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ORIGINAL ARTICLE

Evaluation of management of ureteroceles in our clinic: 8 years of experience

Evaluación del manejo de ureteroceles en nuestra clínica: 8 años de experiencia

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Abstract

Objective: *We aimed to investigate patients who were managed and followed up in our clinic for ureteroceles.* **Method:** *We retrospectively analyzed 52 patients' records with ureterocele diagnoses who were treated at the Pediatric Surgery Clinic of the Medical School of Dicle University between January 2009 and December 2017.* **Results:** *Of the patients 29 were female and 23 were male. Thirty-six patients had left-sided ureteroceles, 12 had right-sided ureteroceles, and four had bilateral ureteroceles. Thirty-three were intravesical and 19 were ectopically located. Twenty-seven were on a duplex system. Ureterocele was diagnosed antenatally in 12 patients and 21 in the first 6 months of the post-natal period. Ultrasonography was the most common diagnostic method. Urinary infection was the most frequent symptom (38.4%). Except for a patient who received conservative follow-up, all ureteroceles were decompressed. Vesicoureteral reflux (VUR), urinary tract infection (UTI), and renal scarring were all significantly higher in patients with the duplex system. Significantly decreased UTI rates were observed in early-diagnosed patients (p = 0.04).* **Conclusion:** *Ureterocele is still a challenging problem due to the high risk of UTI, VUR, and renal scarring. Endoscopic decompression is the most preferable intervention for ureteroceles. UTI and renal scarring could be decreased with early detection and treatment.*

Keywords: *Ureterocele. Children. Diagnosis. Management.*

Resumen

Objetivo: *Investigar pacientes que fueron tratados y seguidos en nuestra clínica por ureteroceles.* **Método:** *Analizamos retrospectivamente los registros de 52 pacientes con diagnóstico de ureterocele.* **Resultados:** *De los pacientes, 29 eran mujeres y 23 eran hombres. Treinta y seis pacientes tenían ureteroceles del lado izquierdo, 12 tenían ureteroceles del lado derecho y 4 tenían ureteroceles bilaterales. Treinta y tres eran intravesicales y 19 estaban localizados ectópicamente. Veintisiete estaban en un sistema dúplex. El ureterocele se diagnosticó antenatalmente en 12 pacientes, y 21 en los primeros 6 meses del periodo posnatal. La ecografía fue el método diagnóstico más común. La infección de tracto urinario (ITU) fue el síntoma más frecuente (38.4%). Excepto un paciente que recibió seguimiento conservador, todos los ureteroceles fueron descomprimidos. El reflujo vesicoureteral (RVU), la ITU y la cicatrización renal fueron significativamente mayores en los pacientes con el sistema dúplex. Se observaron tasas significativamente disminuidas de ITU en los pacientes diagnosticados tempranamente (p = 0.04).* **Conclusión:** *El ureterocele sigue siendo un problema desafiante debido al alto riesgo de ITU, RVU y cicatrización renal. La descompresión endoscópica es la intervención más preferible para los ureteroceles. La ITU y la cicatrización renal podrían disminuir con la detección y el tratamiento tempranos.*

Palabras clave: *Ureterocele. Niños. Diagnóstico. Manejo.*

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Introduction

Ureterocele is defined as congenital cystic dilatation of the intravesical part of the distal ureter[1]. It is frequently left-sided and is 60-80% ectopic located. Eighty percentages of ureteroceles occur with duplicated collecting systems, 10% with a single system, and 10% bilaterally[1]. The most common method for diagnosing ureteroceles during pregnancy and after birth is ultrasonography (US)[2-5]. The alternative procedures include voiding cystourethrography (VCUG), intravenous urography (IVU), and cystoscopy.

Although urinary tract infection (UTI) is the most common symptom, other conditions such as fever, poor growth, and post-natal sepsis may also occur[5,6]. Endoscopic decompression (ED) is the most preferred management method for ureteroceles in recent years despite the lack of a standard treatment protocol. However, for convenient patients, conservative follow-up is advised[7]. Reconstruction and partial/total nephrectomy are the other options (excision of ureterocele and reimplantation of lower pole ureter).

We wanted to share our institution's 8 years of experience with ureterocele follow-up and treatment.

Method

A retrospective analysis was performed on 52 patients' records who had ureterocele diagnoses and were treated at the Pediatric Surgery Clinic of the Medical School of Dicle University between January 2009 and December 2017. The patients' records were examined for age, gender, diagnostic method, age of diagnosis, and location of the ureterocele, as well as for the presence of a UTI, vesicoureteral reflux (VUR), and procedure of management. After receiving approval from the Ethical Council of Medical School of Dicle University, the trial began (permission code: 18, 05, 2018-163). Patients who had < 6 months of follow-up were disqualified.

The data were analyzed using the IBM SPSS-22 system. X^2 and Fisher Exact tests were applied. Statistical significance was defined as $p < 0.05$.

Results

Of the 52 patients, 45% were male and 55% female. Thirty-six patients had left-sided ureterocele, 12 had right-sided ureterocele, and four had bilateral ureterocele. There was a duplicated collecting system for 27 (52%) of the patients. Thirty-three ureteroceles (63.4%) were intravesical, and 19 (36.6%) were ectopically located. Forty-four patients (84.6%) had hydronephrosis noticeable.

Twelve (23%) of the patients had ureterocele diagnosed prenatally, 14 (26.9%) between the ages of 1 and 6 months, 4 (7.6%) between the ages of 6 and 12 months, and 22 (42.3%) after the age of 1 year. The average age of diagnosis was 20 months, and 7 months was the median age at the time of diagnosis.

Forty patients (76%) ureterocele was detected by US, 4 (7.6%) by VCUG, 2 (3.8%) by IVU, and 6 (11.5%) by cystoscopy.

There were no significant physical examination findings or significant pathological laboratory values, with the exception of the vulvar swelling in three patients.

UTI was significantly more frequent in patients diagnosed after 6 months than those diagnosed before 6 months ($p = 0.04$). In 18 (54.5%) of 33 intravesical ureteroceles and 7 (36.8%) of 19 ectopic-located ureteroceles, various grades of VUR were observed. The renal scar was reported in 14 of 19 ectopic ureterocele patients and 19 of 33 intravesical patients, and UTI was confirmed in 15 of 19 patients with ectopic ureterocele and 18 of 33 intravesical patients. VUR, UTI, and renal scar were all significantly higher in patients with the duplex system (Table 1).

Every patient was individually treated under the guidance of our algorithm according to their clinical condition and socio-economical-cultural features (Fig. 1).

For the initial intervention, ED was performed on 23 patients using the electrocoat (Bugbee electrode), 17 patients using laser electrodes, eight patients using resectoscope knives, and three patients undergoing open surgery. One of the three patients who underwent open surgery had a ureterocele with calculi; as a result, the ureterocele was removed, and a ureteroneocystostomy (UNC) was performed. The other patient underwent upper pole heminephrectomy and ectopic ureterocele surgery due to recurrent UTI and a non-functioning upper pole. The third patient, who was 1.5 years old, underwent UNC and ureterocele excision due to severe hydronephrosis. A patient made a cautious follow-up.

At the summary of the initial intervention, the laser's decompression rate was 82% and the Bugbee's was 91%. Twenty-three patients who underwent ED and two who underwent open surgery required secondary surgery. Eleven patients underwent UNC, four sub-ureteric injections, seven partial nephrectomies, and three total nephrectomies.

Table 1. VUR, UTI, and renal scar rates for ureteroceles on single collecting system and duplicated system

Renal collecting system type	Single collecting system		Duplicated collecting system		p
	Present (%)	None (%)	Present (%)	None (%)	
VUR	7 (33.3)	14 (66.7)	17 (63)	10 (37)	0.042
UTI	9 (42.9)	12 (57.1)	23 (85.2)	4 (14.8)	0.02
Renal parenchymal scarring	9 (42.9),	12 (57.1)	23 (85.2)	4 (14.8)	0.03

VUR: vesicoureteral reflux; UTI: urinary tract infection.

Following secondary surgery, three patients required additional surgery. These three patients underwent sub-ureteric injection for persistent VUR, double j catheterization due to hydroureteronephrosis, and cyst excision of a remnant cyst on a previous partial nephrectomy zone, respectively. The average follow-up period was 29 (6-137) months. The management and follow-up of 23 patients are still ongoing.

Discussion

The primary management goals for ureterocele are to prevent UTI and renal damage and to maintain continence[7,8].

Due to the high risk of infection, antibiotic prophylaxis is advised; some authors recommend giving it to children up to the age of three whereas others advocate waiting until they can control their micturition[9,10]. In our clinic, we advise stopping prophylaxis after the 1st year if there are no symptoms after decompression and surgical procedures, or if there is no progressive renal scar and no urinary infection.

With the widespread use in the US, 75% of ureteroceles can be diagnosed antenatally or in early infantile ages[1,11]. The majority of patients were diagnosed by the US in Chowdhary's trial, and Adorisio et al. found 76% of ureteroceles with the US[12,13]. In our study, the US usage rate was 76%, which was comparable to research findings. The other diagnostic methods used in our clinic were VCUG (7.6%), IVU (3.8%), and cystoscopy (11.5%).

VCUG is crucial for the diagnosis of ureterocele[1,14]. By virtue of VCUG which shows ureterocele with associated bladder abnormalities and VUR surgery can efficiently be planned. All of our patients with ureterocele and hydroureteronephrosis underwent VCUG, which we advise doing for that patient population. Several authors assert that ureterocele can be diagnosed using computed tomography (CT) and magnetic resonance imaging (MRI)[15]. Patients with anatomic abnormalities can undergo CT, MRI, and IVU procedures[16,17]. However, these techniques are not preferred due to high radiation exposure in CT scans and high MRI costs, as well as challenges with imaging in children and occasionally the need for anesthesia. Therefore, for any of our patients, we did not use MRI or CT.

Hodhod et al. found 39 (78%) ureteroceles on duplex systems out of 51 patients with ureteroceles in their study[18]. In our study, 40% of patients had a single system, and 52% had a duplex system. For these variable rates, we believe that more clinic data sharing is necessary. According to Hodhod et al., UTI was discovered in 41% of duplex systems and 15% of single systems[18]. In the duplex system, we also discovered notably high rates of UTI, VUR, and renal scar.

The 41-patient trial by Visuri et al. revealed high rates of UTI in ureterocele and also demonstrated decreased rates of UTI with early surgery[18]. According to Hodhod et al.[18], early ureterocele decompression and diagnosis reduce UTI and the need for secondary surgery[19]. It was discovered that delayed diagnosis and decompression led to an increased UTI. UTI was significantly more common in patients diagnosed after 6 months of birth[20,21] than in those diagnosed before 6 months[22,23]. The most popular ureterocele surgery methods are ED procedures. The primary factors determining the need for secondary surgery are the presence of VUR and UTI[1,24].

In a trial comparing ED techniques, there was no discernible difference between laser puncture and electrocautery (Bugbee) incision for decompression success, but the laser puncture group had a lower VUR rate[12,13,24-27]. According to Ilic et al., there is no discernible difference between laser and electrocautery for decompression success and complications, but electrocautery-incised groups have more VUR[25]. For ED, we primarily used the Bugbee electrode (45%) and laser

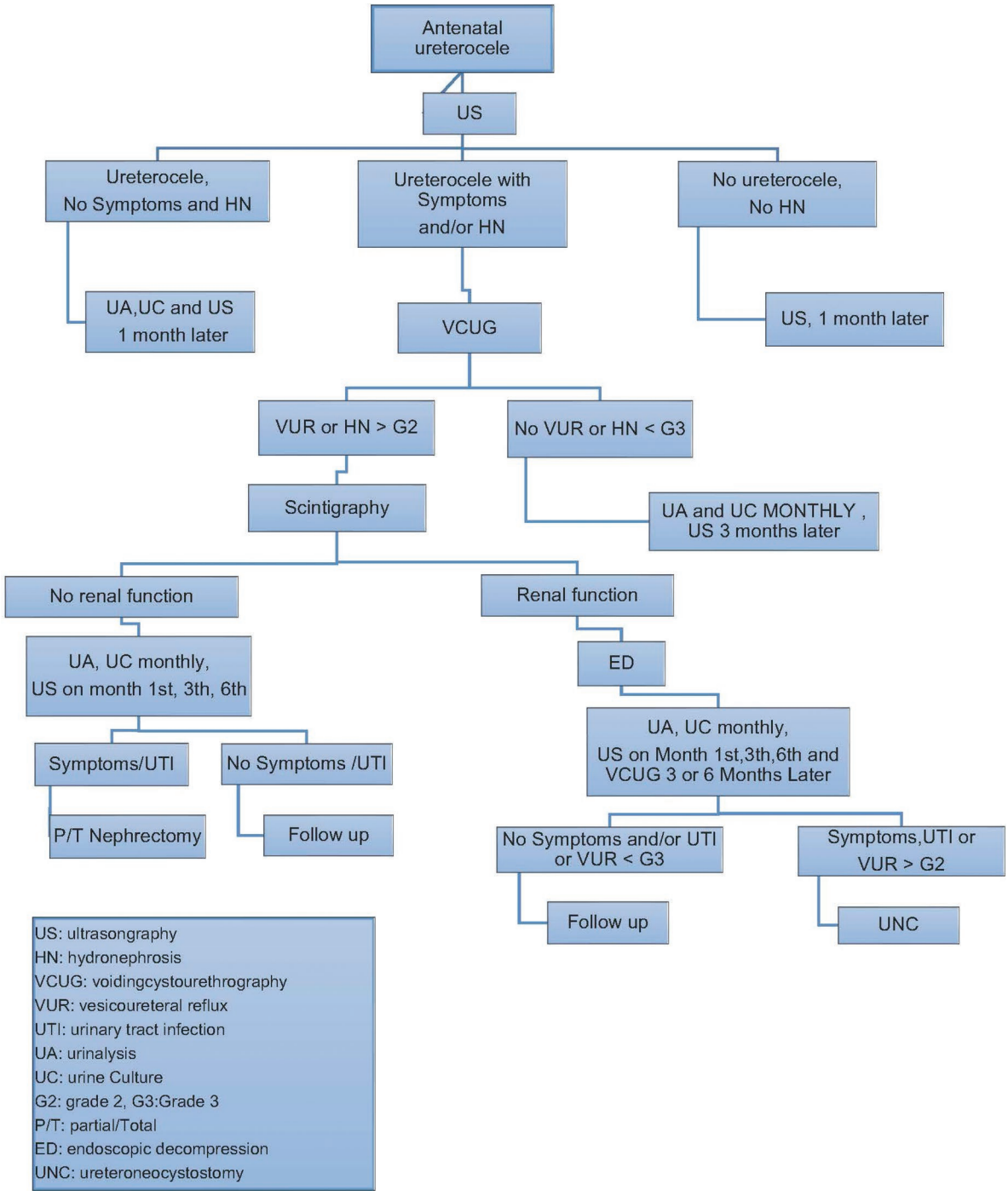

Figure 1. *Our clinics recommended a follow-up algorithm for the management of ureteroceles.*

probe (33%). Decompression success rates were 91.3% in the Bugbee and 83% in the laser, with no discernible difference. Later, decompression VUR was discovered to be 43.5% and 52.9% for laser and Bugbee, respectively. Both procedures were effective for decompression, but there were no advantages to the development of VUR. To determine the best method, we believe that more information is required.

Patients who have healthy kidney function can be treated permanently with ED as the initial procedure, with no need for additional surgery[7,26]. According to Di Renzo et al., 24 out of 45 patients did not require surgery after ED[14,27]. In our study, 52.9% of patients did not require additional surgery after ED, which is consistent with research findings.

Conclusion

Due to the high risk of UTI, VUR, and renal scarring, ureterocele continues to pose a difficult problem for patients, families, and doctors. The risk of urinary infection, VUR, and renal scarring is higher in ureteroceles in a duplex system. Each patient must be managed with an event based on their unique circumstances and clinical setting. UTI and renal scarring could be decreased with early detection and treatment. ED is still the most preferable surgical procedure, and also, we believe that conservative follow-up may be an option for convenient patients.

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No funding was received for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Clinical study of Shenqi Fuzheng decoction directional penetration for the treatment of cancer pain in advanced lung cancer patients

Estudio clínico de penetración direccional de decocción Shenqi Fuzheng para el tratamiento del dolor por cáncer en pacientes con cáncer de pulmón avanzado

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Abstract

Objective: *The study aimed at analyzing the effect of Shenqi Fuzheng Decoction directional penetration for treating advanced lung cancer patients with cancer-related pain.* **Method:** *Eighty-six cases with advanced lung cancer received in Zhoushan Hospital of Traditional Chinese Medicine from June 2022 to June 2023 were divided randomly into a study group (n = 43) and control group (n = 43). Two groups were treated with the same conservative treatment plan, on the basis of which the control group treated with placebo, and study group received Shenqi Fuzheng Decoction directional penetration treatment. The cancer-related pain intensity, analgesic onset time, the frequency of pain outbreak, and analgesic duration were assessed and recorded. Before and after treatment, the cancer-related fatigue, quality of life, and Karnofsky Performance Status (KPS) score were assessed in two groups. Moreover, the adverse reactions of two groups during treatment were recorded.* **Results:** *Compared to the control group, the cancer-related pain intensity of the study group was reduced, the analgesic onset time was shortened, the frequency of pain outbreak was reduced, and the analgesic duration was prolonged ($p < 0.05$). After treatment, Piper Fatigue Scale (PFS) scores in the study group were lower than the control group, and the generic quality of life inventory-74 (GQOLI-74) and KPS scores in the study group were higher than the control group ($p < 0.05$). During the treatment period, no significant adverse reactions were observed in both groups ($p > 0.05$).* **Conclusion:** *Shenqi Fuzheng Decoction directional penetration treatment has a remarkable effect in advanced lung cancer patients with cancer pain, which can relief the pain intensity, prolong the duration of pain relief, reduce the number of pain attacks, relieve patients' cancer-related fatigue, and improve patients' life quality and health status.*

Keywords: *Shenqi Fuzheng Decoction. Advanced lung cancer. Cancer-related pain. Cancer-related fatigue. Directional penetration.*

Resumen

Objetivo: *El objetivo del estudio fue analizar el efecto de la penetración direccional de decocción Shenqi Fuzheng para el tratamiento de pacientes con cáncer de pulmón avanzado con dolor relacionado con el cáncer.* **Método:** *Ochenta y seis casos de cáncer de pulmón avanzado recibidos en el Hospital Zhoushan de medicina tradicional China de junio de 2022 a junio de 2023 se dividieron al azar en grupo de estudio (n = 43) y grupo control (n = 43). Dos grupos fueron tratados con el mismo*

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plan de tratamiento conservador, sobre la base del grupo control tratado con placebo, y el grupo de estudio recibió tratamiento de penetración direccional de decocción Shenqi Fuzheng. Se evaluaron y registraron la intensidad del dolor relacionado con el cáncer, el tiempo de inicio del dolor, la frecuencia del brote del dolor y la duración del dolor. Antes y después del tratamiento se evaluaron el grado de cansancio relacionado con el cáncer, la calidad de vida y el puntaje del estado funcional de Karnofsky (KPS) en dos grupos. Se registraron las reacciones adversas de los dos grupos durante el tratamiento. **Resultados:** *En comparación con el grupo control, se redujo la intensidad del dolor relacionado con el cáncer del grupo de estudio, se acortó el tiempo de inicio analgésico, se redujo la frecuencia del brote de dolor y se prolongó la duración analgésica ($p < 0.05$). Después del tratamiento, los resultados de la escala de fatiga de Piper (EFP) en el grupo de estudio fueron más bajos que en el grupo de control, los del inventario genérico de calidad de vida-74 (GQOLI-74) y los del KPS en el grupo de estudio fueron más altos que en el grupo de control ($p < 0.05$). Durante el periodo de tratamiento no se observaron reacciones adversas significativas en ambos grupos ($p > 0.05$).* **Conclusión:** *el tratamiento de penetración direccional de decocción Shenqi Fuzheng tiene un efecto notable en pacientes con cáncer de pulmón avanzado con dolor de cáncer, que puede aliviar la intensidad del dolor, prolongar la duración del alivio del dolor, reducir el número de ataques de dolor, aliviar la fatiga relacionada con el cáncer y mejorar la calidad de vida y el estado de salud de los pacientes.*

Palabras clave: *Decocción de Shenqi Fuzheng. Cáncer de pulmón avanzado. Dolor relacionado con el cáncer. Fatiga relacionada con el cáncer. Penetración direccional.*

Introduction

As a common malignant tumor worldwide, lung cancer is the main cause of cancer death and poses a threat to human life safety[1]. For lacking typical symptoms, most lung cancer patients have developed to an advanced stage when they are first diagnosed, thus missing the best opportunity for treatment[2,3]. Cancer-related pain and fatigue, as the common symptoms in advanced cancer patients, is also an important factor affecting the life quality of patients[4]. Cancer-related pain can influence the sleep and diet of patients, resulting in gradual weakness and weakening the patient's will to live[5]. Cancer-related fatigue can make patients feel weak and lack the energy and physical strength to carry out daily activities[6]. Therefore, it is necessary to take effective treatment measures to relieve cancer-related pain and fatigue.

