in 1500 live births. Among the rarest cases, SMAS is characterized by the obstruction of the duodenum beneath the SMA causing gastroduodenal dilatation[8]. Predisposing factors leading to a reduction in the angle between the SMA and the aorta resulting in SMAS include diseases associated with significant weight loss with loss of peritoneal and mesenteric adipose tissue responsible for the cushion effect, acute or prolonged trauma, spinal disease or deformity, peritoneal adhesions due to inflammation or thickening of the mesenteric root[7].

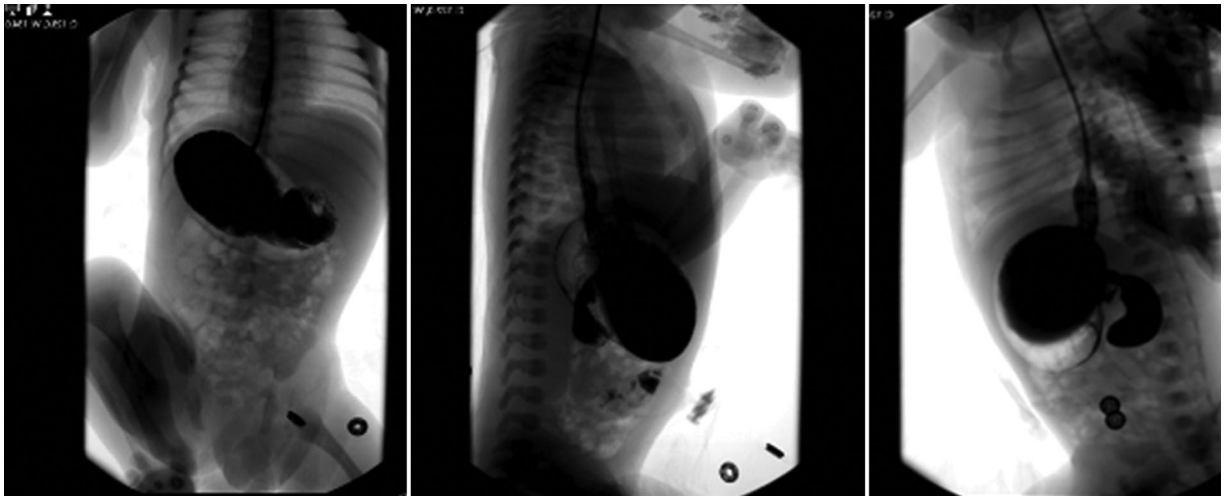

Figure 1. *Upper gastrointestinal system series, obstruction in the 3rd portion and dilatation in the 1st and 2nd portions of the duodenum.*

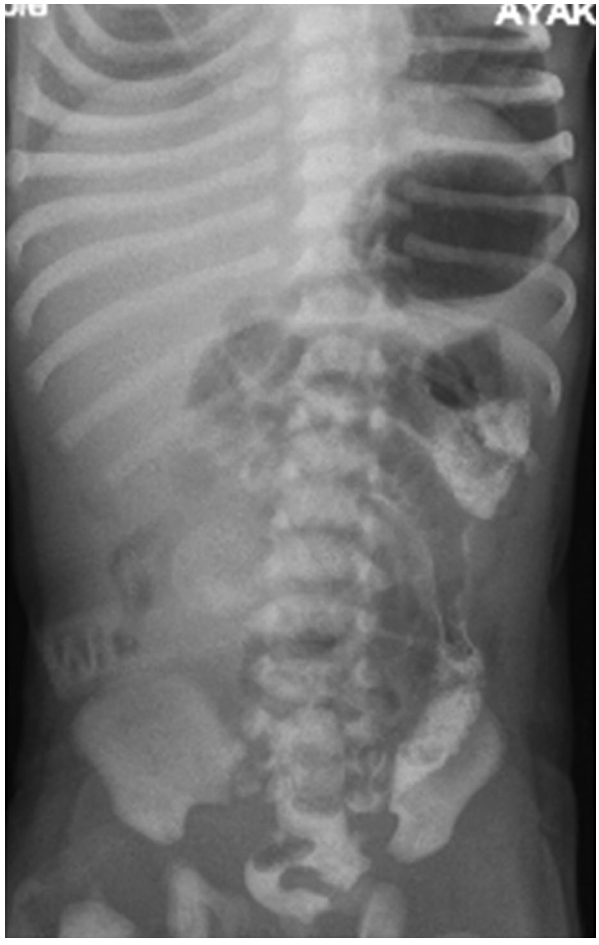

Figure 2. *The babygram performed 6 hours after the administration of contrast agent. Passage of the contrast material beyond the 3rd portion of the duodenum.*

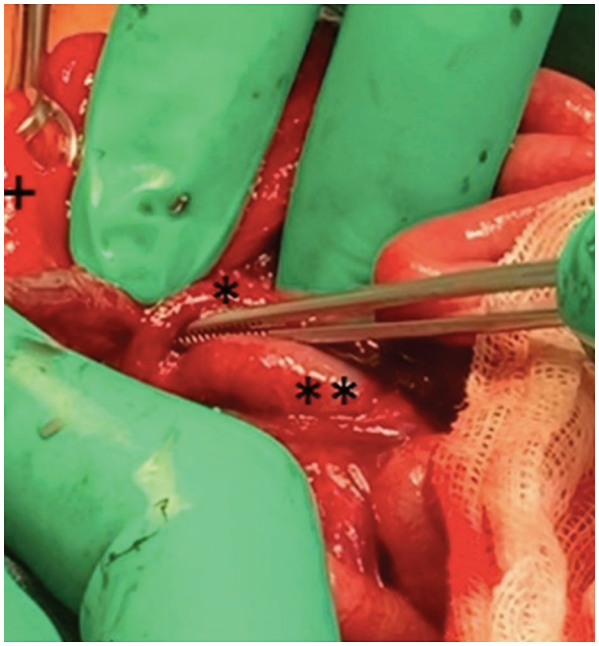

Figure 3. *During the operation, it was observed that the superior mesenteric artery passed over the third portion of the duodenum and caused duodenal obstruction (+: proksimal part of duodenum, *: superior mesenteric artery, **: third portion of the duodenum).*

There are only two familial case series in the literature. The first case included a mother and her daughter; the second included a father and his four daughters[9].

SMAS should be distinguished from the SMA-like syndrome, in which the pressure exerted on the duodenum from SMA is secondary to the duodenal dilatation. The variant with normal aortomesenteric angle and reduced aortomesenteric distance may be associated with diminished mesenteric venous drainage[10].

Table 1. The reported data of superior mesenteric artery syndrome in neonates

No	Author/year	Age at diagnosis	Sex	Symptom	Surgery
1	Caspi et al./2003	0 day (prenatal)	Female	Polyhydramnios is, bilious vomiting	Divided Treitz, stricturoplasty for duodenal stenosis
2	Sözübir et al./2006	1 day	Female	Bilious vomiting	Duodenojejunostomy
3	Mosalli et al./2011	7 days	Male	Abdominal distension, feeding intolerance, deterioration after diarrhea	Divided Treitz
4	Our case	2 days	Male	Feeding intolerance, bilious vomiting	Duodenoduodenostomy

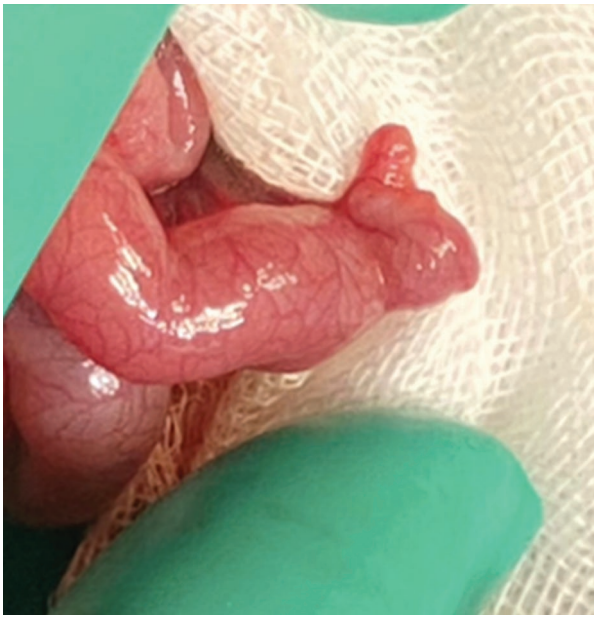

Figure 4. *Meckel's Diverticulum.*

SMAS has been described mainly in adults and rarely in children, but neonatal SMAS is extremely rare. Few cases in infancy and only four neonatal cases including this case have been documented in the literature (Table 1). All these neonatal cases were presented with bilious vomiting and incomplete bowel obstruction soon after birth[7,11,12]. The third case is a newborn SMAS which was provoked after an attack of diarrhea[12]. Clinical signs include gastric enlargement, nausea, and vomiting (may contain bile), aggravated by feeding. The main symptoms in the newborn are vomiting and poor weight gain.

SMAS can be difficult to diagnose and is usually diagnosed by exclusion or laparotomy. Radiological features suggestive of SMAS are enlargements of the proximal part of the duodenum and stomach on plain abdominal radiography. On upper gastrointestinal contrast series, obstruction in the third part of the duodenum, significant delay of gastroduodenal passage by 4-6 h, retrograde movement of contrast agent may be observed. Postural change, left lateral, or prone positioning may resolve the obstruction. In cases with complete obstruction, polyhydramnios, and double bubble signs like duodenal atresia can be detected on prenatal ultrasonography[9].

Contrast-enhanced abdominal computed tomography determines the anatomic location of the obstruction site and the angle formed by the SMA and the aorta. Magnetic resonance angiography is also useful for measuring the aortomesenteric angle. Fiberoptic endoscopy is effective in distinguishing intraluminal causes of occlusion if it can be passed through the obstruction[7].