At present, traditional Chinese medicine has become increasingly prominent for cancer-related pain and fatigue due to its stable curative effect and small side effects. Traditional Chinese medicine believes that the deficiency of vital-qi is the root cause of cancer pain, and it is closely related to the factors of six climatic exopathogens, phlegm and fluid retention, static blood, and damaged by excess of seven emotions[7]. When the vital qi is insufficient or internally weakened, it renders the body vulnerable to invasion by the six climatic exopathogens, and also affects the smooth flow of qi and blood. When the vital qi is insufficient or internally weakened, it renders the body vulnerable to invasion by the six climatic pathogenic factors (the six evils) and also affects the smooth flow of qi and blood. Chronic qi and blood stasis can lead to the generation of cancerous toxins, which develop into cancerous masses. These masses block the meridians and collaterals, leading to qi and blood stagnation and causing pain[8]. Therefore, traditional Chinese medicine believes that invigorating qi and reinforcing the body, promoting blood circulation and regulating qi, resolving blood stasis, and relieving pain are the fundamental treatment methods[9]. Directional penetration therapy belongs to the external treatment of traditional Chinese medicine, which can make the drug directly reach the disease site through the body surface, avoiding the toxic side effects of intestinal administration, and has more advantages in the application of advanced tumor patients[10,11].

Shenqi Fuzheng Decoction as commonly used prescription for advanced malignant tumors in Chinese medicine has a remarkable effect on improving the patients' life quality. However, the application of Shenqi Fuzheng Decoction in advanced cancer patients is mostly taken internally, and the therapeutic effect of external use on cancer pain patients has not been reported[12]. Therefore, this study applied Shenqi Fuzheng Decoction directional penetration in advanced lung cancer patients and discussed its effects on cancer-related pain and fatigue, to provide evidence for its clinical application.

Research methods

Ethical approval

Before participating in this study, ethical approval was obtained from the hospital review board, and written informed consent was obtained from the patients or their guardians.

Patients

This study included patients with advanced lung cancer who were admitted to Zhoushan Hospital of Traditional Chinese Medicine from June 2022 to June 2023. Inclusion criteria: Age 45~70 years old; all patients follow the guidelines of diagnosis and management of lung cancer; tumor node metastasis (TNM) classification Ⅲ~Ⅳ; patients with an expected survival time of more than 3 months; patients have cancer pain symptoms; patients have no other critical illness; patients consented to a follow-up. Exclusion criteria: patients with other malignant tumors, cardiovascular and cerebrovascular diseases; patients have other non-cancer-related pain; pregnant or lactating women; patients with ulcerated or sensitive skin; patients with mental abnormalities; patients dropped out of the study for multiple reasons. Based on these criteria, 86 cases were chosen as study objects and randomly assigned to two groups, with 43 cases in each group.

Therapeutic methods

The control group was given placebo treatment: 50 mg lemon yellow was dissolved in 1000 mL 5% sodium chloride injection, and then evenly mixed, an appropriate amount of liquid was dipped in sterile cotton and gently applied to the cancer pain site, once every 6 h, continuous treatment for 14 days.

The study group was received Shenqi Fuzheng Decoction directional penetration treatment: Shenqi Fuzheng Decoction is composed of Dang-shen, Huang-qi, Bai-shu, Dang-gui, Dan-shen, Ji-xue-teng, Sang-zhi, Chi-shao, and Yan- hu-suo. After the above medicines were soaked for 30 min, they were boiled with a military fire and then boiled over gently. The medicinal liquid was collected and then added nitrogen ketone into the medicinal liquid to make a mixture. Then 10 mL of the medicinal liquid was injected into a special cotton pad. After the liquid permeated, the cotton pad was placed on the electrode plate, the electrode was pressed close to the patient's skin pain point, and the parameters of the traditional Chinese medicine directional penetration instrument were set, 30 min/time, 1~2 times/day, and the treatment was continuous for 14 days.

Outcome measures

After treatment for 7 days, the pain intensity of the patients was evaluated by verbal rating scale, which divided the pain intensity into for grades. The analgesic onset time, analgesic duration, and the number of pain outbreaks were recorded in both groups. Before and after treatment, the Piper Fatigue Scales (PFS) were used to evaluate the fatigue degree of patients from four dimensions: behavior dimension, emotion dimension, perception dimension, and cognition dimension. Each dimension was scored from 0 to 10 points and the higher the score, the more severe degree of cancer-related fatigue. The life quality was evaluated by generic quality of life inventory-74 (GQOLI-74) scale, which including four aspects of physical function, social function, mental health, and health status, with a total score of 100 points. A higher score indicates a better quality of life for patients. The health status of two groups was evaluated by Karnofsky Performance Status (KPS) with a total score of 100 points, and a higher score indicates better health status of patients. The adverse reactions during treatment in two groups were observed.

Statistical methods

The data were analyzed by SPSS 24.0 statistic software. Patient's age, body mass index, analgesic onset time, frequency of pain outbreak, analgesic duration, GQOLI-74, KPS, and PFS scores were represented as mean ± standard deviation and t-test was used to compare between groups. Classification data and grade data were reported by frequency and percent, and analyzed by Chi-squared test and Wilcoxon rank sum test. $p < 0.05$ was considered significant.

Results

Baseline characteristics

No visible differences were observed in terms of sex, age, body mass index, TNM classifications, and squamous carcinoma between two groups ($p > 0.05$) (Table 1).

The pain intensity

After treatment, the pain intensity in the study group was apparently relieved than control group ($p < 0.05$) (Table 2).

Analgesic onset time, analgesic duration, and frequency of pain outbreak

The analgesic onset time and the frequency of pain outbreak in the study group were distinctly reduced,

Table 1. Baseline characteristics in two groups

Variable	Study group (n = 43)	Control group (n = 43)	t/χ^2-values	p
Sex (male/female)	26/17	28/15	0.199	0.655
Age (years)	61.46 ± 6.38	62.03 ± 6.79	0.401	0.689
Body mass index (kg/m^2)	22.23 ± 2.08	21.86 ± 1.64	0.916	0.362
TNM classifications				
III	19 (44.19)	21 (48.84)	0.187	0.665
IV	24 (55.81)	22 (51.16)		
Pathological types				
Squamous carcinoma	16 (37.21)	15 (34.88)	0.724	0.733
Adenocarcinoma	22 (51.16)	25 (58.14)		
Adenosquamous carcinoma	5 (11.63)	3 (6.98)		

Table 2. Comparison of pain intensity between two groups

Groups	Painless	Mild pain	Moderate pain	Severe pain
Study group (n = 43)	7 (16.28)	19 (44.19)	14 (32.56)	3 (6.98)
Control group (n = 43)	1 (2.32)	13 (30.23)	21 (48.84)	8 (18.60)
Z	2.935			
p	0.003			

and the analgesic duration was prolonged compared with the control group ($p < 0.05$) (Table 3).

Cancer-related fatigue

After treatment, the scores of behavior fatigue, emotion fatigue, perception fatigue, and cognition fatigue in the study group were lower than the control group ($p < 0.05$) (Table 4).

The life quality and health status

After treatment, the GQOLI-74 and KPS scores of the study group were increased observably compared to the control group ($p < 0.05$) (Table 5).

Adverse reactions

During treatment, no severe adverse reactions occurred in both groups, one case had dizziness, one case had gastrointestinal discomfort in the study group with a total incidence of 4.65% (2/43); two cases had gastrointestinal discomfort and one case had constipation in control group with a total incidence of 6.98% (3/43) ($p > 0.05$).

Discussions

Lung cancer is a malignant disease threatening human life and health, its morbidity and mortality increase year by year, and the incidence group tends to be younger[13]. Advanced lung cancer patients are intolerant to surgery, radiotherapy, chemotherapy, and other treatments due to decreased physical tolerance, and they also suffer from cancer pain while undergoing treatment pain[14]. Cancer pain can lead to depression, anxiety, depression, and other conditions, affect their sleep and mental state, and greatly reduce the life quality of patients. Therefore, taking valid treatment measures to relieve cancer pain for advanced lung cancer patients is very important for the improvement of patients' life quality. Western medicine mainly uses non-hormone analgesics and opioids to treat cancer pain. Although this type medicines can relieve cancer pain to a certain extent, long-term use of them will lead to intolerance of patients, drug dependence, or accumulation of toxins in the body, which will damage the function of other healthy parts[15,16]. At present, traditional Chinese medicine has gradually shown its superiority in cancer pain due to its high safety, high patient tolerance, low price, and no dependence[17].

In the view of traditional Chinese medicine, the cancer pain is relative to the deficiency of vital qi, the invasion of pathogenic factors, and the stasis of qi and blood in the organs and bones, which can lead to the blockage of qi and blood in the channels and collaterals, and the stasis causes pain[18]. Therefore, the treatment should be based on strengthening the body and removing evil, nourishing qi and activating blood circulation, removing blood stasis, and relieving pain. Shenqi Fuzheng Decoction is a prescription

Table 3. Comparison of analgesic onset time, analgesic duration, and frequency of pain outbreak between two groups

Groups	Analgesic onset time (min)	Frequency of pain outbreak (times/day)	Analgesic duration (h)
Study group (n = 43)	57.69 ± 7.75	2.38 ± 0.55	12.62 ± 2.46
Control group (n = 43)	65.27 ± 8.06	3.45 ± 0.64	10.74 ± 2.67
t	4.428	8.315	3.396
p	0.000	0.000	0.001

Table 4. Comparison of cancer-related fatigue between two groups

Groups	Behavior fatigue		Emotion fatigue		Perception fatigue		Cognition fatigue	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 43)	6.86 ± 1.48	4.08 ± 1.05[a]	6.74 ± 1.47	4.14 ± 1.07[a]	6.87 ± 1.74	4.29 ± 0.86[a]	4.57 ± 1.14	2.72 ± 0.45[a]
Control group (n = 43)	6.43 ± 1.54	5.04 ± 1.26[a]	6.82 ± 1.44	5.26 ± 1.06[a]	6.59 ± 1.68	5.28 ± 1.13[a]	4.39 ± 1.08	3.78 ± 0.64[a]
t	1.320	3.838	0.255	4.876	0.759	4.572	0.752	8.884
p	0.190	0.000	0.799	0.000	0.450	0.000	0.454	0.000

[a]p < 0.05 versus before treatment.

Table 5. Comparison of GQOLI-74 and KPS scores between two groups

Groups	GQOLI-74		KPS	
	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 43)	56.86 ± 8.38	70.08 ± 6.75[a]	50.18 ± 6.37	72.57 ± 7.86[a]
Control group (n = 43)	58.43 ± 7.54	65.44 ± 7.26[a]	49.86 ± 5.46	64.42 ± 6.75[a]
t	0.913	3.069	0.250	5.158
p	0.364	0.003	0.803	0.000

[a]p < 0.05 versus before treatment.

composed of Dang-shen, Huang-qi, Bai-shu, Dang-gui, Dan-shen, and other medicinal herbs. Among them, Dang-shen can tonify middle and replenish qi, Huang-qi can replenish qi and consolidating exterior, Dan-shen can invigorate blood circulation and regulate menstruation, remove blood stasis and relieve pain, Dang-gui can tonify blood and invigorate menstruation, move qi and relieve pain, Bai-shu can invigorate the spleen and benefit qi, Chi-shao can remove blood stasis and relieve pain, Ji-xue-teng and Sang-zhi can remove blood stasis and clear collaterals, and Yan-hu-suo can invigorate blood and relieve pain. The combination of the above herbs can invigorate qi and reinforce the body, promote blood circulation and regulate qi, resolve blood stasis, and relieve pain. Therefore, this study tried to apply Shenqi Fuzheng Decoction to advanced lung cancer patients and explore its therapeutic effect on cancer pain. In addition, considering the gastrointestinal weakness of patients with advanced tumors, this study attempted to use percutaneous directional penetration therapy.

The results in this study displayed the pain intensity in the study group was relived apparently, the analgesic onset time and the frequency of pain outbreak were distinctly reduced, and the analgesic duration was prolonged compared with the control group, suggesting that Shenqi Fuzheng Decoction directional penetration therapy can effectively mitigate the cancer pain of patients. This result also confirmed that the analgesic onset time of directional penetration therapy

is shorter and the effect is more durable and stable. This may be because percutaneous directional penetration absorbs medicine through the skin and mucosal surface, allowing the drug to reach the disease. Luo et al. confirmed that transdermal administration of traditional Chinese medicine has obvious advantages in pain relief[19]. The results showed that the scores of behavior fatigue, emotion fatigue, perception fatigue, and cognition fatigue of the study group were decreased compared with the control group after treatment, revealing that Shenqi Fuzheng Decoction can improve markedly cancer-related fatigue of patients with advanced lung cancer. In Zhu's study[20], a tumor-bearing mouse fatigue model was established to confirm the anti-fatigue effect of Shenqi Fuzheng injection; the results indicated that Shenqi Fuzheng injection might be as a potential therapy for cancer-related fatigue. The results showed that GQOLI-74 and KPS scores in the study group were higher than control group after treatment, illustrating that Shenqi Fuzheng Decoction directional penetration treatment can improve the life quality and health status of patients, which may be related to the alleviation of cancer pain and cancer fatigue in patients. No obvious adverse reactions were found during treatment, suggesting that Shenqi Fuzheng Decoction directional penetration has no obvious safety risks in advanced lung cancer patients, clarifying the feasibility of its application.

Conclusion

Shenqi Fuzheng Decoction directional penetration has a remarkable therapeutic effect on advanced lung cancer patients, which can quickly relieve the cancer pain, prolong the efficacy time, reduce the frequency of outbreak pain, alleviate cancer fatigue, and improve the life quality of patients.

Despite its findings, this study is not without flaws. This study is a single-center analysis, not a large sample study. In the future, multi-center and large sample size prospective researches are still necessary to verify and promote the results of this study, so as to provide a more powerful basis for the treatment of advanced lung cancer patients with cancer pain, further improve the life quality of patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. Ethical approval was given by the Zhoushan Hospital of Traditional Chinese Medicine and written informed consent was obtained from all patients.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

The efficacy of transversalis fascia plane block in pediatric inguinal herniotomy: a randomized controlled study

Eficacia del bloqueo del plano de la fascia transversal en la reparación de la herniotomía inguinal pediátrica: estudio controlado aleatorizado

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Abstract

Objective: *The post-operative analgesic efficacy of transversalis fascia plane (TFP) block is controversial in pediatric patients undergoing herniotomy. This study aims to compare the efficacy of TFP block and standard analgesic methods.* **Method:** *Sixty patients aged 1-8 years who underwent the open procedure of herniotomy were randomly divided into two groups TFP block (n = 30) or control group (n = 30). The TFP group received 0.25% bupivacaine at 0.5 mL/kg. Routine analgesia protocol was applied to Group C. Pain scores (FLACC), family satisfaction, block complications, nausea, sedation score, and additional analgesic requirements were recorded.* **Results:** *FLACC pain scores at post-anesthesia care unit (PACU), 1st, 2nd, and 4th h were statistically significantly lower in Group TFP compared to group control (p < 0.05). Three patients in Group TFP and 12 in group control required rescue analgesics at PACU (p = 0.015). Ibuprofen was required in two patients in Group TFP and 11 in Group Control (p = 0.010). Parental satisfaction is higher in the TFP group than in Group Control (p < 0.001). There was no statistically significant difference between the groups in terms of post-operative nausea and sedation scores (p > 0.05).* **Conclusion:** *We conclude that TFP block in pediatric patients is an appropriate approach as a part of multimodal analgesia. It creates fewer pain scores in the early post-operative period, requires less additional analgesia, and increases family satisfaction.*

Keywords: *Inguinal hernia repair. Herniotomy. Pediatric. Post-operative analgesia. Transversalis fascia plane block.*

Resumen

Objetivo: *Comparar la eficacia del bloqueo del plano de la fascia transversal (PFT) y de los métodos analgésicos estándar.* **Método:** *Sesenta pacientes de 1-8 años de edad sometidos a procedimiento abierto de herniotomía unilateral se dividieron aleatoriamente en dos grupos: bloqueo PFT (n = 30) y control (n = 30). El grupo PFT recibió bupivacaína al 0.25% a razón de 0,5 ml/kg, y en el grupo control se aplicó un protocolo de analgesia de rutina. Se registraron puntuaciones de dolor (FLACC), satisfacción familiar, complicaciones del bloqueo, náuseas, puntuación de sedación y necesidades analgésicas adicionales.* **Resultados:** *Las puntuaciones de dolor FLACC en unidad de cuidados postanestésicos (PACU) a las 1, 2 y 4 horas fueron más bajas en el grupo PFT que en el grupo control, con una diferencia estadísticamente significativa (p < 0.05). Tres pacientes en el grupo PFT y 12 en el grupo control requirieron analgésicos de rescate en PACU (p = 0.015). Dos pacientes del grupo PFT y 11 del grupo control requirieron ibuprofeno (p = 0.010). La satisfacción de los padres fue mayor en el grupo PFT (p < 0.001). No hubo diferencias estadísticamente significativas en términos de náuseas posoperatorias y puntuaciones de sedación (p > 0.05).*

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Conclusiones: *Concluimos que el bloqueo del PFT en los pacientes pediátricos es un abordaje apropiado como parte de la analgesia multimodal. Crea menos puntuaciones de dolor en el período posoperatorio temprano, requiere menos analgesia adicional y aumenta la satisfacción familiar.*

Palabras clave: *Reparación de hernia inguinal Herniotomía. Pediatría. Analgesia posoperatoria. Bloqueo del plano de la fascia transversal.*

Introduction

Inguinal hernia is a frequently encountered problem among pediatric patients requiring surgical intervention that occurs due to failure of processus vaginalis closure[1-4]. Its incidence is approximately 1-5% in full-term babies, and it is 6 times more common in boys[5].

Understanding the surgical procedure thoroughly during a case enhances the anesthesiologists' vision of the anesthetic and analgesic techniques and algorithms they are to use. The open procedure of herniotomy involves separation of the hernia sac from the neighboring structures such as cremasteric muscle, round ligament, vas deferens or the testicular vessels; through a peritoneal incision[6]. There are different options in inguinal hernia surgery, such as laparoscopic and open surgeries. Open surgery is generally recommended for boys, unilateral female hernias, premature newborns, unsuccessful laparoscopic repairs, patients with comorbidities, and cases where technical equipment is inadequate[7].

A complicated fiber network from the ilioinguinal (II), iliohypogastric (IH), and genitofemoral (GFN) nerves innervates the inguinal region. The origin of II and IH nerves is the first lumbar (L1) spinal nerve root, sometimes with addition from the 12th thoracic nerve root. Besides, L1 and L2 nerve roots make up the GFN[8]. Therefore, where one targets efficient pain control for inguinal hernia repair surgery, sensorial blockage of the cutaneous branches of subcostal (T12), ilioinguinal (L1), and iliohypogastric (T12-L1) nerves becomes vital. These nerves run in the transversalis fascia before entering the plane between the transversus abdominis and internal oblique muscles. After passing through the transversus abdominis plane, these nerves emerge into the plane between the external and internal oblique muscles and finally provide the lateral cutaneous branches[8,9].

Although herniotomy is an outpatient surgery, severe pain may occur in the post-operative period and relief of post-operative pain is multifactorial[10]. Transversalis fascia plane (TFP) block has been favored during several procedures like inguinal herniotomy, C/S and iliac crest bone harvesting in adult population, so far[11-14]. In 2018, the first report on TFPB application after C/S was published, where effective post-operative analgesia was guaranteed[15]. The first pediatric report of TFP block was by Ahiskalioglu et al. in two different cases; reimplantation of the ureter into the urinary bladder and unilateral inguinal herniorrhaphy operations[16].

We hypothesized that performing TFP block would be more efficient for analgesia compared with the standard analgesia protocol. The primary goal of this study is to evaluate the effect of TFPB on post-operative analgesia scores in the pediatric population having open inguinal hernia repair surgery. The secondary aims are to investigate analgesic consumption and parent satisfaction.

Method

The Ethical Committee of Ataturk University's ethical approval was attained for this prospective randomized study 29/11/2018-7/3), and registration bofore patient enrollment with a clinical trial registry (ClinicalTrials.gov, NCT04272320) on February 17, 2020, was performed. Sixty American Society of Anesthesiologists (ASA) Classification I-II patients aged 1-8 years who had unilateral open inguinal hernia repair surgery from September 2021 to January 2022 were included in the study. The patients with a history of clinically significant cardiac, hepatic, renal, or neurological dysfunction, coagulopathy, known allergies to amide local anesthetics, and systemic or local infection at the puncture site were to be excluded from this study.

Patients were randomly assigned to two equal groups using Microsoft Office 365 Excel (Microsoft, Redmond, WA, USA) with the RAND function. In the operating room, an anesthesiologist who was not involved in the study used and opened an opaque sealed envelope. Patients were assigned at random to either the TFP block group (Group TFPB, n = 30) or the control group

(Group C, n = 30). Patients were assigned at random to either the TFP block group (Group TFPB, n = 30) or the control group (Group C, n = 30) on the basis of the patient randomization chart.

For premedication, 15 min. before transfer to the operation room, 0.03 mg/kg midazolam was given to patients with IV access. For the ones without IV access, 1 mg/kg oral midazolam was given 30 min. before transfer to the operation room. Vascular access was obtained (22 or 24-gauge IV) after induction with sevoflurane and loss of the eyelash reflex. On delivery in the operation room, heart rhythm and heart rate by electrocardiogram, non-invasive blood pressure measurement, and peripheral oxygen saturation (SpO_2) were monitored, and end-tidal CO_2 ($EtCO_2$) was recorded intraoperatively. Induction of anesthesia was performed with sevoflurane, Fentanyl 1 μg/kg, and Rocuronium 0.6 mg/kg, then rapid serial intubation was carried out. After intubation, ventilation parameters were adjusted to meet these values; $EtCO_2$ of 30-35 mmHg, FiO_2 of 50%, tidal volume 6-7 mL/kg, and ventilation support was initiated. Anesthesia maintenance was provided with sevoflurane (Sevorane, Abbott) 2-3% and rocuronium 0,1 mg/kg intermittently if necessary. Before extubation, all patients were given atropine and neostigmine for reversal as clinical routine practice.