There are two main goals of surgical treatment; either bypassing the obstruction site or duodenal release from the compression. It is known that persistent pain and blind loop syndrome may be observed in duodenojejunal bypasses while iatrogenic malrotation and entrapment may complicate the lysis of the ligament of Treitz[13]. Unfortunately, considerably high failure rates of these procedures provoked us to think of a way to preserve the duodenal function and anatomy while preventing blind loop and re-entrapment. In this case, we preferred to perform end-to-end duodeno-duodenal anastomosis to prevent any long-term complications. The meticulous freeing of the duodenum and the anastomosis went well and both the duodenum and SMA appear fine after 1 year of post-operative evaluation. The patient is thriving.

Conclusion

Although extremely rare in neonates, SMAS should be considered in cases presenting with obstructive

upper gastrointestinal symptoms. Delayed diagnosis will result in prolonged hospital stay and delay in feeding. While duodenoduodenostomy appears as a promising technique, more data is needed further.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The first author (not corresponding author) of article is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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Zidovudina, una breve historia antes del primer antirretroviral en México

Zidovudine, a brief history before the first antirretroviral in Mexico

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Resumen

En el México de la década de 1980, el de la «renovación moral», se vivió la apertura al mercado y la manifestación del virus de la inmunodeficiencia humana (VIH) y el sida. En este escrito se relatan las condiciones históricas y terapéuticas del síndrome en los pacientes mexicanos, hasta la llegada del primer antirretroviral. Se trata de una reconstrucción de los hechos, de los cuales se ha profundizado en aspectos médico-sociales, principales manifestaciones clínicas y terapéutica farmacológica, hasta que interviene en la patogenia del VIH/sida el desarrollo de la zidovudina o azidotimidina (AZT), primer antirretroviral en ser aprobado. No obstante, en el contexto mexicano este suceso no fue determinante para cambiar de manera significativa la morbimortalidad de los infectados.

Palabras clave: *Sida. Antirretrovirales. AZT. México. Historia de la medicina.*

Abstract

In the 1980s in Mexico, that of the «moral renewal», there was the opening to the market and the manifestation of human immunodeficiency virus (HIV) and AIDS. In this writing, the historical and therapeutic conditions are related to alleviate the syndrome until the arrival of the first antiretroviral. It is a reconstruction of the events, of which the medical-social, main clinical manifestations and of course the pharmacological therapy, until de the development zidovudina or azidotimidina of AZT, the first antiretroviral to be approved. Nevertheless, in the Mexican context, this event wasn't decisive to significantly change the morbility and the mortality.

Keywords: *AIDS. Antirretrovirals. AZT. Mexico. History of medicine.*

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Introducción

El virus de la inmunodeficiencia humana (VIH) y el sida (acrónimo de síndrome de inmunodeficiencia adquirida), desde su primer reporte en 1981 en los Estados Unidos de América (EE.UU.) y hasta el día de hoy, se han convertido en una de las infecciones más estudiadas en la historia de la humanidad. Se ha generado conocimiento a través de la literatura biomédica y se ha transformado radicalmente el comportamiento sexual del ser humano.

Desde entonces, la necesidad por seguir estudiando acerca de este virus ha continuado, aunque con sus matices. En México, la población juvenil sigue siendo un foco de atención y pone de relevancia el ímpetu por disponer de narrativas que les acerquen a esta realidad histórica.

Es por ello que en este trabajo se proponga por relato las condiciones históricas y terapéuticas que, en México, permitieron atender el proceso de la inmunodeficiencia hasta la llegada de la monoterapia con el primer antirretroviral: zidovudina o azidotimidina (AZT).

La introducción del VIH/sida a México

Es 1983 y la «renovación moral» baila al ritmo de *Blue Monday* entre vaivenes de cadera de cientos de jóvenes de México. Es un momento álgido en la historia del país. En este binomio tiempo-espacio, la esfera económica tiene un arranque protagónico con Miguel de la Madrid Hurtado a la cabeza del Estado mexicano (1982-1988), allí donde persiste una aguda crisis económica marcada por factores como el incremento del gasto público y privado, la desequilibrada relación entre inflación interna y externa, y el fortalecimiento del proceso de sobreevaluación (por citar algunos).

Neoliberalismo, globalización, desregularización, libre comercio, apertura, liberalización y privatización, son palabras empleadas como *lingua franca*[1] para nombrar y describir este nuevo mundo erigido por la naciente tecnocracia mexicana en las bases de la economía que, estudiada en las principales universidades estadounidenses, está ahora en el gabinete del ya aludido Miguel de la Madrid[2].

La «McDonalización de la sociedad», entre otras cosas, no solo asegura una afluencia en la entrada y salida de mercancía a través de esta desregularización comercial, sino que también, de manera más activa, permite el tránsito de personas a espacios como EE.UU., cuna de la masificación de la cultura popular global y epicentro de la producción y consumo[3]; aspectos que, desde un punto de vista histórico y epidemiológico, serán esenciales para determinar la patogénesis del VIH/sida en México. Así como se estipula en *Diseases and Human Evolution* (2005)[4], la transformación de las sociedades antes basadas en la agricultura hacia un mundo industrializado y globalizado ha alterado de forma radical y definitiva las pautas de las enfermedades infecciosas.