For Group 1 patients, after intubation, a TFP block was performed under aseptic conditions with Xperius™ US systems (Xperius™ Ultrasound System, B. Braun, Melsungen, Germany) with high-frequency linear ultrasound (L12-4 MHz). The patients were placed in the supine position, and the ultrasound probe was placed in a transverse orientation on the abdominal wall so that the external and internal oblique muscles and transverse abdominis muscles were all included in the ultrasound image. Moving the probe laterally, perinephric fat layer, transversalis fascia, and quadratus lumborum muscle were visualized. The sonovisible 50 mm needle was advanced until its tip reached the perinephric fat layer, and after ensuring negative aspiration of blood 0.5-1 mL of 0.9% NaCl as a test dose of was used to confirm appropriate needle tip placement. 0.25% bupivacaine of 0.5 mL/kg volume was used for this procedure (Figs. 1 and 2).

For patients in Group 2, standard analgesia protocol was used, and wound infiltration was applied with 0.2 mL/kg volume of 0.25% bupivacaine before surgical incision.

Surgical procedures

The surgical procedure began with an incision along the inguinal skin crease. On exploration, a hernial sac was discovered without any opening in the inguinal canal. High ligation was carried out using one transfiction and one free ligation. Subsequently, the surgical procedure concluded by suturing the subcutaneous tissue and the skin separately using interrupted sutures.

Post-operative analgesia management

All patients received 15 mg/kg paracetamol every 6 h. The primary outcome of this study was designed to be FLACC pain scores postoperatively, at 30 min., 1, 2, 4, 6, 12, and 24 h. Patients with FLACC > 4 in post-anesthesia care unit (PACU) were given 1 mcg/kg fentanyl intravenous, repeated after 10 min if necessary. Patients with FLACC > 2 in the ward received 7 mg/kg oral ibuprofen. Opioid consumption at PACU and ibuprofen consumption at the ward were recorded. A 3-point Likert scale (1: poor, 2: fair, 3: good) was used to measure parental satisfaction at the 24th h. Data at the 24th h were obtained by calling the parents by phone. Other side effects were also recorded (block-related complications, local anesthetic toxicity, motor weakness, and vascular or abdominal organ puncture).

Sample size and statistical analysis

Conducting a pilot study, the required sample size was determined. The pilot study indicated that our primary outcome, mean FLACC score at the first postoperative hour, should be 2.20 ± 1.65 in the control (n = 10) and 0.95 ± 0.55 in the TFP block group (n = 10). Hence, in total, a sample size of 27 was calculated for the groups through G*Power version 3.1.9.2 (Heinrich Heine University Düsseldorf) with an effect size of 1.016, an α probability of 0.05, and a power of 0.95. Assuming possible dropouts, we decided to include 30 patients in each group.

Statistical Analysis was completed with the “SPSS 20.0 for Windows” (SPSS Inc., IL, ABD) program. The data were checked to fit into a normal distribution using the Kolmogorov–Smirnov test. Data that fit the normal distribution were evaluated with an independent sample t-test. Data that did not fit the normal distribution were evaluated using the Mann–Whitney-U test. Cat-

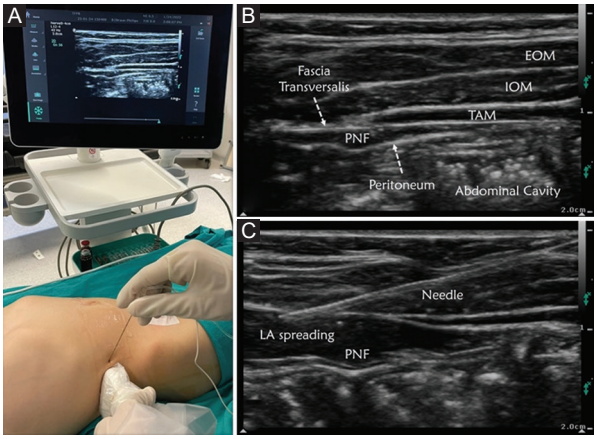

Figure 1. A: *patient and ultrasound set-up for TFP block.* **B:** *sonographic landmarks. EOM: external oblique muscle; IOM: internal oblique muscle; TAM: transversus abdominis muscle; PNF: perinephric fat.* **C:** *transversalis fascia plane block after local anesthetic injection and needle trajectory.*

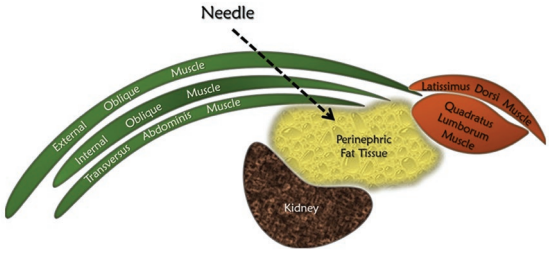

Figure 2. *Basic illustration of transversalis fascia plane block.*

egorical data were evaluated using the X^2 or Fisher's exact tests. Values of $p < 0.05$ were significantly meaningful.

Results

A total of 75 patients were assessed for enrollment in this study, 11 of those did not meet the inclusion criteria while 4 of them did not agree to participate and were therefore excluded from the study. In the end, 60 patients were randomly allocated in two groups of 30 patients each. In Fig. 3, the CONSORT flow diagram of participants is demonstrated. There is no statistically significant difference between groups regarding demographic data, ASA classification, anesthesia duration, and operation time ($p > 0.05$) (Table 1).

FLACC scores in PACU at 1, 2, and 4, h were statistically lower in Group TFP. At 8, 12, and 24 h, there is no significant difference between the groups. Opioid consumption in PACU was statistically higher in the control group than in the TFP group (12/30 vs. 3/30, respectively, $p = 0.015$). The rate of ibuprofen usage at the ward was higher in group control than in group TFP (11/30 vs. 2/30, respectively, $p = 0.010$) (Table 2)

There was no statistically significant difference between the groups regarding post-operative nausea and sedation scores. ($p = 0.671$ and $p = 0.518$ respectively). Parents' satisfaction at the end of 24 h was significantly superior in the TFP group ($p < 0.001$) (Table 3).

Discussion

According to the findings of the current study, performing a TFP block before surgical incision was associated with lower post-operative pain scores in the early post-operative period, less need for rescue opioid consumption, lower post-operative ibuprofen requirements, and higher parental satisfaction than the wound infiltration group.

During the surgical treatment, the surgeon chose not to open the inguinal canal and instead performed a high ligation technique. The incision was confined to the subcutaneous tissue and skin, and the suturing process involved closing the hernial sac, subcutaneous tissue, and skin in a nearly identical manner. It is important to note that all of these tissues are associated with the peripheral nerves of the abdominal wall, not the visceral pleura. While a transversus abdominis plane (TFP) block may not provide visceral analgesic effects, it does have analgesic activity for the structures of the abdominal wall.

Technical simplicity, selective unilateral blockage, lower risk of complications, and comparable or better analgesic outcomes are some of the advantages of interfascial plane blocks on the contrary of neuraxial anesthesia or nerve plexus blocks. Caudal anesthesia is a common neuraxial technique that can be used for perioperative analgesia during open hip surgeries and inguinal herniorrhaphy. However, there are possible complications such as intravascular or intrathecal injection, convulsions, hemorrhage in the retroperitoneal region, urine retention, or renal puncture.[17] Moreover, it leads to a bilateral block that might be undesirable for unilateral hernia repair operations where TFPB would be a proper alternative. Caudal anesthesia is commonly employed for herniotomy to provide effective post-operative analgesia. Anesthesia providers often utilize

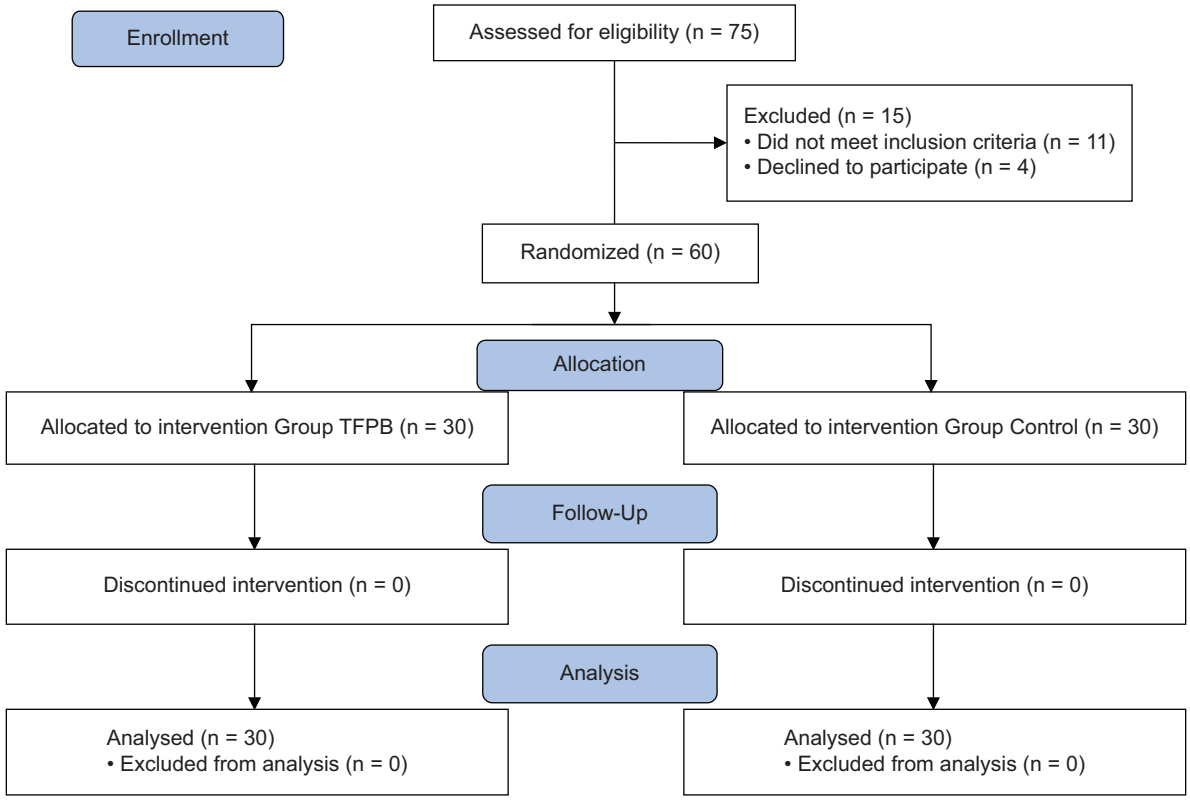

Figure 3. *Consort flow diagram.*

Table 1. Demographic data and comparison of operative procedures between groups

Variables	Group TFP (n = 30)	Group control (n = 30)	p
Age (years)	4.25 (2.25-6)	5 (2.5-8)	0.583*
Weight (kg)	16.5 (11-23)	18.5 (11-24.5)	0.640*
Height (cm)	111 (97.5-127.5)	122.5 (95-140)	0.414*
Gender (f/m)	11/19	9/21	0.785**
ASA (I-II)	27/3	29/1	0.612**
Duration of anesthesia (min)	45 (40-50)	40 (32.5-45)	0.052*
Duration of surgery (min)	27.5 (20-30)	30 (20-30)	0.659*

*p > 0.05 Mann–Whitney U-test. **p > 0.05 Fisher's exact test. Values are expressed median (25-75%) or number, ASA: American Society of Anesthesiologist. Kg: kilogram; cm: centimeter; f: female; m: male; min: minutes.

landmark techniques for this purpose. It is important to note that caudal anesthesia affects both sides of the body. However, unintended complications such as intravascular or intrathecal injections, convulsions, or urine retention may arise. On the other hand, the TFP (Transversus Abdominis Plane) block is performed under ultrasound guidance, enabling clear visualization of anatomical structures. This allows for simple and safe injection administration.

Before the advancement of ultrasonography guidance in regional anesthesia, the blind technique was used for TFP block as follows: 1 cm medial to the anterior superior iliac spine is defined as the suitable puncture side; the needle is advanced until a "pop" is felt as it passes through the external oblique muscle. However, this technique had a very unpredictable success rate[18]. Following the revolutionary introduction of point-of-care ultrasound guidance in regional anesthesia, the acquisition of this skill enabled practice with superior efficacy and safety as local anesthetics could be administered as close as possible to target nerves. A few studies have demonstrated ultrasound guided TFP block's efficacy in different procedures. According to the study by Aydın et al., TFP block is effective in lowering opioid consumption significantly at all-time intervals during the 24-h follow-up in women who underwent cesarean section under spinal anesthesia[19].

Table 2. Comparison of the FLACC score assessment between groups

Variables	Group TFP (n = 30)	Group control (n = 30)	p
Flacc PACU	0 (0-1)	3 (2-5)	< 0.001*
Flacc 1st	0 (0-0)	2 (1-3)	< 0.001*
Flacc 2nd	0 (0-0)	1 (0-2)	0.001**
Flacc 4th	0 (0-0)	0 (0-1)	0.03**
Flacc 8th	0 (0-0)	0 (0-0)	0.429***
Flacc 12th	0 (0-0)	0 (0-0)	NS
Flacc 24th	0 (0-0)	0 (0-0)	NS
Opioid consumption (Y/N)	3/27	12/18	0.015****
Ibuprofen in ward (Y/N)	2/28	11/19	0.010****

*p < 0.001 Mann–Whitney U-test. **p < 0.05 Mann–Whitney-U test. ***p > 0.05 Mann–Whitney U-test. ****p < 0.05 Fisher's Exact test. Y: yes; N: no. Values are expressed median (25-75%) or number. PACU: post-anesthesia care unit.

Table 3. Comparison of the parent's satisfaction and side effects between groups

Variables	Group TFP (n = 30)	Group control (n = 30)	p
Parents satisfaction (f/g/e)	2/12/16	10/18/2	< 0.001*
Nausea (Y/N)	2/28	4/26	0.671**
Sedation (I/II/III)	23/6/1	19/9/2	0.518**

*p < 0.001 Fisher's exact test. **p > 0.05 Fisher's exact test. Values are expressed as a number. F: fair; g: good; e: excellent; Y: yes; N: no; I: awake and alert; II: quietly awake; III: asleep but easily roused.

In another study carried out in 2020 by AbdelBaser et al., 44 patients aged 12-60 months were included to evaluate the preemptive analgesic efficacy of TFP block. In correlation with the results obtained from this study, it demonstrated that TFP block application is associated with decreased post-operative analgesic consumption (paracetamol and fentanyl), lower post-operative pain scores recorded also with the FLACC scale, lower need for rescue analgesia, and enhanced parental satisfaction than the control group in pediatric patients as well[8]. The follow-up period was limited to 12 h in this study while we recorded pain scores for 24 h. This study compares an actual sham group with a TFP block. Unlike in this study, the control group of our study received wound infiltration rather than sham injection. Despite the fact that the control group had low pain scores, the TFP block provided more effective analgesia in the early post-operative period.

Before performing TFPB, possible risks and complications must be studied and discussed. In order to avoid local anesthetic systemic toxicity, maximum doses of local anesthetics should not be exceeded, keeping in mind the physiological and pathological factors of each patient that may influence their metabolism, especially in pediatrics. Local anesthetics can be absorbed through the well-vascularized large surface areas of the fascial planes; and less cardiotoxic agents should be preferred ideally. In our study, bupivacaine was used as it is the only commercially available local anesthetic in Turkey that can be used for regional anesthesia. Lee et al. reported a case that demonstrated quadriceps femoris paralysis due to TFPB application after iliac bone grafting[20]. Local anesthetics administered at the TFP potentially extend over the quadratus lumborum, passing through paravertebral spaces and eventually blocking the roots or branches of the lumbar plexus. In a cadaver study by Rosario et al., this compartment between the transverse abdominis muscle and transversalis fascia was demonstrated to be continuous with the fascia iliaca compartment[21]. In our study, we did not face any complications related to quadriceps paralysis; however, parents must be informed of the quadriceps weakness risk while consent is being obtained.

Another possible complication linked to abdominal wall blocks is the trauma of the adjacent structures and organs. In performing QLB, there is a possible risk of renal injury because the kidney lies anterior to the QL muscle, separated only by perinephric fat and fascia. As the perinephric fat is smaller in size in pediatric patients, there is a higher risk of injury when QLB is performed on children. Ahiskalioglu et al. reported a case of incidental hepatomegaly during QLB block in a pediatric patient in an effort to emphasize that anesthesiologists should keep in mind that solid organ damage must be avoided in plane block applications[22]. To minimize peritoneal penetration and liver or kidney trauma, the block area should be posterior enough so that the perinephric fat is underlying the transversalis fascia. Because the site of intervention for TFP block is more posterior than TAP, there is perinephric adipose tissue under the fascia instead of the peritoneum or liver. Hence, the TFP block is considered as a simple block to apply. On the other hand, the need to move the patient into both lateral positions after the surgery is a disadvantage of QLB block[19]. In this study, none of the patients had any damage to the peritoneum or adjacent

organs, and TFPB might be safer, and alternative to QLB for lower abdominal surgery.

In our institution, pediatric surgeons mostly perform open inguinal hernia repair, however, laparoscopy has been highly utilized throughout the world, as well. The advantages of laparoscopy include the ability to visualize contralateral defects, diminished post-operative pain, improved cosmesis, and lower complication rate. Potential disadvantages are proposed to be increased operation time, learning curves, higher incidence of PONV, and need of orotracheal intubation[23]. In laparoscopy, the periton is penetrated and pneumoperitoneum is required. Therefore, TFP block would not provide adequate intraoperative or post-operative analgesia during a laparoscopic inguinal hernia repair. Hence, it must be noted that laparoscopic surgery might require a more challenging pain control and further techniques must be studied for laparoscopic scenarios where TFP is not adequate.

Genital branch of the GFN partially contributes to the innervation of the inguinal sac, II and IH nerve blocks do not cover this nerve branch which potentially leads to visceral pain due to traction on the hernial sac. Sasaoka et al. demonstrated that GFN block, when applied with II and IH nerve blockade, attenuated the hemodynamic stress response to surgical manipulation of the inguinal hernial sac, but did not have any post-operative analgesic effect[24]. In the upcoming studies, TFPB accompanied by GFN block could also be compared with other analgesic techniques.

There are some limitations to the study. First, it was not possible to evaluate block success through dermatomal analysis as most children are unable to grasp the concept of paraesthesia, and even if they could, it would still not be possible as the patients were under general anesthesia when the block was being performed. In addition, we could not perform the block technique using the same volume saline solution to Group II patients. However, objectivity was key in this study; the same anesthesiologist performed the block each time, and another blinded anesthesiologist from our department's "Pain Crew" performed the post-operative follow-up.

Conclusion

Through this study, we suggest that ultrasound-guided TFP block provides lower post-operative pain scores in pediatric inguinal hernia repair; furthermore, it is a simple, safe and practical technique. Further studies are warranted to verify these findings and define the block's clinical characteristics better.

Funding

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Application value of opioid-free anesthesia in renal cyst decompression by laparoscopy

Valor de la aplicación de anestesia sin opiáceos en la descompresión de quiste renal por laparoscopia

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Abstract

Objective: *The objective of the study was to analyze the application value of opioid-free anesthesia (OFA) in renal cyst decompression by laparoscopy.* **Method:** *A total of 124 patients undergoing renal cyst decompression by laparoscopy in our hospital were selected and divided into opioid anesthesia (OA) and OFA groups (n = 62). Fentanyl and remifentanil were used for anesthesia induction in the OA group, while lidocaine and dexmedetomidine were employed for anesthesia induction in the OFA group. The homeostasis indicators (cortisol [Cor], adrenocorticotropic hormone [ACTH], C-reactive protein [CRP], and interleukin-6 [IL-6]) were also compared 10 min before anesthesia (T_a), at the end of operation (T_b), and 24 h after operation (T_c).* **Results:** *At T_1-T_3, heart rate, mean arterial pressure, mean airway pressure, and partial pressure of end-tidal carbon dioxide were all lower in OFA group than those in OA group ($p < 0.05$). At T_b-T_c, the levels of Cor, ACTH, CRP, and IL-6 were all higher in both groups than those at T_a ($p < 0.05$), while they were lower in OFA group than those in OA group ($p < 0.05$).* **Conclusion:** *OFA is more beneficial to the respiratory and circulatory system and homeostasis of patients, and has higher anesthetic safety.*

Keywords: *Renal cyst decompression. Laparoscopy. Opioid-free. Anesthesia. Respiratory circulatory system.*

Resumen

Objetivo: *Analizar el valor de la aplicación de anestesia libre de opiáceos (ALO) en la descompresión de quiste renal por laparoscopia.* **Método:** *Se seleccionaron 124 pacientes sometidos a descompresión de quiste renal por laparoscopia en nuestro hospital, que se dividieron en grupos de anestesia con opiáceos (AO) y ALO (n = 62). El fentanilo y el remifentanilo se utilizaron para la inducción de la anestesia en el grupo AO, mientras que la lidocaína y la dexmedetomidina se emplearon para la inducción de la anestesia en el grupo ALO. También se compararon los indicadores de homeostasis (cortisol, hormona adrenocorticotropa [ACTH], proteína C reactiva [PCR] e interleucina 6 [IL-6]) 10 minutos antes de la anestesia (T_a), al final de la operación (T_b) y 24 h después de esta (T_c).* **Resultados:** *En T_1-T_3, la frecuencia cardíaca, la presión arterial media, la presión media de las vías respiratorias y la presión parcial de dióxido de carbono al final de la espiración fueron todas más bajas en el grupo ALO que en el grupo AO ($p < 0,05$). En T_b-T_c, los niveles de Cor ACTH, PCR e IL-6 fueron más altos en ambos grupos que en T_a ($p < 0.05$), mientras que fueron más bajos en el grupo ALO que en el grupo OA ($p < 0.05$).* **Conclusión:** *La ALO es más beneficiosa para los sistemas respiratorio y circulatorio, y para la homeostasis, de los pacientes, y tiene mayor seguridad anestésica.*

Palabras clave: *Descompresión de quiste renal. Laparoscopia. Anestesia libre de opiáceos. Sistema circulatorio. Sistema respiratorio.*

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Introduction

Renal cyst is an asymptomatic benign disease with an incidence rate of about 50%. At present, this disease is mainly treated by surgeries, such as renal cyst decompression by laparoscopy that locates and resects renal cysts to relieve clinical symptoms. However, this surgical method poses high requirements to anesthetists. Improper anesthesia leads to intraoperative hemodynamic instability, post-operative pain, and other adverse events. Therefore, reasonable and effective anesthesia modes are particularly important for patients undergoing renal cyst decompression by laparoscopy[1]. General anesthesia can meet the requirements of anesthesia in this surgery, in which opioids are indispensable. With the use of opioid anesthetics, the pain problem has been overcome. However, opioid anesthetics can lead to adverse events such as respiratory depression, urinary retention, and hyperalgesia, which not only delay post-operative recovery but also increase the medical cost[2,3]. To solve the above problems, opioid-free anesthesia (OFA) has been put forward, which is a multi-mode anesthesia combining non-steroidal anti-inflammatory drugs, local anesthetics, and sedatives and primarily used to reduce adverse events caused by opioid anesthetics[4,5]. In this study, the application value of OFA in renal cyst decompression by laparoscopy was explored, thereby providing references for the selection of anesthesia mode.