Desde el 5 de junio de 1981, tras los primeros casos reportados de un extraño padecimiento en EE.UU., se hizo sonar la alarma por las autoridades sanitarias, los Centers for Disease Control and Prevention, a través de la publicación epidemiológica *Morbility and Mortality Weekly Report*. En esta, los pacientes mostraron un cuadro atípico: se trataba de cinco jóvenes, tiempo atrás sanos, de entre 29 y 36 años, del condado de Los Angeles, en California, que luego de la aplicación de estudios de laboratorio todos habían sido reactivos para neumonía por el agente *Pneumocystis jirovecii,* con infecciones por citomegalovirus y candidiasis en la mucosa; además, se estableció que dos de los cinco habían sucumbido en un periodo corto.

Ahora bien, en lo que corresponde a los índices de mortandad, desde el inicio se advirtió que una grave deficiencia del sistema inmunitario era un indicador clave (en un conteo, menos linfocitos CD4 o 200 células por milímetro cúbico, ahora CD4 < 200), ocasionando que estos inmunodeprimidos estuvieran expuestos a diversas infecciones[5].

Geográficamente, en cuanto a la diseminación del sida, al principio se creyó que este se había originado en lugares como California y luego Nueva York, puesto que ahí se dio la alarma. No obstante, gracias a las futuras investigaciones en filogenética se lograría establecer un patrón en la distribución de la naciente pandemia: en EE.UU., el VIH/sida se hizo visible en el estado neoyorkino, luego pasó a Georgia, para después estar de forma paralela en Pensilvania y California, y posteriormente en Nueva Jersey. Sin embargo, antes de haber tocado suelo estadounidense, el sida ya se encontraba presente en Haití y aún antes en el continente africano[6].

Sobre la validez de lo mencionado, ahora a la inversa, se explica que desde la naciente República Democrática del Congo, con su bullente progreso, tanto por su descolonización como por la oleada de movilizaciones de trabajadores congoleños hacia

plantaciones de caña en Haití, el virus llegó a la isla caribeña[7] y a partir de ahí, con cierta prevalencia, viajó hacia EE.UU. a través del burbujeante turismo sexual[8].

En lo que corresponde a la introducción del VIH/sida en México, hay evidencia que sostiene que se trató de una enfermedad importada, cuando los primeros pacientes mexicanos declararon haber vivido o viajado fuera del país por un tiempo, particularmente en EE.UU. En otros casos, la infección ocurrió mientras se encontraban en suelo mexicano y estos declararon haber mantenido prácticas sexuales de riesgo con turistas estadounidenses[8]. Para cualesquiera de los casos, lo que se suscitó fue algo que López y Van Broeck (2015)[9] luego explicarían en el hombre BH (bisexual y homosexual) extranjero, y es que «fuera de sus condiciones cotidianas de vida, [el viajero] se siente con mayor libertad para ampliar ciertas limitaciones sociales, físicas o intelectuales... [y en consecuencia] ver potenciada su interacción sexual...".

Fue así, *de vita et morbidus,* que las autoridades sanitarias recabaron información, algunas veces sensible, otras veces honda; lo necesario como para establecer un perfil, un patrón en la transmisión del sida en el mexicano y, como es de suponer, la actividad y la identidad sexuales formaban parte de ello. De esto y otros apuntes, en comparación con lo registrado en EE.UU., se tienen pocas investigaciones en México. Aquí, dos de ellas se sirven para el presente escrito y son fuentes primarias.

Se trataba, por lo tanto, de un perfil epidemiológico esbozado básicamente por jóvenes hombres mexicanos, con un promedio de 34.8 años, que correspondían a una clasificación económica de media a alta; poco más de la mitad se identificaron como homosexuales y en menor medida como bisexual; alrededor del 92% se encontraban solteros. En lo concerniente al lugar de residencia, hubo una mayor distribución entre Ciudad de México y luego en el Estado de México, Jalisco y Monterrey, los Estados de la República Mexicana con mayor realización industrial[10,11].

En lo que respecta a las manifestaciones iniciales más frecuentes en el síndrome, el doctor Ponce de León (2011)[11], pionero en atención con estos pacientes, rememora que eran «las de un hombre joven con pérdida de peso importante, diarrea crónica, lesiones violáceas en la piel, candidiasis bucal y neumonía con insuficiencia respiratoria».

Tabla 1. En contraste, la Secretaría de Salud y hospitales del IMSS informaron modestas diferencias en los primeros pacientes mexicanos

INCMNSZ	IMSS
Diarrea	Diarrea crónica
Pérdida de peso	Candidiasis
Fiebre	Trastornos respiratorios
Debilidad	Tuberculosis
Linfadenopatía	Linfadenopatía
Candidiasis oral	Cefalea
Anorexia	Fiebre
«Dermatitis»	«Dermatosis»
Parestesias	

IMSS: Instituto Mexicano del Seguro Social; INCMNSZ: Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán.

De fuera hacia dentro

No pasó mucho tiempo para que, a la suma de un perfil epidemiológico, más los signos y síntomas iniciales, se volviese decisiva la necesidad de disponer de pautas que guiasen presuntivamente los diagnósticos para sida. ¿Cómo? A través de un criterio de casos, más o menos homogeneizado y abrazado en los hospitales e institutos de mayor envergadura en el país. Apuntando además que, de acuerdo a las limitaciones económicas propias de la época, un diagnóstico para sida sin pruebas de laboratorio era una apremiante realidad[10].

Habrase visto en las primeras anamnesis casos como en el Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán (primero en registrar el primer caso de VIH/sida en México) y hospitales del Instituto Mexicano del Seguro Social[10,12] (Tabla 1).

En México, la atención de las manifestaciones clínicas discurrió esencialmente a través de la terapéutica con antifúngicos, antivirales y antibióticos, ya fuese como intervención terapéutica o profiláctica[10,13,14] (Tabla 2).

El primer antirretroviral

La historia del primer antirretroviral no comienza a finales de 1980, o al menos no con la intención de tratar el VIH/sida, sino que más bien data de varios años atrás, cuando en 1964, en la Wayne State University School of Medicine (ubicada en Detroit, Michigan, EE.UU.), el científico estadounidense Jerome Phillip

Tabla 2. Se observa que, debido a la falta de un medicamento efectivo contra el virus, se recurrió al uso de antibióticos, antivirales y antifúngicos para tratar las infecciones que surgieron

Manifestaciones clínicas	Agente infeccioso	Tratamiento
Candidiasis oral	*Candida albicans*	Fluconazol
Neumonía por *Pneumocystis jirovecii*	*Pneumocystis jirovecii*	Trimetoprima-sulfametoxazol/pentamidina
Tuberculosis	*Mycobacterium tuberculosis*	Isoniazida
Virus herpes simple tipos 1 y 2	Virus herpes simple	Aciclovir
Diarrea en la coinfección por VIH/sida	*Cryptosporidium* spp./*Isospora belli*	Espiramicina/trimetoprima-sulfametoxazol
Infección por citomegalovirus	*Citomegalovirus*	Aciclovir (para casos con retinitis)
Criptococosis	*Cryptococcus neoformans* var. *neoformans* y *Cryptococcus neoformans* var. *gatti*	Fluconazol
Toxoplasmosis	*Toxoplasma gondii*	Azitromicina/trimetoprima-sulfametoxazol

Horwitz, de la mano de sus colegas, había sintetizado por primera vez la droga AZT, expeditamente con el propósito de tratar los tipos de cáncer generados por retrovirus (familia *Retroviridae*), pero con resultados pobres, lo cual hizo que la AZT quedara «a la espera de la enfermedad adecuada», como dijo el doctor Horwitz.

Y así transcurrieron muchos años más para que esta situación diera entrada a uno de los más reconocidos y controvertidos actores en la historia del primer antirretroviral, el oncólogo e investigador estadounidense Samuel Broder, que para aquellos momentos se encontraba laborando para el National Cancer Institute (NCI) en Michigan (EE.UU.).

En efecto, la importancia de la irrupción del doctor Broder (un «personaje dinámico» en la efervescente historia del fármaco AZT) radica en que con él se amalgaman dos eventos importantes para generar una alianza estratégica entre industria privada y pública. Por un lado, Burroughs Wellcome (BW) se encontraba con la apertura para involucrarse en conjunto para un ensayo clínico, y por el otro se encontraba Broder, que había estado viajando por el país exhortando a diversas compañías farmacéuticas para que estas se animasen a estudiar más acerca del VIH/sida, considerando que para aquellos años la mayoría de estas se percibían recelosas y desconfiadas en el tema. Incluso, Broder llegó a instarles para que le hicieran llegar al NCI sus compuestos más prometedores.

Ascenso y caída de la AZT

Y así sucedió, tras la recomendación de la científica Jane Rideout, en conjunto con la pericia ganada estudiando tipos de retrovirus (sobre todo en fármacos antivirales), cuando la BW —ni corta ni perezosa— despachó para finales de 1984 aproximadamente 50 compuestos al equipo de Broder, todos marcados con un código de una o más letras, con la esperanza de que, en lo particular, el compuesto tras la inscripción «S» fuese el elegido. Por supuesto, esa «S» correspondía al código otorgado a la AZT mientras estuvo en el estante: 509US1. De modo que, para febrero de 1985, el equipo de Broder había marcado la AZT como la más eficaz de entre todas las muestras remitidas, y en julio de 1985 pasó de ser una investigación en probeta a su aplicación en seres humanos, con resultados que expresaban ser adecuados; a esas alturas, ya se habían confirmado casos de VIH/sida en todo el mundo.

Tales circunstancias —entiéndase tanto el clima social ante los incipientes casos tratados con AZT como el hambre de vida— sirvieron como parteaguas para el desarrollo de un nuevo ensayo clínico hacia marzo de 1986, uno que pudiese concentrar una población más extensa, aunado al desarrollo de pruebas diseñadas y dirigidas cabalmente por científicos propios de la BW, sin subestimar que se trataba del ensayo clínico que más discusión ha desencadenado por los entredichos éticos, procedimentales y económicos que desde sus entrañas se fueron generando.