Method

Subjects

A total of 124 patients undergoing renal cyst decompression by laparoscopy in our hospital from February 2021 to February 2022 were selected and divided into opioid anesthesia (OA) group (n = 62) and OFA group (n = 62) using a random number table. In the OA group, there were 38 males and 24 females aged 35-63 years, with a body mass index (BMI) of 22-28 kg/m^2. In the OFA group, there were 35 males and 27 females aged 35-65 years, with a BMI of 22-28.5 kg/m^2. The general data were comparable between the two groups (Table 1). Inclusion criteria were as follows: (1) patients with renal cysts diagnosed by imaging examinations, (2) those with unilateral cysts, (3) those undergoing renal cyst decompression by laparoscopy, meeting the surgical indications and without contraindications to surgery and anesthesia, (4) those in American Society of Anesthesiologists Grade I-III, (5) those not pregnant or lactating, and (6) those who voluntarily participated in this study. Exclusion criteria were as follows: (1) patients with local or systemic infection, (2) those with drug allergy, (3) those with a history of renal cyst decompression by laparoscopy, (4) those with abnormal pain sensitivity or unable to perceive pain, (5) those with coagulation dysfunction, (6) those with dysfunction of vital organs, such as the heart, liver and kidney, (7) those with cognitive or communication disorders, or (8) those with mental disorders.

Anesthesia methods

The patients in both groups were routinely deprived of food and water before the operation. After they entered the operating room, the venous access was opened, and the vital signs were routinely monitored. Fentanyl (intravenous [IV], 3 μg/kg) and remifentanil (IV pumping, 15.0 μg/kg·h) were used for anesthesia induction in OA group. In the OFA group, dexmedetomidine was intravenously pumped at 0.5 μg/kg within 10 min and then maintained at 0.5 μg/kg·h, and lidocaine was intravenously injected at 1.0 mg/kg and then maintained at 2.0 mg/kg·h. Other anesthetics were the same in both groups, including propofol (IV, 2 mg/kg), midazolam (IV, 0.03 mg/kg), and vecuronium (IV, 0.15 mg/kg). After anesthesia induction, the laryngeal mask was inserted and the bispectral index (BIS) monitor was connected. Based on the BIS, the dosage of propofol was adjusted and kept at 40-60. If the patient's heart rate (HR) was lower than 50 beats/min during operation, 0.5 mg of atropine would be intramuscularly injected. If the patient's blood pressure greatly fluctuated (>30% of the baseline value) during the operation, vasoactive drugs would be used. Extubation was performed after the recovery of consciousness. Routine analgesia, anti-inflammation, and anti-infection were all performed after the operation.

Surgical methods

After anesthesia, the patient in the lateral decubitus position was elevated at the waist on the affected side. A 15-mm transverse incision was made at the lower border of the 12th rib of the midaxillary line. Then the lumbar fascia and muscle layer were separated, and the peritoneum was pushed open, into which laparoscope (Tekno-Medical Optik-Chirurgie GmbH,

Germany; Registration Certificate for Medical Device: 20163061348) and laparoscopic surgical instruments (Olympus Winter and Ibe GmbH, Japan; Registration Certificate for Medical Device: 20173016482) were placed. Carbon dioxide was infused, and the pneumoperitoneum pressure was maintained at 14 mmHg. The extraperitoneal fat was removed, and three approximately avascular planes of the retroperitoneal cavity were dissected. The fat sac and perirenal fascia were separated to fully expose the renal cyst. The hernia sac wall was excised with an ultrasonic scalpel (Soering GmbH, Germany; Registration Certificate for Medical Device: 20163012365) at a distance of 00 cm from the renal parenchyma, and subjected to pathological examination. After hemostasis, the surgery was routinely completed when there was no active bleeding.

Evaluation of respiratory and circulatory system indicators

The stability of the respiratory and circulatory system was monitored and assessed by the HR, mean arterial pressure (MAP), partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), and mean airway pressure (P_{mean}) at 10 min before anesthesia (T_0), at the time of anesthesia induction (T_1), 10 min after anesthesia (T_2), and 30 min after anesthesia (T_3).

Assessment of homeostasis

The homeostasis of patients was assessed by cortisol (Cor), adrenocorticotropic hormone (ACTH), C-reactive protein (CRP), and interleukin-6 (IL-6). At 10 min before anesthesia (T_a), at the end of operation (T_b), and 24 h after operation (T_c), 2 mL of venous blood was drawn, and the serum was separated. Then, the levels of Cor and ACTH were measured by radioimmunoassay, and the levels of CRP and IL-6 were measured using a DK-3506 automatic multifunctional microplate reader.

Efficacy evaluation

The anesthetic efficacy (excellent, good, and poor) was evaluated. The efficacy was excellent if no pain or discomfort occurred during the operation and the effect of muscle relaxation was good. The efficacy was good if mild pain or discomfort occurred during the operation, and drug-assisted sedation was needed. The efficacy was poor if unbearable severe pain occurred, and the anesthesia mode needed to be changed. Excellent/good rate of anesthesia = ([excellent cases + good cases]/total cases) ×100%.

Safety evaluation

The incidence of anesthesia-related adverse reactions, including nausea and vomiting, bucking, dysphoria, respiratory depression, and urinary retention, was recorded in the two groups.

Evaluation of post-operative recovery time

The recovery time of spontaneous breathing, awakening time, and observation time was compared between the two groups.

Analysis of incidence of post-operative cognitive impairment

The patient's cognitive status was assessed using the mini-mental state examination at 12 h, 24 h, and 48 h after operation. The total score < 17 points for illiteracy, < 20 points for primary school, < 22 points for technical secondary school and senior high school, and < 23 points for junior college and above indicated cognitive impairment.

Statistical analysis

SPSS22.0 software was used for statistical analysis. Measurement data were described by ($\bar{x} \pm s$) and compared by the independent-samples *t*-test between two groups and at each time point within the same group by repeated measures analysis of variance. Count data were described by percentage and compared between two groups by the χ^2 test. The rank sum test was conducted on ranked data. $p < 0.05$ was considered statistically significant.

Results

General data

There were no significant differences in the general data between OA and OFA groups ($p > 0.05$) (Table 1).

Levels of respiratory and circulatory system indicators

The respiratory and circulatory system indicators (HR, MAP, P_{mean} and $P_{ET}CO_2$) had no statistically

Table 1. General data

Indicator	OA group (n = 62)	OFA group (n = 62)	χ^2/t	p
Gender				
Male	38 (61.29)	35 (56.45)	0.300	0.584
Female	24 (38.71)	27 (43.55)		
Age (years)	50.62 ± 3.41	50.29 ± 4.25	0.477	0.634
BMI (kg/m^2)	25.63 ± 2.33	25.72 ± 2.34	0.215	0.830
ASA grade	11 (17.74)	14 (22.58)		
I	29 (46.77)	30 (48.39)	0.777	0.678
II	22 (35.48)	18 (29.03)		
III				
Type of surgery				
Lithotripsy of ureteral calculi	12 (19.35)	14 (22.58)	0.585	0.989
Urethroplasty	3 (4.84)	4 (6.45)		
Excision of renal cyst	10 (16.13)	9 (14.52)		
Removal of renal calculi	13 (20.97)	12 (19.35)		
Excision of renal tumor	15 (24.19)	13 (20.97)		
Excision of bladder tumor	9 (14.52)	10 (16.13)		

OA: opioid anesthesia; OFA: opioid-free anesthesia; BMI: body mass index; ASA: American Society of Anesthesiologists.

significant differences between OA group and OFA group at T_0 ($p > 0.05$). At T_1-T_3, HR, MAP, P_{mean}, and $P_{ET}CO_2$ all increased in OA group compared with those at T_0 ($p < 0.05$), and they also increased in OFA group compared with those at T_0, but there were no statistically significant differences ($p > 0.05$). At T_1-T_3, HR, MAP, P_{mean}, and $P_{ET}CO_2$ were all lower in OFA group than those in OA group ($p < 0.05$) (Table 2).

Perioperative homeostasis

The levels of homeostasis indicators (Cor, ACTH, CRP, and IL-6) had no statistically significant differences between OA group and OFA group at T_a ($p > 0.05$). At T_b-T_c, they were all higher in both groups than those at T_a ($p < 0.05$), while they were lower in OFA group than those in OA group ($p < 0.05$) (Table 3).

Anesthetic efficacy

The anesthetic efficacy had no statistically significant difference between OA group and OFA group ($p > 0.05$) (Table 4).

Table 2. Levels of respiratory and circulatory system indicators ($\bar{x} \pm s$)

Indicator	Time point	OA group (n = 62)	OFA group (n = 62)	t	p
HR (beat/min)	T_0	76.89 ± 10.73	76.93 ± 10.32	0.022	0.983
	T_1	86.67 ± 7.93	77.89 ± 7.09	6.499	< 0.001
	T_2	96.76 ± 10.15	79.43 ± 9.22	9.951	< 0.001
	T_3	84.52 ± 8.93	80.92 ± 8.15	2.345	0.021
MAP (mmHg)	T_0	85.42 ± 9.91	85.53 ± 9.98	0.062	0.951
	T_1	94.62 ± 8.93	87.71 ± 9.42	4.192	< 0.001
	T_2	104.53 ± 10.32	88.92 ± 9.87	8.607	< 0.001
	T_3	96.78 ± 10.34	87.45 ± 7.93	5.638	< 0.001
P_{mean} (cmH_2O)	T_0	32.15 ± 2.19	32.18 ± 2.22	0.076	0.740
	T_1	36.74 ± 3.33	33.42 ± 3.89	5.105	< 0.001
	T_2	39.09 ± 3.12	35.71 ± 3.51	5.667	< 0.001
	T_3	36.18 ± 3.52	34.29 ± 3.20	3.128	< 0.001
$P_{ET}CO_2$ (mmHg)	T_0	3.10 ± 0.24	3.12 ± 0.23	0.474	0.637
	T_1	4.12 ± 0.20	3.67 ± 0.21	12.220	< 0.001
	T_2	5.89 ± 0.42	3.98 ± 0.16	33.460	< 0.001
	T_3	4.32 ± 0.14	3.71 ± 0.13	25.140	< 0.001

OA: opioid anesthesia; OFA: opioid-free anesthesia; T_0: 10 min before anesthesia; T_1: at the time of anesthesia induction; T_2: 10 min after anesthesia; T_3: 30 min after anesthesia; HR: heart rate; MAP: mean arterial pressure; P_{mean}: mean airway pressure, $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide.

Table 3. Perioperative homeostasis ($\bar{x} \pm s$)

Indicator	Time point	OA group (n = 62)	OFA group (n = 62)	t	p
Cor (ng/mL)	T_a	123.42 ± 10.79	123.51 ± 10.86	0.046	0.963
	T_b	165.82 ± 18.93	143.44 ± 11.73	7.913	< 0.001
	T_c	150.92 ± 13.54	130.92 ± 10.02	9.349	< 0.001
ACTH (pg/mL)	T_a	24.53 ± 2.06	24.56 ± 2.13	0.080	0.937
	T_b	48.07 ± 6.89	33.19 ± 2.34	16.100	< 0.001
	T_c	30.42 ± 3.41	27.80 ± 2.31	5.009	< 0.001
CRP (ng/mL)	T_a	334.52 ± 48.91	334.61 ± 47.93	0.010	0.992
	T_b	469.08 ± 55.03	389.09 ± 41.28	9.156	< 0.001
	T_c	400.01 ± 45.81	352.01 ± 28.93	6.976	< 0.001
IL-6 (pg/mL)	T_a	10.32 ± 1.17	10.54 ± 1.09	1.083	0.281
	T_b	23.51 ± 1.23	18.90 ± 3.29	10.330	< 0.001
	T_c	18.98 ± 1.28	14.28 ± 2.13	14.890	< 0.001

OA: opioid anesthesia; OFA: opioid-free anesthesia; T_a: 10 min before anesthesia; T_b: at the end of operation; T_c: 24 h after operation; Cor: cortisol; ACTH: adrenocorticotropic hormone; CRP: C-reactive protein; IL-6: interleukin-6.

Table 4. Anesthetic efficacy (n [%])

Anesthetic efficacy	OA group (n = 62)	OFA group (n = 62)	χ^2	p
Excellent	45	43		
Good	12	15		
Poor	5	4		
Excellent/good rate	57 (91.34)	58 (93.55)	0.120	0.729

OA: opioid anesthesia; OFA: opioid-free anesthesia.

Table 5. Anesthetic safety (n [%])

Adverse reaction	OA group (n = 62)	OFA group (n = 62)	χ^2	p
Nausea and vomiting	3	2		
Bucking	1	0		
Dysphoria	2	1		
Respiratory depression	3	0		
Urinary retention	3	0		
Total incidence rate	12 (19.35)	3 (4.84)	6.143	0.013

OA: opioid anesthesia; OFA: opioid-free anesthesia.

Anesthetic safety

In OFA group, the anesthetic safety was higher, that is, the incidence of anesthesia-related adverse reactions was lower, than that in OA group ($p < 0.05$) (Table 5).

Post-operative recovery time

There was no significant difference in the recovery time of spontaneous breathing ([10.43 ± 1.29] vs. [10.47 ± 1.33] min), awakening time ([6.78 ± 0.89] vs. [6.90 ± 0.81] min) or observation time ([54.63 ± 4.51] vs. [54.89 ± 4.82] min) between OA and OFA groups ($p > 0.05$).

Incidence rate of post-operative cognitive impairment

The incidence rate of cognitive impairment in OFA group was lower than that in OA group at 12 h after the operation ($p < 0.05$), while it had no statistically significant difference between the two groups at 24 and 48 h after the operation ($p > 0.05$) (Table 6).

Table 6. Incidence rate of post-operative cognitive impairment (n [%])

Indicator	OA group (n = 62)	OFA group (n = 62)	χ^2	p
12 h after operation	14 (22.58)	4 (6.45)	6.499	0.011
24 h after operation	3 (4.84)	2 (3.23)	0.208	0.648
48 h after operation	1 (1.61)	0	1.008	0.315

OA: opioid anesthesia; OFA: opioid-free anesthesia.

Discussion

Opioid anesthetics have a good analgesic effect in traditional general anesthesia and solve many clinical problems. However, they have been gradually abused in clinical surgery due to the limitation of the quantitative evaluation method of pain, and the number of deaths due to opioids is increasing[6]. To solve the above problem, OFA has been gradually applied in general anesthesia. OFA combines a variety of non-opioid anesthetics, improving the safety of anesthetics, such as non-steroidal anti-inflammatory drugs, acetaminophen, sodium channel antagonists, and α_2-receptor agonists[7-9].

Studies have shown that lidocaine, a sodium channel antagonist, can reduce the dosage of analgesics during operation, effectively relieve the body stress response, and maintain hemodynamic stability[10,11]. Moreover, lidocaine intravenously injected can effectively relieve the internal environment disturbance caused by tracheal intubation and reduce the interference of tracheal intubation on the patient's autonomic nerve during the induction of general anesthesia[12,13]. Hanson et al.[14] found that as compared to ultrasound-guided unilateral single-injection TAP block, continuous infusion of lidocaine could achieve non-inferior post-operative analgesia without causing internal environment disturbance during the first 24 h after renal transplantation. Besides, dexmedetomidine is an α_2-receptor agonist and one of the most commonly used alternatives to opioids in OFA, which has a wide range of effects, such as sedation, analgesia, antianxiety, and anti-post-operative nausea and vomiting[15,16]. It has been found[17] that dexmedetomidine can activate α_2-receptors in the central nervous system to increase the vagus nerve activity, reduce the sympathetic outflow, and block peripheral ganglia, thereby exerting an anti-sympathetic effect. It has been reported[18,19] that dexmedetomidine inhibits the release of Cor through restraining the excitability of sympathetic nervous system, thus keeping homeostasis. Wang et al.[20] applied dexmedetomidine plus propofol IV

anesthesia in pediatric urological laparoscopic surgery and found that dexmedetomidine plus propofol IV anesthesia might help shorten the extubation time, recovery time, and residence time in anesthesia recovery room, improve the analgesic effect, and reduce the inflammatory response and expression of serum inflammatory cytokines, without increasing the risk of adverse reactions. In this study, OFA with lidocaine plus dexmedetomidine was used in renal cyst decompression by laparoscopy. The results showed that the anesthetic effect and post-operative recovery time were comparable between the two groups, but the incidence rate of adverse reactions was lower in OFA group, suggesting that OFA can reduce the incidence of anesthesia-related adverse reactions while ensuring the quality of anesthesia, which can be used for anesthesia in renal cyst decompression by laparoscopy.

According to studies[21-23], the patients are prone to respiratory and circulatory system disorders, and homeostasis changes under the stimulation of surgery and anesthesia, during which the expressions of Cor and ACTH will rise. With the increase in Cor, the secretion of CRP and IL-6 is enhanced. Therefore, the patient's homeostasis is often clinically assessed by Cor, ACTH, CRP, and IL-6. In this study, the influences of different anesthesia modes on the respiratory and circulatory system and homeostasis were analyzed. The results showed that compared with OA, OFA did not lead to respiratory and circulatory system disorders and homeostasis changes. In addition, the incidence of post-operative cognitive impairment was analyzed in the two groups. It was found that the incidence rate of cognitive impairment was lower in the OFA group than that in OA group at 12 h after the operation, but it had no significant difference between the two groups at 24 and 48 h after the operation. It can be inferred that OFA can lower the risk of post-operative short-term cognitive impairment and facilitate rapid post-operative cognitive recovery, further verifying the safety of OFA.

Conclusion

OFA and OA have comparable anesthetic effects on renal cyst decompression by laparoscopy. OFA is more beneficial to the respiratory and circulatory system and homeostasis of patients, has higher anesthetic safety, and contributes to rapid post-operative recovery, so it is potentially applicable to clinical practice.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Association between complete blood count parameters and histologically proven acute appendicitis

Asociación entre los parámetros del hemograma y la apendicitis aguda histológicamente probada

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Abstract

Objectives: *The objective of the study was to assess the role of complete blood count (CBC) parameters in the detection of acute appendicitis (AA) severity in children and adults.* **Method:** *This is a retrospective analytic cross-sectional study on cases operated for AA between June 1, 2020, and February 28, 2021, in Salmaniya Medical Complex, Bahrain. Patients of all ages and genders were included in the study. Exclusion criteria included other appendiceal pathologies, the presence of another intraoperative pathology that is the likely cause of abdominal pain, normal appendix, and missing parameters. Data included patient demographics, CBC parameters, and histopathology. Patients were divided into groups based on age and severity of AA.* **Results:** *A total of 569 patients were included in the study. Ages ranged from 4 to 75 years. Majority of the patients were males (74.87%) and adults (89.81%). A quarter of the patients were diagnosed with complicated AA, while the rest had simple AA. A statistically significant difference was observed between adults with complicated and simple AA in white blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). None of the parameters was statistically significant in children.* **Conclusion:** *WBC, ANC, ALC, NLR, and PLR can be useful parameters in the discrimination between complicated and simple AA in adults. PLR was found to be the least predictive.*

Keywords: *Platelet-to-lymphocyte ratio. Neutrophil-to-lymphocyte ratio. Lymphocyte. Neutrophil. Leukocyte. Appendicitis.*

Resumen

Objetivos: *Evaluar la función de los parámetros del conteo sanguíneo completo (CSC) en la detección de la gravedad de la apendicitis aguda (AA) en niños y adultos.* **Método:** *Se trata de un estudio transversal analítico retrospectivo de casos operados por AA en nuestro hospital. Se incluyeron pacientes de todas las edades y sexos. Los criterios de exclusión incluyeron otras patologías apendiculares, presencia de otra patología intraoperatoria que es la causa probable de dolor abdominal, apéndice normal y ausencia de parámetros. Los datos incluyeron datos demográficos de los pacientes, parámetros de CSC e histopatología. Los pacientes se dividieron en grupos según la edad y la gravedad de la AA.* **Resultados:** *Se incluyeron un total de 569 pacientes. Las edades oscilaron entre los 4 y los 75 años. La mayoría de los pacientes eran hombres (74.87%) y adultos (89.81%). Una cuarta parte de los pacientes fueron diagnosticados con AA complicada. Se observó una diferencia estadísticamente significativa entre adultos con AA complicada y simple en GB, RAN, RAL, INL e IPL. Ninguno de los parámetros fue estadísticamente significativo en niños.* **Conclusión:** *GB, RAN, RAL, INL e IPL pueden ser útiles en la discriminación entre AA complicada y simple en adultos. IPL fue el menos predictivo.*

Palabras clave: *Índice plaqueta-linfocito. Índice neutrófilo-linfocito. Linfocito. Neutrófilo. Leucocito. Apendicitis.*

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Introduction

Acute appendicitis (AA) is a common surgical problem. There were an estimated 17.7 million cases worldwide in 2019[1]. The diagnosis is guided by clinical assessment, laboratory investigations, radiological studies, and clinical scores and can often be challenging[2]. Hence, there is always a need to explore additional tools to aid in the diagnosis of this common disease.