Se tienen, por ejemplo, casos como que la BW no contaba con la infraestructura necesaria para llevar a cabo de forma íntegra los procesos de investigación y atención, ya que, de acuerdo con las fuentes

consultadas, esta se encontraba bajo construcción. Asimismo, se necesitaba encontrar un medicamento alternativo a la AZT, pues lo tipificado era tener otro fármaco para poder cotejar resultados; sin embargo, solo se contaba con AZT. Por tal motivo, la situación se traducía en el uso de un placebo, algo espinoso aún para la comunidad biomédica, la cual tildaría tal proposición como deshonesta; y por último, pero no menos importante, el país enfrentaba un desabasto de timidina (de ahí que el medicamento sea nombrado como azidotimidina [AZT]), materia prima para su producción, lo cual complicaba el panorama, pues las reservas mundiales resultaban insuficientes[15].

¿Cómo se fueron distendiendo tales tesituras? En el primero de los casos, se presume que la solución vino de la mano del doctor Broder, quien posibilitó la infraestructura del NCI (instancia gubernamental) para que allí se efectuasen los procedimientos necesarios. En el segundo caso, acerca del dilema por el uso de un placebo, se sabe que, sin medicamento alternativo, se mantuvo la orden de administrar esta sustancia inoperante a unos pacientes, mientras que a otros se les dio AZT. Y finalmente, con respecto al abasto de timidina, se obtuvo un desenlace favorable con el jefe de desarrollo técnico de la BW, David Yeowell, cuando declaró en 1960 que una empresa farmacéutica había producido cantidades considerables de timidina y logró que esta le surtiera a lo largo del ensayo clínico AZT. Incluso llegó a un acuerdo para que este suministro en toneladas fuese con miras hacia el futuro. Esta farmacéutica era Pfizer.

En fin, una vez reunido lo necesario, y sin ánimo de obviar las dificultades ya mencionadas, en el ensayo clínico a doble ciego se involucraron 282 pacientes en un total de 12 centros médicos en EE.UU. Entre ellos, se mostraba un perfil conformado por hombres homosexuales, casi en su totalidad caucásicos, que habían tenido cuadros de neumonía por *P. jirovecii*. Es preciso subrayar que no hubo datos que señalaran el uso de AZT en hombres latinos, aunque tampoco figuró como criterio de exclusión de la investigación.

Ahora bien, de los 282 pacientes, 145 recibieron AZT en dosis de 1500 mg y 137 recibieron el placebo, y la BW tomaba nota de lo que sucedía, en el supuesto de que ellos desconocían quién recibía qué, excepto un panel de médicos externos cuya labor era monitorear los resultados. Hasta que, de forma premeditada, el ensayo se clausuró debido a la muerte de 19 pacientes, quienes estaban consumiendo el placebo, en contraposición a aquellos que habían recibido AZT, de los que solo había muerto uno. Para estos últimos, se describió que el medicamento tuvo incidencia en tres aspectos fundamentales:

- Reducción de la mortalidad en pacientes con sida (en comparación con los que recibieron el placebo).
- Reducción de las infecciones oportunistas (especialmente neumonía por *P. jirovecii*).
- Incremento del número de linfocitos CD4.

A partir de ese momento, el tiempo de aprobación por parte de la Food and Drug Administration para que la AZT viera la luz ha sido uno de los lapsos más cortos en la historia de los antirretrovirales. Así las cosas, fue comercializada el 19 de marzo de 1987 bajo un nuevo nombre de patente: Retrovir®.

No obstante, la premura con que se aprobó el medicamento, en calidad de «alta prioridad», trajo consigo un costal de interrogantes que no se pudieron resolver para aquel momento, como los posibles efectos secundarios o los costes del medicamento. La toxicidad generaba una supresión de la médula ósea, con subsecuentes cuadros de anemia cursando con neutropenia, situaciones que los pacientes referían con síntomas como náusea, dolores de cabeza, insomnio y fatiga al inicio del tratamiento, y si llegaban a un año con este, miopatía[15,16]. De lo contrario, aseguraban, permitía un periodo de sobrevida de 21 meses, el tiempo suficiente para que los pacientes pudieran poner en orden sus asuntos.

Lo anterior sin mencionar el elevado coste del Retrovir®, que era de entre $8,000 y $12,000 dólares estadounidenses por paciente, lo que para aquel entonces fue calificado como el medicamento más caro en la historia[16]. Era una medicina prácticamente inasequible para el bolsillo común y para la cobertura de algunos sistemas de salud en el mundo.

Por todo lo dicho, y bajo mucha presión, la BW tuvo que enfrentarse a audiencias gubernamentales para tratar de reducir el costo. Nueve meses después se redujo un 20% y se explicó que tal decisión se debió a que habían bajado los costes de fabricación. Pero eso no sería suficiente para amortiguar la ira de las personas y la cobertura de los medios, pues se fueron sumando controversias que cuestionaban cada aspecto del fármaco, empezando por el ensayo clínico y sus deficiencias elementales, como el enmascaramiento de la AZT y el placebo, pues se aseguraba que los pacientes siempre supieron qué estaban consumiendo, ya fuese por el sabor, el olor o porque algunos llevaban sus píldoras a químicos para que las analizasen, lo que tiró por los suelos el tema del ensayo doble ciego[15].

Otro aspecto fue el abaratamiento y la ayuda que obtuvo la BW para hacer sus investigaciones en el NCI y el poco reconocimiento que luego dieron a los investigadores universitarios y gubernamentales (al no considerarlos categóricamente como coinventores), pero sobre todo se criticaba la forma en que se administraba el medicamento, que muchas veces era a dosis elevadas, lo cual aseguraba una compra de manera recurrente, sin tener que obviar las dificultades médicas que enfrentaban los «AZTados»[15,16].

En México, mientras tanto, la posibilidad de adquirir Retrovir® fue casi remota desde el inicio, pues se había logrado su aprobación apenas en febrero de 1990, aunque para 1988 era posible obtenerla a través de una petición escrita y expedida por la Secretaría de Salud, en la que se solicitaba la venta de Retrovir® en los laboratorios de BW o a través de involucrarse en algunos ensayos clínicos que a cuentagotas llevaron algunos institutos. Sin embargo, a decir verdad, hubo mucho escepticismo alrededor de ello, ya fuese por las luchas internas que se estaban librando en suelo estadounidense o porque se pregonaba que el fármaco era tan citotóxico que te mataba antes que el propio síndrome; inventos y creaciones propias de la imaginación de los llamados «vampiros iatrogénicos»[16]. También brillaron por su ausencia quienes tomaban decisiones en materia médica en México, quienes poco se pronunciaron y dieron espacio a la especulación y la desinformación[17]. El doctor Gustavo Terán, fundador del Centro de Investigación en Enfermedades Infecciosas, apenas comentó que el Retrovir® tenía efectos «marginales» y de «poca duración», y que la sobrevida entre los mexicanos alcanzaba solo unos 6 u 8 meses.

No pasó mucho tiempo para que luego apareciera el uso de la didanosina (ddI) como sucedáneo al Retrovir®, y luego la zalcitabina (ddC), que eclipsaría a la AZT, hasta que en 1996 llegaron desde Vancouver, Canadá, los resultados del empleo del tratamiento antirretroviral de gran actividad (TARGA), que demostraron de manera fehaciente que la combinación de tres o cuatro antirretrovirales reducía la morbimortalidad, permitía un grado de supresión del VIH y confería una mayor tolerancia; por tales motivos, es usado hasta nuestros días[18].

Conclusiones

La irrupción del VIH/sida supuso, entre todas sus vicisitudes, un avance en el ámbito biomédico. Estos progresos incluyeron tanto los intentos por explicarse la patogenia como las aspiraciones de paliar dicho mal.

Tales avances (entiéndase la terapéutica farmacológica) fueron posibles gracias a determinadas condiciones, pero otras no los favorecieron. En México, la parte económica tuvo un papel fundamental, puesto que permitió el uso de la terapéutica con antifúngicos, antibióticos y antivirales como base para el tratamiento de las manifestaciones de VIH/sida, pero no para la compra del primer antirretroviral, ya fuese por las consecuencias de las políticas neoliberales que enfrentaba el país o por el debilitamiento del Estado benefactor, pero aún más por el eminente costo de la AZT. En tal sentido, se entiende que haya resultado más funcional en términos económicos el uso de los fármacos antes mencionados.

De igual importancia fueron las pruebas realizadas en EE.UU., que no arrojaron información concluyente acerca del uso de AZT en la población latina y que dejaron un cerco de interrogantes, porque para la población caucásica fue significativa en términos de mayor sobrevida y de reducción de la morbimortalidad, en especial de la neumonía por *P. jirovecii,* la cual no era la principal causa de muerte entre los casos mexicanos.

Para concluir, es importante mencionar que la ralentización en la adquisición de AZT, y el encarecimiento de su uso en ensayos clínicos en algunos institutos, se debieron en buena parte al silencio por parte de las autoridades ante la presencia del VIH/sida en México, lo cual obstaculizó e invisibilizó la sección de una «generación perdida» que no conoció los albores del porvenir.

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CARTA AL EDITOR

Un comentario acerca de las consideraciones generales del diámetro del conducto colédoco en pacientes adultos sin patología de la vía biliar

A comment about the general considerations of the diameter of the common bile duct in adult patients without pathology of the bile duct

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Se ha estudiado con gran interés el artículo de Herrea-LeBlanc et al.[1] titulado *Diámetro del conducto colédoco por grupos de edad en pacientes adultos sin patología biliar.* Pina et al.[2] analizan el diámetro del conducto colédoco y enfatizan que, a pesar de que las muestras fueron extraídas de preparados cadavéricos, obtuvieron conclusiones muy similares a las encontradas en la literatura respecto al valor del diámetro. Describen también que el diámetro del conducto puede variar según la porción anatómica específica analizada, describiendo valores de 5.88 mm y 6.51 mm para las porciones retropancreática e intrapancreática, respectivamente. Además, señalan que estas medidas están sujetas a variaciones que puedan derivar de alteraciones o anormalidades de las estructuras adyacentes a cada porción en particular.

En contraste, Worku et al.[3] analizaron el diámetro del conducto biliar común (colédoco) teniendo en cuenta otros factores además de la edad, entre los cuales se mencionan el peso, el índice de masa corporal, la colecistectomía previa, los medicamentos y el tipo de modalidad de imagen. En sus resultados hallaron una discrepancia entre la mayoría de los datos descritos en la literatura respecto al límite superior de diámetro del colédoco, siendo este inferior a los que se mencionan en otros textos (5.9 mm).