White blood cell (WBC) count is a marker that is well-studied and known to be associated with AA. It forms part of the Alvarado score that is used to aid in diagnosing AA[3-6]. Absolute neutrophil count (ANC) has been found to be associated with AA[6]. Several recent studies have investigated the use of other complete blood count (CBC) parameters as new biomarkers in the diagnosis of AA with varying results. Absolute lymphocyte count (ALC), particularly lymphocytopenia, has been reported to be associated with gangrenous AA[7]. Platelets play a role in inflammation. Accordingly, platelet indices including platelet (PLT) count, platelet size distribution or platelet distribution width (PDW), and mean platelet volume (MPV) have been studied and found to be associated with various inflammatory conditions. For example, MPV was found to be altered in several inflammatory conditions, including AA. A systematic review reported high MPV values in complicated AA and low values in non-complicated cases[8,9]. Red blood cell distribution width (RDW) is another marker that has been found to be associated with inflammatory pathologies in addition to AA[10,11]. Ratios including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are recognized as novel inflammatory markers in several conditions[12]. Their role in the diagnosis of AA and assessing its severity has been studied with promising results[13,14].

The aim of this study is to evaluate the utilization of the aforementioned CBC parameters in the detection of simple and complicated AA in children and adults.

Method

Study design

This is a retrospective, analytic, cross-sectional study on cases operated for AA between June 1, 2020, and February 28, 2021, in Salmaniya Medical Complex, Kingdom of Bahrain. Data included patient demographics (age and gender), laboratory parameters, and histopathological evaluation. CBC parameters included are as follows (with laboratory reference range): WBC count (normal: 3.6-9.6 × 10^9/L), RDW (11.6-13.7 fL), PLT count (150-400 × 10^9/L), MPV (8-11.5 fL), PDW (46-50%), ANC (2.3-8.1 × 10^9/L), and ALC (not defined). Investigations were obtained preoperatively at the time of presentation to the emergency department. NLR and PLR were calculated. Data were collected from the National Health Information System (I-SEHA) using current procedural terminology (CPT®) codes from operating theater logs and pathology department records.

Table 1. Excluded cases

Exclusion criteria	n	%
Presence of another significant intraoperative pathology that is the likely cause of abdominal pain (in which the appendix was included with another specimen)	8	1.36
Other pathologies within the appendix (polyp, mucocele, neuroendocrine tumor)	6	1.02
Incomplete laboratory parameters	4	0.68
Normal appendix	0	0.00
Total number of patients	18	3.07

Participants

Patients of all ages, both males and females, were included in the study. Exclusion criteria included other pathologies within the appendix, the presence of another significant intraoperative pathology that is the likely cause of abdominal pain, normal appendix, and incomplete laboratory parameters (Table 1).

Patients were initially divided into two groups according to age: adults and pediatrics. They were further divided into subgroups according to histopathological diagnosis and operation records: complicated (including perforated, gangrenous by histopathology, early mass-forming or mass-forming appendicitis, and presence of abscess or pus) and simple (any case that does not satisfy the above criteria, also including fibrous obliteration of the lumen and reactive lymphoid hyperplasia) AA.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS®)

Table 2. Descriptive statistics of the study groups

Parameter	Group I: adults			Group II: pediatrics		
Cases (%)	511 (89.81%)			58 (10.19%)		
Histopathological diagnosis	**Complicated AA (%)**	**Simple AA (%)**	**p**	**Complicated AA (%)**	**Simple AA (%)**	**p**
	124 (86.11%)	387 (91.06%)		20 (13.89%)	38 (8.94%)	
Age (years)†	35.63 ± 10.97 (15-62)‡	31.30 ± 9.66 (14-75)‡	0.000	8.85 ± 3.18 (4-13)‡	9.82 ± 2.41 (4-13)‡	0.303
Male (%)	101 (81.45%)	288 (74.42%)	0.110	14 (70.00%)	23 (60.53%)	0.479
Female (%)	23 (18.55%)	99 (25.58%)		6 (30.00%)	15 (39.47%)	
WBC (× 10^9/L)	13.44§	11.48§	0.000	13.38 ± 3.01†	11.85 ± 4.57†	0.183
RDW (fL)	13.65§	13.80§	0.218	13.55§	13.95§	0.226
PLT (× 10^9/L)	227.50§	238§	0.090	259.50§	266.50§	0.851
MPV (fL)	9.20§	8.90§	0.095	8.56 ± 1.93†	8.75 ± 1.59†	0.685
PDW (%)	42.30§	42.70§	0.814	36.42 ± 10.33†	37.10 ± 9.44†	0.800
ANC (× 10^9/L)	11.00§	9.00§	0.000	10.80 ± 2.90†	9.68 ± 4.62†	0.330
ALC (× 10^9/L)	1.36§	1.74§	0.000	1.27§	1.29§	0.819
NLR	7.77§	4.76§	0.000	9.02§	7.26§	0.659
PLR	158.78§	140.65§	0.028	214.20§	202.37§	0.545

†Mean ± SD.
‡: (min-max).
§Median.
AA: acute appendicitis; WBC: white blood cells; RDW: red blood cell distribution width; PLT: platelets; MPV: mean platelet volume; PDW: platelet size distribution or platelet distribution width; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

software for Windows, version 28.0, and Microsoft Excel for Mac, version 16.54. Categorical variables were reported as the absolute frequency and percentage (%). Shapiro–Wilk test and histograms with Bell curves were used to test for normality of data distribution. Normally distributed continuous variables were reported as the mean ± standard deviation (SD) and compared using the independent sample t-test while continuous variables with deviation from normality were reported as the median and compared using Mann–Whitney U test. Receiver operating characteristic (ROC) curves were created to measure the ability of CBC parameters to distinguish complicated cases. The area under the curve (AUC) and the optimal cutoff point for significant parameters were determined. AUC ranges were classified as: 0.9-1.0 (Excellent), 0.8-0.9 (Good), 0.7-0.8 (Fair), 0.6-0.7 (Poor), and 0.5-0.6 (Failure). Sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated. A significance level of probability (p) of less than 0.05 was considered statistically significant.

Ethical consideration

This study was approved by the Secondary Health Care Research Committee, Kingdom of Bahrain.

Results

A total of 569 patients were included in the study. The age range of the patient population was from 4 to 75 years. The majority of the patients were males; 426 (74.87%) and adults; 511 (89.81%). One hundred forty-four (25.31%) patients were diagnosed with complicated AA while 425 (74.69%) patients were diagnosed with simple AA. Descriptive data of all patients and a comparison of CBC parameters are presented in Table 2. A statistically significant difference was observed between adult patients with complicated and simple AA in WBC, ANC, ALC, NLR, and PLR values. None of the CBC parameters was found to be statistically significant in pediatric patients.

Table 3. Significant CBC parameters in adults

CBC parameter	Proposed optimal cutoff point	AUC	p	Sensitivity (%)	Specificity (%)	LR+	LR−
WBC (× 10^9/L)	12.46	0.632	0.000	58.9	58.9	1.43	0.70
ANC (× 10^9/L)	9.50	0.652	0.000	65.3	55.3	1.46	0.63
ALC (× 10^9/L)†	1.55	0.613	0.000	58.1	58.9	1.41	0.71
NLR	6.52	0.651	0.000	62.1	60.7	1.58	0.62
PLR	146.16	0.566	0.028	51.6	52.2	1.08	0.93

†For small values.
CBC: complete blood count; AUC: area under the curve; LR+: positive likelihood ratio; LR-: negative likelihood ratio; WBC: white blood cells; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

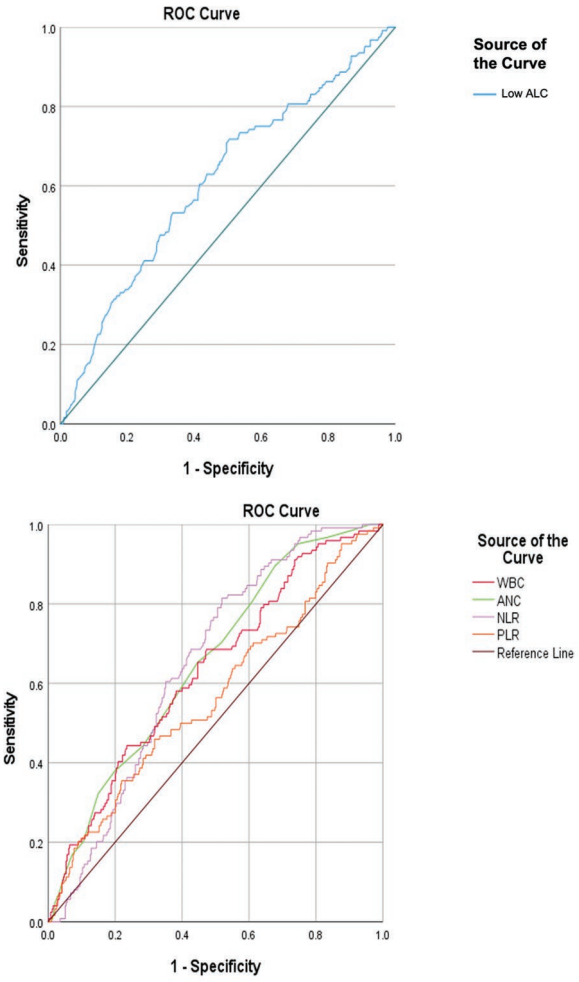

Figure 1. *ROC curves for significant CBC parameters in adults. ROC: receiver operating characteristic; ALC: absolute lymphocyte count; WBC: white blood cells; ANC: absolute neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.*

The ability of CBC parameters to distinguish the two groups was evaluated by generating ROC curves for the significant parameters in adults. AUC ranges were considered poor for WBC, ANC, NLR and low ALC or lymphocytopenia and a failure for PLR. AUC was found to be statistically significant for all parameters (Table 3 and Fig. 1).

Discussion

The diagnosis of AA can often be challenging and hence, there is a need to explore biomarkers to aid in the diagnosis of this common disease and detect complicated cases early. CBC is a widely available and routinely requested test for patients presenting with abdominal pain and suspected AA.

Leukocytosis refers to elevated WBC count and is associated with acute and chronic inflammatory stressors. The specific value of elevation varies between laboratories depending on their defined reference ranges[15]. In this study, the means and medians of WBC count were found to be high among all patient groups. Higher values were observed in patients in the complicated AA group. At a cutoff point of 12.46, it has a sensitivity and specificity of 58.9%, LR+ of 1.43, and LR- of 0.70 (AUC = 0.632) in distinguishing cases of complicated and simple AA in adult patients. In a study by Yang et al., it was reported that elevated WBC count was found to be associated with a higher risk of perforation in children[4]. However, in the present study, a statistically significant difference was found among adult patients of the two groups with regard to elevated WBC counts but not in pediatrics. Similarly, Peksöz et al. reported WBC count as an important factor in predicting complicated AA[16]. On the other hand, Sevinç et al. have found that WBC count is not associated with perforated cases in adults[3].

RDW is a part of the CBC panel and is a measure of variation in the size of red blood cells or anisocytosis[17]. There is a recent increased interest in RDW as an inflammatory biomarker. It has been found to be

elevated in several conditions including post-operative complications in surgical patients, active systemic lupus erythematosus, viral infections, cardiovascular, and cerebrovascular diseases, among many others[10,18-20]. The medians of RDW were found to be high in all groups except for pediatrics with complicated AA (upper limit of normal). No statistically significant difference was found among the groups for the detection of complicated AA. A study conducted on children found that RDW has no diagnostic value in predicting the severity of AA[21]. Maghsoudi et al. as well did not favor the use of RDW when studied on patients with negative and positive appendectomies[22]. However, two other studies have found that RDW was significantly higher in complicated AA cases[11,23]. Moreover, a systematic review and meta-analysis of 5,222 cases revealed no statistical significance in RDW among cases with AA and others[24].

Platelets play a role in inflammation, including recognizing microorganisms and facilitating immune responses[8]. Platelet indices were found to be altered in several medical and surgical conditions, including diabetes mellitus, active Crohn's disease, acute cholecystitis, and AA, among others[9]. Platelet indices were investigated in the present study in relation to AA, namely, PLT count, MPV, and PDW. The means and medians of PLT count and MPV were found to be within normal ranges among all patients, while PDW was found to be lower than normal. No statistically significant difference was observed among the groups. In a meta-analysis including nine studies on the role of platelet indices in the diagnosis of AA and prediction of its complications, it was concluded that low MPV was useful in the diagnosis of AA but could not predict its complications[25].

Neutrophils are considered the first line of defense by the innate immune system as they destroy microorganisms and also act as mediators of inflammation[26]. Together with the WBC count, they are the earliest indicators of inflammation in AA but are not specific to it[27]. In this study, the values of ANC were found to be higher than normal in all groups and to be statistically significant among adult patients but not in pediatrics. Higher values were detected in patients in the complicated AA group. At a cutoff point of 9.50, it has a sensitivity of 65.3%, specificity of 55.3%, LR+ of 1.46, and LR- of 0.63 (AUC = 0.652) in distinguishing cases of complicated and simple AA in adults. It is well known that elevated neutrophil counts or neutrophilia is correlated with AA and forms part of the Alvarado score that is used to aid in diagnosing AA, along with high WBC count[5,6]. In addition to that, neutrophilia was found in some studies to be useful in determining the severity of AA in adolescents and adults[16]. Moreover, in pediatrics, neutrophil percentage was reported to be useful in detecting perforated AA by Yang et al.[4]

Lymphocytopenia associated with gangrenous AA has been reported in the literature[7]. In the present study, reduced ALC values were used in the comparison between complicated and simple AA groups with a statistically significant difference. When the cutoff point was set at 1.55, low ALC was found to have a sensitivity of 58.1%, specificity of 58.9%, LR+ of 1.41, and LR- of 0.71 (AUC = 0.613) in adults. In a study by Platon et al., leukocytosis, together with lymphocytopenia, was associated with significant pathology on computed tomography (CT) scan of the abdomen, including one case of AA out of 71 cases with other pathologies[28].

There is a growing interest in novel CBC-based inflammatory indices or ratios including NLR and PLR as markers and prognostic factors in a number of disease conditions[12]. Their role in AA and the detection of complicated cases was explored in the present study. The values of NLR were found to be higher than normal with a statistically significant difference between the two age groups. At a cutoff point of 6.52, it has a sensitivity of 62.1%, specificity of 60.7%, LR+ of 1.58, and LR- of 0.62 (AUC = 0.651) in distinguishing cases of complicated and simple AA in adults. This is in line with other studies that reported NLR as a useful biomarker in predicting complicated AA. NLR was useful in diagnosing AA and predicting its severity by Peksöz et al. Furthermore, Sevinç et al. observed that NLR >3.0 was significantly associated with a definite diagnosis of AA in suspected cases while in confirmed cases, NLR >4.8 was significantly associated with perforated AA[3].

Finally, the levels of PLR were found to be higher than normal with a statistically significant difference between the two age groups. At a cutoff point of 146.16, it has a sensitivity of 51.6%, specificity of 52.2%, LR+ of 1.08, and LR- of 0.93 (AUC = 0.566) in distinguishing cases of complicated and simple AA in adults. PLR has been reported in the literature to be a useful marker in the diagnosis of AA and its complications. Celik et al. evaluated the role of both NLR and PLR in 334 pediatric patients who underwent surgery for AA. Subjects with higher NLR and PLR values were more likely to

develop complicated AA[29]. Comparably, Pehlivanlı et al. found that patients with normal appendix on pathological assessment had lower values of NLR and PLR compared to those with AA and perforated AA[30]. In a systematic review and meta-analysis, significant increase in PLR values was detected in patients with AA[13]. Additional studies are required to confirm and support the above reported findings and to establish the appropriate cutoff values in relation to AA.

There are several limitations to this study. The retrospective design of the study meant that some data could not be retrieved due to documentation factors. Patients who were diagnosed with AA but were not operated on for any reason were not included in the study. Timing of symptom onset to presentation and blood sample extraction could influence the results.

Conclusion

There is no specific biomarker for the diagnosis of AA and its complications. CBC is a comprehensive and widely available test. WBC, ANC, ALC, NLR, and PLR can be useful parameters in the discrimination between complicated and simple AA in adults. PLR, however, was found to be the least predictive among these parameters.

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The author declares that no funding was received for this study.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Exenatide improves cisplatin induced ovarian damage through NLRP3, Nrf-2, and TLR4 pathways

La exenatida mejora el daño ovárico inducido por cisplatino a través de las vías NLRP3, Nrf-2 y TLR4

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Abstract

Objective: *Cisplatin (CP) toxicity causes ovarian damage by oxidative stress, inflammation and fibrosis. The aim of the present study is to investigate the possible beneficial effects of exenatide on the experimental ovarian damage model produced by CP.* **Method:** *For 14 rats, CP was administered by intraperitoneally (i.p) twice a week for 5 weeks. No drug was administered to the remainder of rats (n = 7) (Group 0). The rats taken CP were divided into two groups. Group 1 rats (n = 7) were given 1 mL/kg/day saline i.p., and Group 2 rats (n = 7) was given with 20 μg/kg/day exenatide.* **Results:** *The number of primordial, primary, secondary, and tertiary follicle was significantly lower in Group1 compared with Group 0 and Group 2. The ovarian fibrosis percent was significantly higher in Group 1 than Group 0 and 2. The plasma anti-Mullerian hormone value was lower in Group1compared with Group 0 and 2. Over Nuclear factor-erythroid factor 2-related factor 2 level, Over Toll-like receptor 4 level and over nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 were higher in Group 1 compared with Group 0 and 2.* **Conclusion:** *exenatide has possible beneficial effect on ovarian damage induced by CP by anti-inflammatory actions and can be a promising candidate for ovarian damage caused by CP.*

Keywords: *Cisplatin. Exenatide. Ovarian. Toxicity.*

Resumen

Objetivo: *La toxicidad del cisplatino causa daño ovárico por estrés oxidativo, inflamación y fibrosis. El objetivo del presente estudio fue investigar los posibles efectos beneficiosos de la exenatida en el modelo experimental de daño ovárico producido por el cisplatino.* **Método:** *A 14 ratas se les administró cisplatino por vía intraperitoneal (i.p.) dos veces por semana durante 5 semanas. No se administró fármaco al resto de la ratas (n = 7, grupo 0). Las ratas que recibieron cisplatino se dividieron en dos grupos. Las ratas del grupo 1 (n = 7) recibieron 1 ml/kg/día de solución salina i.p. y las ratas del grupo 2 (n = 7) recibieron 20 μg/kg/día de exenatida.* **Resultados:** *El número de folículos primordiales, primarios, secundarios y terciarios, fue significativamente menor en el grupo 1 en comparación con los grupos 0 y 2. El nivel superior a NrF2, el nivel superior a TLR-4 y el nivel superior a NLRP-3 fueron más altos en el grupo 1 en comparación con los grupos 0 y 2.* **Conclusión:** *La exenatida tiene un posible efecto beneficioso sobre el daño ovárico inducido por el cisplatino por acciones antiinflamatorias, y puede ser un agente candidato prometedor para el daño ovárico causado por el cisplatino.*

***Palabras clave*:** *Cisplatino. Exenatida. Ovario. Toxicidad.*

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Introduction

In 1978, the food and drug administration (FDA) authorized the use of cisplatin (CP) (cis-diamminedichloroplatinum [II]) as a chemotherapeutic agent and it is a widely used for a wide range of solid tumors[1]. Dose-dependent toxicity is one of the most significant obstacles to CP treatment[2], CP-induced ovarian damage in women of reproductive age is an important problem.

CP therapy causes injury to the ovary of experimental animals and 70% of animals treated with CP are sterile[3,4]. The most widely accepted mechanisms of CP toxicity10 are the production of reactive oxygen species (ROS) and the onset of oxidative stress. CP also increased the levels of proinflammatory cytokines in ovarian tissue[4]. Therefore, antioxidative and anti-inflammatory drugs may be beneficial for treating oxidative and inflammatory ovarian damage caused by CP-induced infertility.

The FDA approved exenatide, a peptide with similar physiological effects to glucagon-like peptide 1 (GLP-1) but a prolonged half-life, as a new type of hypoglycemic medication in 2005. GLP-1 was found to have vascular protection, neuroprotection, and anti-inflammatory properties[5,6]. Furthermore, GLP-1 and its analogs (such as exenatide) have been studied for the treatment of liver, kidney, and lung fibrosis[7-10].

The GLP-1 analogs are considered important in terms of their antitumor properties and their ability to prevent chemotherapy-cytostatic drug-induced injury to normal tissue[11]. Furthermore, exenatide was found to reduce ovarian and endometrial damage in streptozocin-induced diabetic rats[12].

The aim of the present study is to investigate the possible beneficial effects of exenatide in CP-induced experimental ovarian damage model.

Method

Animals

Twenty-one adult female Wistar rats, weighing 200-210 g, were used in the study. The experiments performed in this study have been carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (U.S.A). Having received Animal Ethics Committee's consent (University, Ethical number: 17210316). The rats used in the experiment were obtained from Experimental Animal laboratory of Science University. Rats were fed ad libitum and housed impairs in steel cages having a temperature-controlled environment (22 ± 2°C) with 12-h light/dark cycles[13].

Experimental protocol

For 14 rats, CP (Sisplatin, Kocak Pharma) (2 mg/kg/day) was administered by intraperitoneally (i.p) twice a week for 5 weeks (total CP dose 20 mg/kg). No drug was administered to the remainder of rats (n = 7) (Group 0). The rats taken CP were divided into two groups. Group 1 rats (n = 7) were given 1 mL/kg/day 0.9% NaCl (saline) i.p., and Group 2 rats (n = 7) was given with 20 μg/kg/day Exenatide (Byetta, Lilly, 0.25 mg/mL) were administrated by i.p. every day for 5 weeks.

At the end of the study, all animals were sacrificed (cervical dislocation) with ketamine (100 mg/kg, Ketasol, Richterpharma AG Austria)/xylazine (50 mg/kg, Rompun, Bayer, Germany) anesthesia, and their blood samples were collected by cardiac puncture for biochemical analysis. Their ovaries were removed for histological and biochemical examinations[13].

Histological examination

Ovarian tissues were formalin-preserved and embedded in paraffin. The ovaries were sectioned at a thickness of 4 μm with a microtome. The sections were then stained with hematoxylin and eosin and mounted onto glass slides. All sections were photographed with an Olympus C-5050 digital camera mounted on an Olympus BX51 microscope. Histopathological examination of the ovaries was performed by a computerized image analysis system (Image-Pro Express 1.4.5, Media Cybernetics, Inc., Rockville, MD, USA) on ten microscopic fields per section at a magnification of ×20, performed by an observer who was blinded to the study groups. Primary follicles consist of an oocyte surrounded by a single layer of cuboidal granulosa cells. Secondary follicles include multiple layers of cuboidal granulosa cells and an invisible antrum. Tertiary follicles are characterized by a stratum granulosum along with fluid-filled antral space. Stromal fibrosis in ovarian tissue was calculated as a percentage[13].

Measurement of plasma anti-mullerian hormone (AMH) levels

Blood was centrifuged at 3000 rpm for 10 min at room temperature and stored at −20°C until the analysis for

AMH. AMH level was measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Biosciences, Seattle, WA, USA). Samples from each rat were determined in duplicate according to the manufacturer's guide.

Determination of lipid peroxidation

Lipid peroxidation was determined in plasma samples through measuring malondialdehyde (MDA) levels as thiobarbituric acid reactive substances (TBARS), which are the end product of lipid peroxidation. Trichloroacetic acid and TBARS reagent were added to the tissue samples, then mixed and incubated at 100°C for 60 min. The samples were centrifuged at 3000 rpm for 20 min, and the absorbance of the supernatant was read at 535 nm after cooling on ice. MDA levels of tissue were calculated from the calibration curve using 1,1,3,3-tetraethoxypropane and expressed as nmol/gr protein.

Over tissue biochemical analysis

After sacrification, over were rapidly removed and stored at –20°C until to biochemical analysis. For tissue analysis, tissues were homogenized with a glass homogenizer in 5 vol of phosphate buffered saline (Ph, 7.4) and centrifuged at 5000 g for 15 min. Nuclear factor-erythroid factor 2-related factor 2 (Nrf-2), Toll-like receptor 4 (TLR-4), nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3 (NLRP-3) level in the tissue supernatants were measured using commercially available rat ELISA kits. All samples from each animal were measured in duplicate according to the manufacturer's guidelines. A microplate reader was used for the measurement of the Absorbances (MultiscanGo, Thermo Fisher Scientific Laboratory Equipment, NH, US)[14].

Statistical analysis

Data analysis was performed using GraphPad Prism 8.3.0 a software (GraphPad Software, La Jolla, CA, USA). The groups of parametric variables (biochemical data) were compared by student's t-test and analysis of variance. The groups of non-parametric variables (histopathology) were compared by the Mann–Whitney U test. Results are presented as the mean ± standard error of mean. A value of $p < 0.05$ was accepted as statistically significant. $p < 0.001$ was accepted as statistically highly significant.

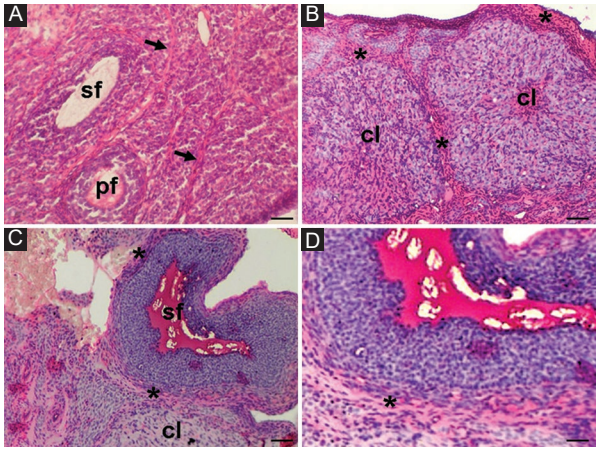

Figure 1. *Histopathological examination of ovaries. Hematoxylin and eosin stain.* **A:** *normal Control group of ovaries with normal morphology, normal stroma of ovary (arrow) (hematoxylin and eosin, ×10 magnification).* **B:** *cisplatin+saline group with stromal fibrosis of the ovary (asterisk).* **C:** *cisplatin+Exenatide group demonstrating significant decrease of stromal fibrosis of the ovarian tissue (asterisk) (×10 magnification).* **D:** *cisplatin +Exenatide group, reduction of stromal fibrosis appears to be better in higher magnification (hematoxylin and eosin, ×40 magnification). pf: Primary follicle sf: secondary follicle, cl: corpus luteum.*

Results

The number of primordial follicles was significantly lower in Group 1 compared with Group 0 and Group 2 ($p < 0.001$ and $p < 0.01$, respectively). The number of primary follicles was significantly higher in Group 2 and group 0 compared with Group 1 ($p < 0.01$ and $p < 0.01$, respectively). The secondary follicle number was found to be significantly lower in Group 1 compared with Group 0 and Group 2 ($p < 0.01$ and $p < 0.01$, respectively). Tertiary follicle number was also significantly lower in Group 1 compared with Group 0 and Groups 2 ($p < 0.01$ and $p < 0.01$, respectively). The ovarian fibrosis percent was significantly higher in Group 1 than Group 0 and Group 2 ($p < 0.001$ and $p < 0.001$, respectively) (Fig. 1 and Table 1).

The plasma AMH value was lower in Group 1 compared with Group 0 and Group 2 ($p < 0.01$ and $p < 0.01$, respectively). The plasma MDA level was found to as significantly higher in Group 1 compared with Group 0 and Group 2 ($p < 0.0001$ and $p < 0.01$, respectively). Over NrF2 level was higher in Group 1 than Group 0 and Group 2 ($p < 0.001$ and $p < 0.01$, respectively). Over TLR-4 level was found as significantly higher in Group 1 compared with Group 0 and Group 2 ($p < 0.0001$ and $p < 0.01$, respectively). Over NLRP-3 level was significantly higher in Group 1 than Group 0 and Group 2 ($p < 0.0001$ and $p < 0.001$, respectively) (Table 2).

Discussion

The main finding of the present study is the beneficial effects of the GLP-1 agonist exenatide on CP-damaged ovarian tissue. These advantages include the preservation of primordial, primary, secondary, and tertiary follicular pools as well as the amelioration of ovarian fibrosis.

CP-induced ovarian toxicity is an important for women of reproductive age[15,16]. CP suppresses mitosis[17] in tumor cells by cross-linking their DNA. CP is lethal to healthy cells due to increased ROS production[4,18]. Increased production of proinflammatory cytokines such TNF-, IL-1, and IL-6 also leads to non-tumor cell death[4,18]. The NF-kB pathway is activated as proinflammatory cytokines increase. The suppressed NF-kB-Ikb complex in the cytoplasm becomes active and translocate to the nucleus with proinflammatory cytokines, where it promotes target genes and initiates inflammatory events[19]. Damage caused by inflammation causes lipid peroxidation and increases MDA release.

AMH is produced by ovarian granulosa cells and could indicate ovarian reserve[20]. Menopause reduces AMH[21,22]. AMH protects primordial and preantral follicles[23,24]. Follicle degeneration and apoptosis diminish ovarian reserve and AMH levels[24]. The CP and saline group showed lower primordial and preantral follicle counts, as well as serum AMH, than the control and CP and exenatide groups. Exenatide appears to decrease follicular degeneration detected by lower AMH levels in rodents exposed to CP.

NLRP3 is a member of the inflammasome protein family[25]. Hereditary Cryopyrin-associated periodic syndrome has been connected to the NLRP3 gene. NLRP3 inhibitors have been used to treat these diseases[26]. However, little is known about the effects of NLRP3 on ovarian tissue. Recent research indicates that the NLRP3 inhibitor MCC950 is effective in treating ovarian endometriosis increasing the functionality of endometriotic ovaries[27]. Exenatide, was shown to[28] inhibit the inflammasome pathway in rodents and decrease oxidative stress[29] in an experimental model of nonalcoholic fatty liver disease. In the current study, the CP and saline groups had significantly higher levels of NLRP3 than the control group and the CP and exenatide group. Exenatide appears to prevent CP-induced damage to the ovary by inhibiting the NLRP3 pathway.

Nrf-2 is the primary regulator of oxidative status in numerous tissues. It is believed that Nrf-2 regulates catalase, thioredoxins, glutathione, glutathione reductase, and other antioxidants[30]. Agents that enhance Nrf-2 activity have been utilized for the control of oxidative stress in several neurological diseases. Nrf-2 inhibitors are also used to increase oxidative stress in tumor tissues. In the present investigation, the highest Nrf-2 levels were found in the CP and saline groups. We believe that this increase was due to the oxidative damage induced by CP exposure. In addition, the serum MDA level, a sensitive indicator of oxidative stress in tissue, was found to be higher in the CP and saline group compared to the control and CP and exenatide

Table 1. Comparisons ovarian stromal degeneration, ovarian follicle degeneration and ovarian stromal fibrosis scores between groups

Variables	Normal control group	Cisplatin and saline group	Cisplatin and exenatide group
Primordial follicle	15.1 ± 0.9	4.5 ± 0.8*	11.4 ± 1.7##
Primary follicle	13.4 ± 2.5	6.7 ± 0.6*	9.1 ± 0.9#
Secondary follicle	11.5 ± 0.6	5.4 ± 0.3*	8.3 ± 0.2#
Tertiary follicle	3.9 ± 0.1	1.7 ± 0.2	2.6 ± 0.3#
Ovarian fibrosis percent (%)	2.2 ± 0.3	15.1 ± 1.4**	7.5 ± 3.06##

Results were presented as mean ± standard error of mean. Statistical analyses were performed by one- way analysis of variance.
*p < 0.01.
**p < 0.0001 different from normal groups.
#p < 0.01.
##p < 0.001.

Table 2. Comparisons Plasma AMH level, Plasma MDA level, Over NrF2 level, Over TLR-4 level and Over NLRP-3 level between groups

Variables	Normal control group	Cisplatin and saline group	Cisplatin and exenatide group
Plasma AMH (ng/mL) level	2.9 ± 0.18	0.6 ± 0.09*	1.1 ± 0.15#
Plasma MDA level (nM)	45.6 ± 7.5	131.7 ± 14.2**	68.4 ± 5.09#
Over NrF2 level (pg/mg)	415.4 ± 22.7	747.1 ± 34.5*	621.3 ± 19.6#
Over TLR-4 level (ng/mg)	5.08 ± 0.4	16.1 ± 1.8**	9.4 ± 1.05#
Over NLRP-3 level (pg/mg)	32.9 ± 4.4	89.8 ± 6.5**	57.7 ± 8.1##

Results were presented as mean ± standard error of mean. Statistical analyses were performed by one- way analysis of variance.
*p < 0.01.
**p < 0.0001 different from normal groups.
#p < 0.01.
##p < 0.001.
AMH: anti-müllerian hormone; MDA: malondialdehyde; NrF2: Nuclear factor-erythroid factor 2-related factor 2; NLRP-3: nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3; TLR: Toll-like receptor.

groups. In previous studies[12,31,32], exenatide was shown to reduce oxidative stress. On ovarian tissue damaged by CP, exenatide can act as an antioxidant system activator.

TLR4 is an essential component of the host's innate immune system. There is evidence linking TLR4 to the development and progression of cancer[33]. TLR4[33] has been shown to modulate several cytokines, including IL-1b, IL-6, and TNF-. TLRs are presented in numerous tissues, including the ovary. Various ovarian cells, including cumulus, granulosa, and theca cells, contain TLRs[34]. Exenatide decreased the expression of TLR4 and other inflammatory markers in diabetic patients, according to Chaudhuri and colleagues[35]. In this study, we found that the CP and saline groups had significantly increased ovarian TLR4 levels than the other groups. We believe that the rapid anti-inflammatory effect of exenatide improved ovarian injury.

This is the first study to demonstrate the beneficial effects of exenatide on CP-induced ovarian injury. Pathways NLRP3, Nrf-2, and TLR4 can connect the potential mechanisms. Exenatide can contribute to the reversal of CP-induced damage to ovarian tissue and is a promising candidate for women who have experienced CP-induced ovarian damage.

Conclusion

Present study is the first to demonstrate beneficial effects of exenatide on ovarian damage which was induced by cisplatin. The possible mechanisms can be related via NLRP3, Nrf-2 and TLR4 pathways. Exenatide can lead reverse the damage of cisplatin on ovarian tissue and can be promising candidate for women who had ovarian damage by cisplatin damage.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Hemoglobin glycation index and triglyceride-glucose index are related to diabetic nephropathy

El índice de glucosilación de la hemoglobina y el índice de triglicéridos-glucosa están relacionados con la nefropatía diabética

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Abstract

Objective: *Diabetic nephropathy (DN) is a significant complication of diabetes. Despite strict management of fasting plasma glucose (FPG), DN may progress to end-stage renal disease. HbA1c, the best biomarker for glycemic management, may differ in similar FPG. Hemoglobin glycation index (HGI) = HbA1c as determined minus HbA1c as predicted. The triglyceride-glucose index (TGI) is found to detect insulin resistance and correlates with DN. The aim of this study is to see the association of TGI and HGI with diabetic nephropathy in type 2 diabetes patients.* **Method***: 234 patients with type 2 diabetes were analyzed retrospectively.* **Results:** *87 (37.2%) of 234 patients were male, and the mean age was 57.2 ± 11.1 years. 76 of the patients had DN. HGI and TGI were significantly higher in the DN group (2.59 ± 1.7 vs. 1.18 ± 0.34; p = 0.00 and 9.9 ± 0.7 vs. 9.7 ± 0.7; p = 0.024). In logistic regression analysis, microalbuminuria was associated with TGI (OR = 3.35, 95% CI, 1.778- 6.32, p = 0.01) and HGI (OR = 2.579, 95% CI, 1.89-3.516, p = 0.00).* **Conclusions:** *In conclusion, TGI and HGI were independently associated with diabetic nephropathy. These markers may be useful in DN, especially in anemic individuals, since anemia might affect HbA1c levels.*

Keywords: *Hemoglobin glycation index. Triglyceride glucose index. Diabetic nephropathy.*

Resumen

Objetivo: *La nefropatía diabética (ND) es una complicación importante de la diabetes. A pesar del manejo estricto de la glucosa plasmática en ayunas (GPF), la ND puede progresar a enfermedad renal terminal. La hemoglobina glucosilada (HbA1c), el mejor biomarcador para el manejo glucémico, puede diferir en una GPF similar. Índice de glucosilación de hemoglobina (HGI) = HbA1c según lo determinado menos HbA1c según lo previsto. Se ha encontrado que el índice de triglicéridos-glucosa (TGI) detecta la resistencia a la insulina y se correlaciona con la ND. El objetivo de este estudio es ver la asociación de TGI y HGI con ND en pacientes con diabetes tipo 2.* **Método:** *Se analizaron retrospectivamente 234 pacientes con diabetes tipo 2.* **Resultados:** *Ochenta y siete (37.2%) de 234 pacientes eran varones, y la edad media fue de 57.2 ± 11.1 años. Setenta y seis pacientes tenían ND. HGI y TGI fueron significativamente mayores en el grupo ND (2.59 ± 1.7 vs 1.18 ± 0.34; p = 0.00 y 9.9 ± 0.7 vs 9.7 ± 0.7; p = 0.024). En el análisis de regresión logística, la microalbuminuria se asoció con TGI (odds ratio [OR]: 3.35; IC95%: 1.778-6.32; p = 0.01) e HGI (OR: 2.579; IC95%: 1.89-3.516; p = 0.00).* **Conclusiones:** *En conclusión, TGI y HGI se asociaron de forma independiente con la ND.*

Palabras clave: *Índice de glucosilación de la hemoglobina. Índice de glucosa en triglicéridos. Nefropatía diabética.*

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Introduction

Diabetic nephropathy (DN) is one of the most significant consequences of diabetes, affecting about one-third of diabetes patients[1]. Because the mechanisms underlying DN development are complex, therapeutic outcomes are poor. Strict fasting plasma glucose (FPG) and blood pressure management are insufficient to prevent mortality and the progression of DN into end-stage renal disease[2,3]. Many processes have a role in the start and progression of DN, including oxidative stress, the angiotensin II system, and inflammation[4].

Despite the fact that HbA1c is regarded as the most reliable glycemic management biomarker, studies have shown that there are considerable disparities between HbA1c and mean blood glucose levels. Because of changes in glucose metabolism and hemoglobin glycation rate, patients with comparable blood glucose levels may have different HbA1c values[5,6]. Hemoglobin glycation index (HGI) was calculated as observed HbA1c minus predicted HbA1c. Predicted HbA1c is calculated by linear regression equation reflecting the relationship between baseline HbA1c and FPG. Hempe et al.[7] recommend using the HGI to compare mean blood glucose levels to HbA1c readings. HGI was found to be related to macrovascular problems[8] and diabetic nephropathy[9].

Previous research has shown that the triglyceride-glucose index (TGI), is an excellent tool for detecting insulin resistance in both diabetic and non-diabetic patients[10,11]. Furthermore, previous research has linked TGI to diabetic nephropathy[12].

The goal of this research is to see the association of TGI and HGI with diabetic nephropathy in people with type 2 diabetes.

Method

This was a retrospective analysis of 234 patients with type 2 diabetes who attended an internal medicine outpatient clinic between January and December of 2022.

Moreover, it was done in accordance with the Helsinki Declaration. Because the research was conducted retrospectively, informed consent was not obtained. The following criteria were used to determine study eligibility: (1) patients with a diagnosis of type 2 diabetes according to the World Health Organization criteria; (2) ≥ 18 years old; (3) have had diabetes for at least a year; and (4) had no documented ketoacidosis in the 3 months before enrolment. Participants were excluded if they had a febrile or infectious illness, obstructive uropathy, severe heart failure, stroke, liver disease, cancer, autoimmune disease, and pregnancy. An albumin excretion rate (AER) of 30 mg/gr was discovered in at least two of three consecutive spot urine albumin-creatinine ratios to diagnose DN. Albuminuria in non-diabetic renal disease is another exclusion criterion for patients with DN. The files included all biochemical results and HbA1c levels. TGI was calculated as ln [fasting triglycerides (mg/dL) × FPG (mg/dL)/2]. HGI was calculated as observed HbA1c minus predicted HbA1c. The linear regression equation reflecting the relationship between baseline HbA1c and FPG in our cohort was HbA1c (%) = 5.69 + 0.018 FPG (mg/dL) for the 234 individuals. The predicted HbA1c for each patient in our study was calculated from this equation.

A statistical investigation using SPSS 25.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). For continuous variables, data are reported as the mean standard error, or median (interquartile range), and for categorical variables, as percentages. The student's t-test and Mann–Whitney U-test were used to compare the two groups (DN vs. non-DN). A univariate regression analysis was used to examine the potential risk factors for the development of DN, and a binary logistic regression multivariable analysis with DN categorized as a binary variable (presence or absence of DN) was used to assess the associations between the measured risk factors and DN. A P-value of 0.05 was used to establish statistical significance.

Results

A total of 234 patients were involved in the study, of whom 87 (37.2%) were male. The mean age was 57.2 ± 11.1 years and the mean DM vintage was 9.7 ± 7.5 years. 132 (56.4%) of the patients had HT, and 123 (52.6%) of the patients had hyperlipidemia. The mean BMI was 31.05 ± 7.19 kg/m^2. The mean FBG was 215 ± 97.7 mg/dL, mean HbA1c was 9.7 ± 2.5. The mean HGI was 1.7 ± 1.01 and mean TGI was 9.75 ± 0.74 (Table 1).