Es preciso mencionar que existe una gran cantidad de variantes anatómicas y de factores que pueden influir y modificar el diámetro de las vías biliares, en particular del colédoco, siendo generalmente no modificables y difíciles de identificar con anticipación para disminuir el riesgo de complicaciones derivadas de intervenciones quirúrgicas. Así pues, serían de gran utilidad investigaciones futuras que permitan seguir esclareciendo qué repercusiones podrían tener estas variables sobre los procedimientos que involucren la manipulación y el contacto con las estructuras de la vía biliar.

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Cadáver humano sintético SynDaver®: un simulador 3D para la enseñanza de la anatomía y el adiestramiento quirúrgico

SynDaver® synthetic human cadaver: a 3D simulator for anatomy education and surgical training

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Sr. Editor:

La enseñanza de la anatomía humana y de las técnicas quirúrgicas ha sido siempre la base de la formación médica y del cirujano general. Desde sus inicios, el conocimiento anatómico y las destrezas quirúrgicas han estado basados en la disección de cadáveres humanos. Sin embargo, los estudiantes y los residentes de medicina y cirugía, por términos de bioseguridad, se enfrentan a un problema complejo, ya que los cadáveres humanos cada vez son más difíciles de conseguir, y aún más las piezas del sistema nervioso central, sin olvidar su difícil manejo fuera de los anfiteatros[1].

Por esta razón, se han estado fabricando simuladores que complementen la disección y el adiestramiento quirúrgico frente al uso de cadáveres humanos. Uno de estos simuladores es el cadáver humano sintético SynDaver®, de la empresa norteamericana SynDaver Laboratories, fabricado con polímeros parecidos al látex, los cuales permiten realizar procedimientos quirúrgicos como suturas, nudos quirúrgicos, disecciones, colecistectomías y apendicectomías (Fig. 1).

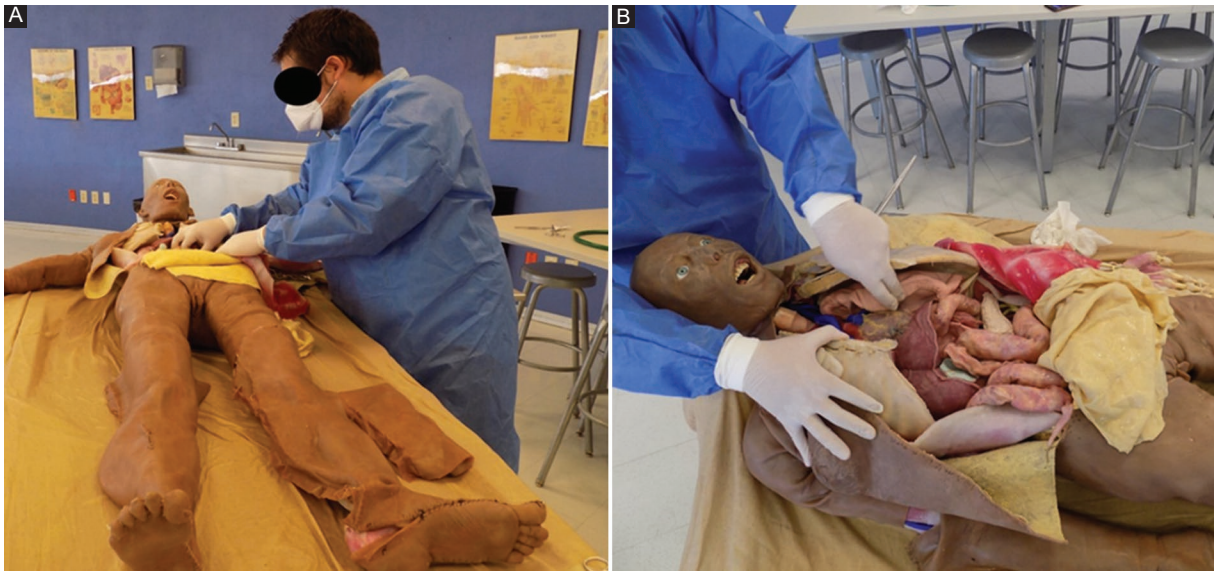

Figura 1. A: *estudiante de medicina realizando una disección en la cavidad abdominal.* **B:** *exposición de la cavidad toracoabdominal.*

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Del mismo modo, sirven para visualizar grandes vasos, músculos, órganos y diferentes planos anatómicos que permiten a los estudiantes y residentes conocer la textura y las dimensiones similares a las del cadáver fresco, en comparación con los cadáveres fijados con formaldehído, los cuales presentan modificaciones en su color y forma[2]. Por otro lado, podemos mencionar que el costo de un cadáver humano sintetico SynDaver® es de US$ 80,000. Sin embargo, es necesario tener sumergido completamente al cadáver humano sintético en agua corriente con sal de mesa común y detergente líquido para trastes, requiriendo un cambio de agua quincenal con la finalidad de conservar fresco y flácido el material con el que está fabricado[3].

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