The patients were grouped in 2 with respect to the presence of microalbuminuria. 76 of the patients had microalbuminuria (MA), while 148 did not. The patients with MA were older (60.6 ± 10.2 vs. 52.2 ± 11.1; p = 0.00). BMI was higher in the MA group (32.4 ± 9.1 vs. 30.3 ± 5.7; p = 0.036) and systolic blood pressure (SBP) was

Table 1. Baseline characteristics

Demographics	n = 234
Males, n (%)	87 (37.2%)
Age, years	57.2 ± 11.1
DM vintage, years	9.71 ± 7.5
HT, n (%)	132 (56.4)
Hyperlipidemia, n (%)	123 (52.6%)
BMI, kg/m^2	31.05 ± 7.19
SBP, mm/hg	124.4 ± 14.1
DBP, mm/hg	76.8 ± 11.3
Hemoglobin, g/dL	13.7 ± 6.2
CRP, gr/dL	2.19 ± 1.45
Ferritin, ng/dL	95.6 (4.2-1191)
FBG, mg/dL	215 ± 97.7
Serum albumin, g/dL	4.3 ± 0.5
GFR, mL/min	87.8 ± 26.3
Serum total cholesterol, mg/dL	193.8 ± 48.9
Serum triglycerides, mg/dL	200.9 ± 107.1
HbAıc	9.7 ± 2.5
HGI	1.7 ± 1.01
TGI	9.75 ± 0.74

DM: diabetes mellitus; HT: hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; GFR: glomerular filtration rate; CRP: C-reactive protein.

Table 2. Comparison of patients in terms of microalbuminuria

Demographics	MA(-) (n = 148)	MA(+) (n = 76)	p
Males, n (%)	54 (36.5%)	33 (38.4%)	0.774
Age, years	52.2 ± 11.1	60.6 ± 10.2	0.00
DM vintage, years	9.5 ± 7.5	10.1 ± 7.6	0.466
HT, n (%)	78 (52.7%)	54 (62.8%)	0.134
Hyperlipidemia, n (%)	77 (52%)	46 (53.8%)	0.829
BMI, kg/m^2	30.3 ± 5.7	32.4 ± 9.1	0.036
SBP, mm/hg	123 ± 14.5	126.9 ± 13.2	0.040
DBP, mm/hg	76.5 ± 10.4	77.3 ± 12.8	0.659
Hemoglobin, g/dL	14.1 ± 1.7	13.0 ± 1.8	0.053
CRP, gr/dl	2.02 ± 0.9	2.5 ± 1.9	0.017
Ferritin, ng/dl	80.6 (4.2-489)	121.3 (10-1192)	0.013
FBG, mg/dl	210.1 ± 92.8	224 ± 105.5	0.42
Serum albumin, g/dL	4.4 ± 0.4	4.2 ± 0.7	0.014
GFR, ml/min	92.7 ± 24.5	78.9 ± 27.3	0.00
Serum total cholesterol, mg/dL	189.7 ± 42.3	200.8 ± 58.2	0.182
Serum triglycerides, mg/dL	187.8 ± 96.7	223.3 ± 120.1	0.014
HbAıc	9.6 ± 2.4	9.8 ± 2.6	0.069
HGI	1.18 ± 0.34	2.59 ± 1.7	0.00
TGI	9.7 ± 0.7	9.9 ± 0.7	0.024

DM: diabetes mellitus; HT: hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; GFR: glomerular filtration rate; CRP: C-reactive protein.

increased MA group (126.9 ± 13.2 vs. 123 ± 14.5; p = 0.040). CRP and ferritin were increased in the MA group (Table 2). FBG and HbA1c were statistically similar between groups (Table 2). Serum triglyceride was increased in the MA group (223.3 ± 120.1 vs. 187.8 ± 96.7; p = 0.014). HGI and TGI were significantly higher in the MA group (2.59 ± 1.7 vs. 1.18 ± 0.34; p = 0.00 and 9.9 ± 0.7 vs. 9.7 ± 0.7; p = 0.024) (Table 2).

Table 3 shows the multivariate-adjusted odds ratios for microalbuminuria outcome measures. Multiple logistic regression adjusted for potential confounders demonstrated that microalbuminuria was associated with age (odds ratio [OR] = 1.064, 95% confidence interval [CI], 1.027-1.100, p = 0.001), SBP (common OR = 1.034, 95% CI, 1.005-1.065, p = 0.022), TGI (OR = 3.35, 95% CI, 1.778-6.32, p = 0.01) and HGI (OR = 2.579, 95% CI, 1.89-3.516, p = 0.00). HbA1c was statistically related to the development of DN (OR 1.6, 95% CI, 1.85-2.1, p = 0.003) (Table 3).

Discussion

Individuals with DN showed significantly higher levels of metabolic syndrome markers such as BMI, SBP, triglycerides, and CRP, according to this research. Although HbA1c levels did not differ across groups, the DN group had substantially higher HGI and TGI levels. A multivariate logistic regression analysis found that the most significant predictors of DN were age, systolic blood pressure, HGI, TGI, and Hba1c.

Diabetic nephropathy (DN) is a frequent and serious complication that increases the risk of both mortality and morbidity in diabetic individuals[1]. The number of diabetics in the United States who started therapy for end-stage renal disease (ESRD) grew from 40,000 to more than 50,000 between 2000 and 2014[13].

Previous study has shown that the TGI is a trustworthy and accurate predictor of metabolic syndrome,

Table 3. Logistic regression analysis

Multiple logistic regression		
Predictors	**OR (95% CI)**	**p**
HGI	2.579 (1.89-3.516)	0.000
HbA1c	1.6 (1.85-2.1)	0.003
Age	1.064 (1.027-1.10)	0.001
SBP	1.034 (1.005-1.065)	0.022
TGI	3.35 (1.778-6.321)	0.000

95% CI: 95% confidence interval; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; SBP: systolic blood pressure.

insulin resistance[14-16], and macrovascular disease[17-19]. In this study, we concluded that TGI serves as an independent indicator for the development of DN.

Prior research has shown the significance of insulin resistance in the progression of DN. Increased renal vascular permeability is the mechanism through which insulin resistance induces glomerular hyperfiltration. The result is an increase in pressure inside the glomeruli[20]. Among the likely pathophysiological mechanisms underlying the association between insulin resistance and DN include inflammation, oxidative stress, metabolic acidosis, and lipotoxicity[21-24].

Multiple studies have shown that dyslipidemia has a role in the advancement of renal failure in both type 1 and type 2 diabetes[25,26]. Prior research discovered a relation between DN and HOMA-IR, an additional biomarker of insulin resistance. Over the course of a prospective cohort study spanning 5 years, researchers identified a correlation between baseline HOMA-IR and the start of microalbuminuria[27]. Endothelial cell damage in microalbuminuria, according to Deckert et al., causes considerable vascular damage by reducing endothelial lipoprotein lipase levels[28]. This injury causes hypertriglyceridemia by increasing plasma triglyceride levels. The current findings are consistent with previously published studies, which makes sense given that TGI is a marker of insulin resistance.

It has been postulated that insulin treatment, in addition to blood glucose and blood pressure, may have a role in the development of nephropathy[29]. Kim et al.[30] identified unique relationships between fasting plasma insulin levels, systolic blood pressure, and microalbuminuria. Individuals who have high plasma glucose levels have a combination of abdominal obesity, high blood pressure, elevated lipid levels, and metabolic syndrome[31,32]. According to the present study, the TGI is more sensitive than the metabolic syndrome-related indicators in DN[33], which is consistent with earlier results.

Another notable result from this research is that the glycation index was found to be higher in the DN group despite HbA1C being comparable in both groups. Both of these features were linked to the development of diabetic nephropathy in a regression analysis.

The HGI illustrates the link between HbA1c and plasma glucose levels[11]. The HGI is the difference between the actual HbA1c and the value predicted by a simple linear model that predicts HbA1c from FPG concentration for each patient in a study population, i.e., the residual from the fitted linear regression line for each patient in a study population. The HGI is calculated by subtracting the observed HbA1c from the value predicted by the basic linear model.

Previous studies[10,34-36] have shown that the HGI has a consistent value throughout a broad range of blood glucose concentrations, as well as a uniform distribution and stability over time. According to the results of the DCCT study, a high HGI was associated with an increased risk of developing retinopathy and nephropathy in type 1 diabetes patients[6].

A non-enzymatic mechanism that glycates hemoglobin is the Maillard reaction. The interaction of reducing sugars with terminal amines is definitely required for the development of advanced glycation end products. The pathophysiology of advanced glycation end products has been linked to diabetic complications, aging, and Alzheimer's disease[37]. The DCCT findings, which link biological variation in HbA1c to microvascular complications, suggest that the mechanisms that cause biological variation in non-enzymatic hemoglobin glycation may also influence a patient's susceptibility to diabetes complications[38-40]. The non-enzymatic glycation of hemoglobin is regulated by intracellular glucose as well as factors that affect the hemoglobin's capacity to bind glucose. The pH of the intracellular environment, the concentration of 2, 3-bisphosphoglycerate, and the activity of glycolytic enzymes all impact hemoglobin glycosylation[41,42]. There is no association between erythrocyte survival and HGI; however, depending on creatinine levels, erythrocyte survival may effect HbA1c levels[11]. The risks of having consistently high glucose levels are well known, but the impact of non-glucose factors on HbA1c biological variation is little understood. This is due to the fact that HbA1c is a measure of blood glucose levels over time. Despite the fact that medication

and lifestyle adjustments may bring blood glucose levels as close to normal as possible, lowering blood glucose may not be enough to avoid retinopathy in DCCT patients due to the higher risk of retinopathy in individuals with low BG but a high HGI(6). Despite the fact that the underlying mechanism is not fully understood, further therapy to correct the variation indicated by HGI may be required. Understanding these pathways might help to generate new therapeutic options and patient-specific treatment regimens.

The current research has a number of limitations. To begin with, the total number of patients is small. Second, since the inquiry was done retrospectively, the indices were created using the experiment's starting values. We don't have any data on how these factors have changed over time. Second, since participants in medical checkups at a certain hospital are chosen at random, it is possible that they may not accurately reflect the whole population and are subject to the effects of natural selection bias.

Conclusion

We discovered that a greater TGI and HGI were detected in diabetic nephropathy. These markers may be useful in the determination of metabolic control and progression to DN, especially in anemic individuals since anemia might affect HbA1c levels. More research with prospective design is needed to determine whether or not these indices have a role in the occurrence and progression of diabetic microvascular problems.

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Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Factors affect progressive sperm motility

Factores que afectan la motilidad espermática progresiva

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Abstract

Objective: *In this study, it was aimed to investigate the effects of age, body mass index, and diet factors on sperm parameters and developing a novel index (Artuklu Sperm Quality Index [ASQI]).* **Method:** *The study incorporated a total of 115 patients who sought medical attention due to infertility and underwent semen analysis (spermiogram). The ASQI score was developed.* **Results:** *About 73% reported eating three meals daily, while 62% consume fruits a few times a week. When considering grain consumption, 30% rarely do, mirroring the 25% who never do. Carbonated drinks are consumed a few times in 15 days by 39% of respondents. Salt consumption showed 47% taking very little, whereas 42% consume caffeine very minimally. Sausage/salami is minimally consumed by 44%, and 32% of participants reported never being exposed to air pollution. ASQI score ranges from 6 to 61 point. A lower score indicates good nutrition and quality of life, while a higher score suggests deteriorating nutrition and increasing unhealthy habits. Cronbach alfa value was noted as 0.72. A negative correlation was found between ASQI and sperm progressive motility ($p < 0.001$, $r = -0.405$).* **Conclusions:** *This study revealed a clear negative correlation between the ASQI score, which signifies deteriorating nutrition and escalating unhealthy habits, and sperm progressive motility.*

Keywords: *Sperm. Urology. Fertility. Sperm quality.*

Resumen

Objetivo: *Investigar los efectos de la edad, del índice de masa corporal y de los factores dietéticos sobre los parámetros espermáticos, y desarrollar un índice novedoso.* **Método:** *El estudio incorporó 115 pacientes que buscaron atención médica debido a infertilidad y que se sometieron a análisis de semen. Se desarrolló la puntuación ASQI.* **Resultados:** *El 73% informaron que comían tres comidas diarias, mientras que el 62% consumían frutas unas pocas veces a semana. En cuanto al consumo de granos, el 30% rara vez lo hace y el 25% nunca. Las bebidas carbonatadas son consumidas unas pocas veces en 15 días por el 39% de los encuestados. El 47% refieren que toman muy poca sal, mientras que el 42% consumen cafeína de manera muy mínima. Embutido/salami es consumido mínimamente por el 44%. El 32% de los participantes informaron que nunca estuvieron expuestos a contaminación del aire. El puntaje ASQI varía de 6 a 61 puntos. Un puntaje más bajo indica buenas nutrición y calidad de vida, mientras que un puntaje más alto sugiere deterioro de la nutrición y aumento de los hábitos no saludables. El valor alfa de Cronbach fue de 0.72. Se encontró una correlación negativa entre el puntaje ASQI y la motilidad progresiva de los espermatozoides ($p < 0.001$; $r = -0.405$).* **Conclusiones:** *Este estudio revela una clara correlación negativa entre el puntaje ASQI alto, que significa deterioro de la nutrición y escalada de hábitos no saludables, y la motilidad progresiva de los espermatozoides.*

Palabras clave: *Esperma. Urología. Fertilidad. Calidad del esperma.*

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Introduction

Approximately 15% of people globally (equivalent to 60-70 million couples) experience infertility, with male-related issues accounting for 40-50% of these instances[1,2]. A comprehensive review of 185 studies, which analyzed data from over 42,000 men without identified fertility problems, highlighted a concerning 50-60% decrease in human semen quality, such as sperm concentration and count, over the past four decades[3]. This decline in sperm quality, a universal issue, is especially pronounced in developed and industrialized regions. This suggests that modifiable lifestyle elements may be significant contributors. Key suspected causes include pollution, stress, smoking, alcohol intake, food pesticides, and poor dietary habits. Both developed and developing nations are witnessing a rise in the consumption of nutrient-poor, calorie-dense foods, often characterized as the Western-style diet. This diet not only impacts fertility but also has been linked to metabolic disorders and conditions like type 2 diabetes, hypertension, and cardiovascular diseases[4,5].

Many studies have investigated how various risk factors negatively affect the protein makeup of sperm[6,7]. Beyond diseases, an increasing number of elements are noted to adversely impact male fertility. Age is a primary factor; while men can reproduce throughout their lives, there is a noticeable decline in sperm quality from age 35 onward. Other elements affecting fertility include diet, caffeine consumption, weight, exercise levels, stress, smoking, drug or alcohol usage, medication intake, diabetes, exposure to artificial chemicals, clothing choices, and sleep patterns[8,9].

In this study, it was aimed to investigate the effects of age, body mass index (BMI), and diet factors on sperm parameters and developing a novel index (Artuklu Sperm Quality Index [ASQI]).

Method

The study incorporated a total of 115 patients who sought medical attention due to infertility and underwent semen analysis (spermiogram). For each patient, comprehensive data were recorded, which included: age, weight, height, BMI, dietary habits, nutritional contents of their consumed foods, quantity and frequency of their food consumption, and semen analysis parameters.

Only patients who had normal testicular examination findings were included in the study. In addition, ultrasound examinations were conducted to ensure that the patients had normal testicular size and echogenicity. Patients with a history or clinical evidence of testicular atrophy, testicular torsion, or those who had undergone orchiopexy were excluded from the study.

The ethical approval was obtained from Artuklu University Local Ethical Committee (no: 2023/8-2, date: August 07, 2023). After obtaining Ethics Committee approval, data were collected from the patients through a survey. Informed consent was obtained from all patients.

Definition of the ASQI

In this study, a 15-question questionnaire was developed using the patients' BMI, dietary habits, substance use, and habits of smoking and alcohol consumption. The scoring of this questionnaire is presented in table 1. The ASQI score ranges from 6 to 61 points. A lower score indicates good nutrition and quality of life, while a higher score suggests deteriorating nutrition and increasing unhealthy habits. The Cornchbach alfa value was noted as 0.72 (Table 1).

Statistical analysis

The data analysis was conducted using IBM SPSS 26.0 software (IBM, Armonk, New York, US). We assessed data distribution with the Shapiro–Wilk and Kolmogorov–Smirnov tests. Data following a normal distribution were expressed as mean and standard deviation. We presented categorical variables as count and percentage. The Pearson correlation test was employed to evaluate the correlation of the ASQI. A p value below 0.05 was deemed statistically significant.

Results

The study encompassed a diverse range of 115 patients, capturing varying demographics and lifestyle habits. When broken down by age, the younger participants (18-25 years) accounted for 31%, with 36 individuals in this bracket. However, the most prominent age group was 26-35 years, representing 57% or 65 individuals. Those between 36 and 45 years made up 10% with 12 individuals, and the smallest group, those over 46 years,

Table 1. Artuklu Sperm Quality Index

1	**Number of meals eaten per day**				
Definition	**Once**	**Twice**	**3 times**	**4 times**	**5 times**
Point	1	2	3	4	5
2	**Number of water drink per day**				
Definition	**> 11 glasses**	**8-10 glasses**	**5-7 glasses**	**3-5 glasses**	**< 3 glasses**
Point	1	2	3	4	5
3	**Number of fast-food eaten per day?**				
Definition	**Never**	**A few in a month**	**A few in 2 weeks**	**A few in a weeks**	**Everyday**
Point	0	1	2	3	4
4	**How many times do you eat fruit?**				
Definition	**Every day**	**A few in a week**	**A few in a month**	**Rare**	**Never**
Point	1	2	3	4	5
5	**How many times do you consume grains?**				
Definition	**Every day**	**A few in a week**	**A few in a month**	**Rare**	**Never**
Point	1	2	3	4	5
6	**How many times do you consume carbonated drinks?**				
Definition	**Never**	**A few in a month**	**A few times in 15 days**	**Daily 1-2 times**	**Daily>3 times**
Point	0	1	2	3	4
7	**How much salt do you consume?**				
Definition	**Never**	**Very little**	**Little**	**Moderate**	**So much**
Point	0	1	2	3	4
8	**How much do you consume caffeine?**				
Definition	**Never**	**Very little**	**Little**	**Moderate**	**So much**
Point	0	1	2	3	4
9	**How much do you consume sausage/salami?**				
Definition	**Never**	**Very little**	**Little**	**Moderate**	**So much**
Point	0	1	2	3	4
10	**How much are you exposed to air pollution?**				
Definition	**Never**	**Little**	**Moderate**	**So much**	
Point	0	1	2	3	
11	**BMI**				
Definition	**< 20**	**20, 1-25**	**25, 1-30**	**30, 1-25**	**35**
Point	1	2	3	4	5
12	**Smoke**				
Definition	**Never**	**A few in a month**	**A few times in 15 days**	**Daily a few**	**Min 1 packet a day**
Point	0	1	2	3	4

(Continues)

Table 1. Artuklu Sperm Quality Index *(continued)*

13	Alcohol abuse			
Definition	**Never**	**A few in a month**	**A few times in 15 days**	**Daily a few**
Point	0	1	2	3
14	**Substance abuse**			
Definition	**No**	**Yes**		
Point	0	1		
15	**Active phone use (daily)**			
Definition	**< 1 h**	**2-3 h**	**3-4 h**	**4-5 h**	**5 h**
Point	1	2	3	4	5

Total score between 6 and 61.

comprised 2% or 2 individuals. In assessing BMI, a notable 48% (n = 55) had a BMI ranging from 20.1-25, suggesting a majority had a healthy weight. Those below 20 constituted 8% (n = 9), while 30% (n=34) fell within the 25.1-30 range. The overweight bracket (30.1-35) held 11% or 13 patients, and the higher end of the scale, with a BMI over 35, had four patients, making up 3% of the total. Regarding marital status, a significant 75% (n = 86) were married, while the unmarried group constituted 25% or 29 patients. As for education, almost half, 47% or 54 patients had completed high school. University graduates followed at 23% (n = 27), primary school attendees at 14% (n = 16), and those who finished secondary school at 16% (n = 18). Lifestyle habits also offered intriguing insights. Almost half of the participants, 49% or 56 patients were smokers. Those who consumed alcohol regularly stood at 10% (n = 11), and a minimal 2% or two individuals reported substance abuse (Table 2).

The questions we posed to patients related to their dietary habits are summarized in Table 3. In summary, 73% reported eating three meals daily, while 62% consume fruits a few times a week. When considering grain consumption, 30% rarely do, mirroring the 25% who never do. Carbonated drinks are consumed a few times in 15 days by 39% of respondents. Salt consumption showed 47% taking very little, whereas 42% consume caffeine very minimally. Sausage/salami is minimally consumed by 44%, and 32% of participants reported never being exposed to air pollution.

A negative correlation was found between ASQI and sperm progressive motility ($p < 0.001$, $r = -0.405$) (Fig. 1).

Table 2. Demographic data

Parameter	n	%
Age		
18-25	36	31
26-35	65	57
36-45	12	10
> 46	2	2
BMI		
< 20	9	8
20.1-25	55	48
25.1-30	34	30
30.1-35	13	11
> 35	4	3
Marital status		
Married	86	75
Not-married	29	25
Highest level of education		
Primary school	16	14
Secondary school	18	16
High school	54	47
University	27	23
Abuses		
Smoke abuse	56	49
Alcohol abuse	11	10
Substance abuse	2	2
Active phone use (daily)		
< 1 h	16	14
2-3 h	13	11
3-4 h	21	18
4-5 h	24	21
> 5 h	41	36
Comorbidities	7	6

Discussion

The principal intent of this study was to investigate the effects of age, BMI, and diet factors on sperm

Table 3. Dietary habits of the patients

1	**Number of meals eaten per day**				
	Once	**Twice**	**3 times**	**4 times**	**5 times**
	2 (2%)	21 (18%)	84 (73%)	6 (5%)	2 (2%)
2	**How many times do you eat fruit?**				
	Every day	**A few in a week**	**A few in a month**	**Rare**	**Never**
	27 (24%)	72 (62%)	9 (8%)	6 (5%)	1 (1%)
3	**How many times do you consume grains?**				
	Every day	**A few in a week**	**A few in a month**	**Rare**	**Never**
	13 (11%)	29 (25%)	9 (8%)	35 (30%)	29 (25%)
4	**How many times do you consume carbonated drinks?**				
	Never	**A few in a month**	**A few times in 15 days**	**Daily 1-2 times**	**Daily > 3 times**
	4 (4%)	42 (37%)	45 (39%)	16 (14%)	8 (7%)
5	**How much salt do you consume?**				
	Never	**Very little**	**Little**	**Moderate**	**So much**
	2 (2%)	54 (47%)	16 (14%)	41 (35%)	1 (2%)
6	**How much do you consume caffeine?**				
	Never	**Very little**	**Little**	**Moderate**	**So much**
	18 (16%)	48 (42%)	22 (19%)	22 (19%)	5 (4%)
7	**How much do you consume sausage/salami?**				
	Never	**Very little**	**Little**	**Moderate**	**So much**
	34 (30%)	51 (44%)	12 (10%)	17 (15%)	1 (1%)
8	**How much are you exposed to air pollution?**				
	Never	**Little**	**Moderate**	**So much**	
	37 (32%)	33 (29%)	32 (28%)	13 (11%)	
9	**Number of water drink per day**				
	> 11 glasses	**8-10 glasses**	**5-7 glasses**	**3-5 glasses**	**< 3 glasses**
	44 (38%)	42 (36%)	17 (15%)	11 (10%)	1 (1%)
10	**Number of fast-food eaten per day**				
	Never	**A few in a month**	**A few in 2 weeks**	**A few in a week**	**Everyday**
	18 (16%)	43 (37%)	26 (22%)	19 (17%)	9 (8%)

parameters. Derived from a sample of 115 patients, the results have illuminated several correlations and insights that fortify and expand upon existing literature. One major finding was the negative correlation between ASQI and sperm progressive motility. Simply put, as the ASQI score increases, indicating deteriorating nutrition and a rise in unhealthy habits, sperm motility progressively diminishes. This dovetails with the broader literature, which has underscored the detrimental influence of lifestyle factors such as diet, smoking, and substance use on sperm quality.

A recent meta-analysis of six studies, which included over 8,200 participants, found that those with the lowest adherence to healthy dietary patterns had notably lower

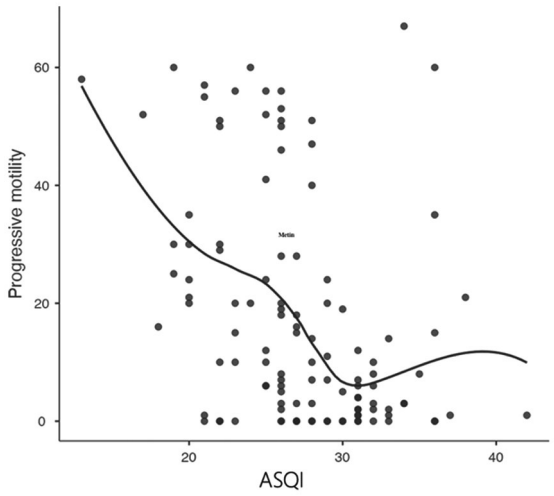

Figure 1. *Corellation graph between Artuklu Sperm Quality Index and sperm progressive motility.*

sperm concentrations compared to those with the highest adherence[9]. However, this meta-analysis did not identify significant relationships with other sperm quality metrics. Most of the information on how food affects sperm quality is derived from observational studies. A systematic review done[10], which encompassed 35 studies with 12,672 participants, revealed that eating vegetables, fruits, nuts (high in antioxidants), fiber-abundant grains and cereals, fish, other seafood, poultry, and low-fat dairy might bolster sperm quality. On the other hand, diets heavy in processed meats, soy products, potatoes, full-fat dairy, coffee, alcohol, and sugary drinks and treats seem to negatively impact sperm quality. Fruits and vegetables are abundant in antioxidants. These antioxidants may regulate sperm reactive oxygen species (ROS), subsequently lessening sperm DNA damage and enhancing their motility and vitality. Consuming a lot of fruits and vegetables also means a higher intake of folate, which can be beneficial for sperm health. Specifically, Young and his team found that men who consumed more folate were less likely to have sperm aneuploidy[11], hinting at folate's critical role in sperm development. Research on animals has shown that a lack of folate in the diet can modify sperm DNA methylation in genes crucial for development and some metabolic functions. Furthermore, male mice on a folate-deficient diet were linked to unfavorable pregnancy results compared to those with adequate folate[12].

A diet focused on fruits, vegetables, fish, legumes, and whole grains characterizes a health-conscious eating pattern. Vujkovic et al.[13] is the only study that examined this dietary trend. Their findings indicated that men who followed this health-conscious diet exhibited reduced sperm DNA damage compared to those on a 'traditional Dutch' diet, which is heavy on meat, potatoes, and whole grains but low in sugary drinks and sweets. Interestingly, men who closely followed the 'traditional Dutch' diet had higher sperm concentrations, presenting some contradictory results that require further exploration. Considering nutrition and diet, it seems to affect sperm parameters seriously. Therefore, in our study, we separated nutrition, healthy nutrition, and unhealthy nutrition and included them in the score system. We rated malnourished people high and well-fed low scores.

Although alcohol is widely accepted socially, its negative impact on male reproductive health is well-established. Many studies conducted over the years have highlighted the adverse effects of alcohol intake on male fertility[11]. Sperm cells, like all living cells, exist in conditions that need oxygen. The metabolism of oxygen produces ROS. Elevated levels of ROS can damage cell membranes and lead to increased DNA fragmentation, as highlighted in studies by Abdel-Zaher et al., and Bakar et al.[14,15]. This damaging effect is amplified by cigarette and morphine use, which promotes lipid peroxidation. Beyond the overproduction of ROS due to prolonged morphine consumption, opioids can directly reduce testosterone levels, diminish semen quality, lower sperm count, alter sperm morphology, and promote the release of prolactin, as noted by Bolelli et al.[16]. However, in our study, almost half of the participants, 49% were smokers. Those who consumed alcohol regularly stood at 10% (n = 11), and a minimal 2% or 2 individuals reported substance abuse. Therefore, thought to include this abuse to the ASQI. However there was a negative correlation between ASQI score and sperm progressive motility.

Our study is the first study in terms of making such a combination and developing a scoring system, but of course, our study also has limitations. While categorizing nutrition into healthy and unhealthy, we may have oversimplified complex dietary patterns. Relying solely on a scoring system may not capture the full nuances of individual diets. In addition, the criteria for "malnourished" versus "well-fed" might not represent the entire spectrum of dietary health, potentially leading to skewed results.

Conclusions

This study revealed a clear negative correlation between the ASQI score, which signifies deteriorating nutrition and escalating unhealthy habits, and sperm progressive motility. Such findings emphasize the

significance of a healthy lifestyle, particularly regarding diet, in maintaining and potentially enhancing sperm quality. This knowledge underscores the crucial need for educational campaigns and proactive interventions targeting lifestyle modifications to combat the observed decline in male fertility, especially in developed regions.

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The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Decreased plasma visfatin concentrations in pediatric aneurysmal bone cyst: a pilot study

Disminución de las concentraciones plasmáticas de visfatina en el quiste óseo aneurismático pediátrico: un estudio piloto

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Abstract

Objective: *This is a prospective study and visfatin values of patients with aneurysmal bone cysts (ABC) were compared with those of healthy individuals.* **Method:** *This study consists of 20 patients diagnosed with ABC (Group 1) and 30 healthy patients (Group 2). Age, gender, cyst sizes, and visfatin values of all patients were recorded and evaluated.* **Results:** *A total of 50 patients, 20 from Group 1 and 30 from Group 2, were included in our study. The mean age was 13.80 ± 3.98 years in Group 1 and 14.67 ± 4.24 years in Group 2, and no statistically significant difference was found between the groups ($p > 0.05$). While 60% of the patients in Group 1 were male, in Group 2, 53% of the patients were male. Cyst area was recorded as 1171 (512-2310) mm^2. The visfatin value was 10.70 ± 5.91 ng/mL in Group 1 and 15.23 ± 5.86 ng/mL in Group 2. The visfatin value in the ABC group was found to be statistically significantly lower than the control group ($p < 0.05$). No correlation was found between cyst area and visfatin ($p > 0.05$).* **Conclusion:** *Our study found that visfatin levels are significantly lower in patients with ABC s compared to healthy controls, suggesting its potential as a diagnostic biomarker. The ROC analysis showed a good diagnostic ability.*

Keywords: *Visfatin. Aneurysmal bone cyst. Pediatric.*

Resumen

Objetivo: *Este es un estudio prospectivo en el cual se compararon los valores de visfatina de pacientes con quistes óseos aneurismáticos con los de individuos sanos.* **Método:** *En el estudio participaron 20 pacientes diagnosticados de quiste óseo aneurismático (grupo 1) y 30 pacientes sanos (grupo 2).* **Resultados:** *Se incluyeron en nuestro estudio un total de 50 pacientes, 20 del grupo 1 y 30 del grupo 2. La edad media fue de 13.80 ± 3,98 años en el grupo 1 y de 14.67 ± 4.24 años en el grupo 2, y no se encontró diferencia estadísticamente significativa entre ambos grupos ($p > 0.05$). El área del quiste se registró como 1,171 mm^2 (512-2,310 mm^2). El valor de visfatina fue de 10.70 ± 5.91 ng/mL en el grupo 1 y de 15.23 ± 5.86 ng/mL en el grupo 2. Se encontró que el valor de visfatina en el grupo de quistes óseos aneurismáticos era significativamente menor desde el punto de vista estadístico que en el grupo de control ($p < 0.05$). No se encontró correlación entre el área del quiste y la visfatina ($p > 0.05$).* **Conclusión:** *Nuestro estudio encontró que los niveles de visfatina son significativamente más bajos en pacientes con quistes óseos aneurismáticos en comparación con los controles sanos, lo que sugiere su potencial como biomarcador diagnóstico. El análisis ROC mostró una buena capacidad diagnóstica.*

Palabras clave: *Visfatina. Quiste óseo aneurismático. Pediátrico.*

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Introduction

Aneurysmal bone cyst (ABC) diseases are known as benign tumors and tumor-like formations of the bone that involve the musculoskeletal system and cause disease, especially in children and young people in the first two decades, causing pain, pathological fractures, deformity in the extremity, functional loss, and neurological problems depending on the site of involvement[1-3]. In these diseases, the etiology of which has not yet been determined and can cause destructive bone lesion, conditions such as delay in diagnosis and inadequate or inappropriate treatment cause serious increases in national health expenditures together with high rates of morbidity. Although cystic bone lesions are common lesions encountered by all orthopedic physicians throughout their professional life, the fact that many benign and malignant tumors and tumor-like lesions are included in the differential diagnosis may put a physician in a difficult position to reach the correct diagnosis and treatment. Preservation of maximum function is essential in treatment, and percutaneous and minimally invasive surgeries are increasingly gaining prominence as the first choice in some of these diseases[4,5].

In musculoskeletal disorders, C-reactive protein, sedimentation, and complete blood count are common tests routinely requested by physicians in the first stage, in addition to radiology and clinical findings, while diagnosing the disease. However, despite all these developments, difficulties in diagnosis sometimes persist, routine laboratory findings are often insufficient in evaluating the prognosis of these patients, and determining the course of treatment and the morbidity of the disease creates problems for physicians[1]. Molecules that have been studied in recent years such as apelin, adropin, irisin, presepsin, dynamic thiol/disulfide balance, and visfatin have been found to play a role in the pathogenesis of many diseases. For this purpose, studies are carried out on various molecules and enzymes. With the developing medical technology and treatment options, new methods are gaining more and more importance in determining the course and prognosis of musculoskeletal diseases[4,5].

Visfatin, an adipocytokine secreted from adipose tissue, has been found to be decreased in numerous inflammatory diseases[2]. Given that ABC are associated with inflammation, we hypothesized that visfatin might also be involved in this condition. This is a prospective study and visfatin values of patients with ABC s were compared with those of healthy individuals.

Method

Patients and groups

This study consists of patients diagnosed with ABC, who applied to the orthopedics and traumatology clinic of Dicle University Faculty of Medicine. Our study consists of 20 patients diagnosed with ABC (Group 1) (Fig. 1) and 30 healthy patients (Group 2). Age, gender, cyst sizes, and visfatin values of all patients were recorded and evaluated.

Visfatin measurement

For the visfatin test, the blood was taken into flat biochemistry tubes, centrifuged, serum separated, and stored in a deep freezer at −80°C. Enzyme-linked immunosorbentassay (Human Elabela ELISA, Human Visfatin ELISA) method was used for the visfatin test. Serum visfatin levels were measured using the BioTek ELx50 Microplate Washer and BioTek ELx800 Microplate Reader (BioTek Instruments, Inc. USA) devices in accordance with the commercially obtained kit content (E Visfatin; Elabscience Biotechnology, USA. Catalog No: E-EL-H1763).

Inclusion criteria

Patients who were diagnosed with ABC, whose visfatin value was studied at the time of diagnosis, and who agreed to participate in the study and healthy individuals were included in the study.

Exclusion criteria

The presence of another disease that could affect the concomitant visfatin value at the time of diagnosis was accepted as exclusion criteria.

Ethical approval

Ethical approval was obtained from the Local Ethical Committee of the Dicle University with number 385/2021.

Statistical analysis

Statistical analysis was performed for patient data, including descriptive statistics, frequency, and other characteristics for all categories. Continuous data

Figure 1. *Aneurismal bone cyst.*

were expressed as mean ± standard deviation. Continuous variables were analyzed with the Shapiro-Wilk and Kolmogorov-Smirnov tests to determine whether the data fit the normal distribution. Continuous and normally distributed variables were compared using Student's t-test. Non-parametric tests were chosen when the data were not normally distributed. Correlation analysis was performed by Pearson correlation test. Analyses were performed using the Statistical Package for the Social Sciences Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). All p-values were considered two-sided and $p \leq 0.05$ was statistically significant.

Table 1. General findings

Characteristics	Group 1 (n = 20)	Group 2 (n = 30)	p
Age	13.80 ± 3.98	14.67 ± 4.24	> 0.05
Gender (male)	60%	53.3%	> 0.05
Cyst area (mm^2)	1171 (512-2310)		
Visfatin (ng/mL)	10.70 ± 5.91	15.23 ± 5.86	< 0.05
Median (IQR)			

IQR: interquartile range.

Results

A total of 50 patients, 20 from Group 1 and 30 from Group 2, were included in our study. The mean age was 13.80 ± 3.98 years in Group 1 and 14.67 ± 4.24 years in Group 2, and no statistically significant difference was found between the groups ($p > 0.05$). While 60% of the patients in Group 1 were male, in Group 2, 53% of the patients were male. The cyst area was recorded as 1171 (512-2310) mm^2. Our results show that the visfatin value was 10.70 ± 5.91 ng/mL in Group 1 (ABC) and 15.23 ± 5.86 ng/mL in Group 2 (control group). The visfatin value in the ABC group was found to be statistically significantly lower than the control group ($p < 0.05$) (Table 1). No correlation was found between cyst area and visfatin ($p > 0.05$) (Table 2). To determine the diagnostic value of visfatin in ABC s, a ROC analysis was performed. The area under the ROC curve (AUC) was 0.81, suggesting a good diagnostic performance. The optimal cutoff value for visfatin was determined as 8.2 ng/mL, which yielded a sensitivity of 93% and a specificity of 60% (Fig. 2).

Discussion

ABCs are benign lytic bone lesions that are typically found in kids and teenagers. A simple bone cyst is a

Table 2. Correlation between items

Characteristics	Cyst area (mm²)	Visfatin
Cyst area		
r	1.000	0.107
P		0.704
Visfatin		
r	0.107	1.000
p	0.704	

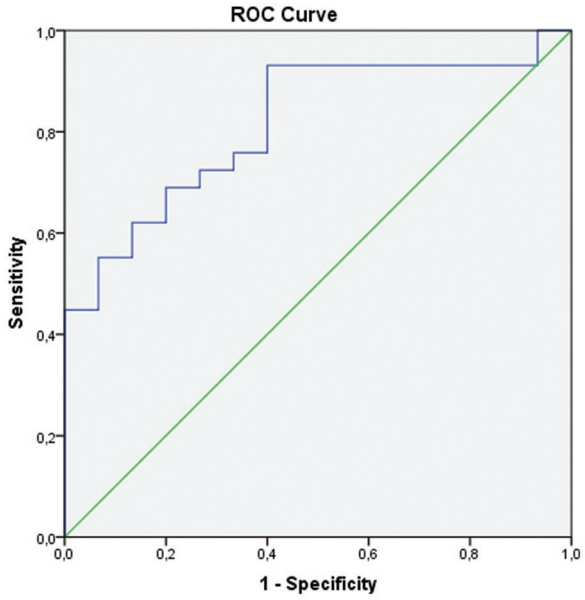

Figure 2. *Receiver operating characteristic analysis for visfatin levels in aneurismal bone cysts.*

fluid-filled, or partially separated lesion that is cystic in nature. The traditional ABC is a large, hemorrhagic tumor that typically exhibits a distinctive translocation. A third of ABCs, without translocation, is secondary and develops in response to another, typically benign, bone lesion. ABCs are a challenging lesion that can be confused for other diseases[1].

Visfatin is a new insulin-like adipocytokine secreted from adipose tissue. Visfatin, otherwise named nicotinamide phosphoribosyltransferase (NAmPRTase or Nampt), is also known as pre-B cell colony-enhancing factor 1 (PBEF1). Nampt/PBEF/visfatin was originally cloned as a putative cytokine shown to enhance the maturation of B-cell precursors in the presence of interleukin-7 and stem cell factor; it was therefore named “pre-B cell colony-enhancing factor” (PBEF)[4].

In a study by Chan et al. with 20 gestational diabetes mellitus (GDM) and 20 normal healthy pregnant women, serum visfatin levels were found to be significantly lower in women with GDM compared to the control group[6]. In comparison to controls, osteoarthritis (OA) patients have higher levels of circulating and local visfatin, with levels in OA synovial fluid being higher than paired OA plasma. As compared to control samples, it has been demonstrated that OA cartilage and synovium release more visfatin. In addition, OA IPFPs express visfatin at levels higher than the relating subcutaneous adipose tissue[7]. According to Gonzalez-Gay et al.,[8] finding’s the serum visfatin level in rheumatoid arthritis is not associated with the level of inflammation or the severity of the disease. In the research carried out by Sezen et al.,[9] it was found that the visfatin level in the serum samples taken from Behcet’s patients was significantly lower than that of the healthy control group. This probably plays a role in the pathogenesis of inflammatory diseases.

The most significant limitations of our research are the limited sample size (a relatively small number of patients participated), the fact that it was carried out only in a single location, and the fact that the healthy participants made up the control group. However, to the best of our knowledge, this study is the first prospective controlled study investigating the diagnostic value of visfatin in ABCs in pediatric patients.

In our study, a total of 50 patients, 20 from Group 1 and 30 from Group 2, were included. Cyst area was recorded as 1171 (512-2310) mm². The visfatin value was 10.70 ± 5.91 ng/mL in Group 1 and 15.23 ± 5.86 ng/mL in Group 2. The visfatin value in the ABC group was found to be statistically significantly lower than the control group ($p < 0.05$). No correlation was found between cyst area and visfatin ($p > 0.05$). Our findings suggest that visfatin may serve as a potential biomarker for ABCs. The ROC analysis revealed an AUC of 0.81, indicating a good diagnostic ability of visfatin, with a high sensitivity of 93% at a cutoff value of 8.2 ng/mL. However, the specificity was relatively low (60%), suggesting that while visfatin is good at detecting the presence of ABCs, it may also indicate other conditions. Further studies are needed to confirm these findings and to investigate the exact role of visfatin in the pathogenesis of these cysts.

Conclusion

Our study found that visfatin levels are significantly lower in patients with ABCs compared to healthy controls, suggesting its potential as a diagnostic biomarker. The ROC analysis showed a good diagnostic ability of visfatin with an AUC of 0.81, a sensitivity of 93%, and a specificity of 60% at a cutoff value of

8.2 ng/mL. More research is needed to confirm these results and to further explore the clinical significance of visfatin in the context of ABCs.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

A marker for acute cholecystitis severity: thiol-disulfide balance and ischemia-modified albumin

Un marcador de la gravedad de la colecistitis aguda: equilibrio de tiol-disulfuro y albúmina modificada por isquemia

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Abstract

Objective: *According to the Tokyo 2018 guidelines, white blood cells (WBCs) are the only markers used in the staging of acute cholecystitis. We aimed to investigate the role of thiol-disulfide and ischemia-modified albumin (IMA), which are used in the diagnosis of inflammatory diseases, in the diagnosis, and severity of acute cholecystitis.* **Method:** *A total of 108 patients hospitalized with acute cholecystitis and 42 healthy volunteers were included in the study. Plasma total thiol (TT), native thiol (NT), and disulfide levels were measured and IMA was calculated using disulfide/native, disulfide/total, and native/TT ratios.* **Results:** *Significant differences were found in both inflammatory and antioxidant markers, age, and symptom duration between disease stages (Stages I, II, and III) and control group ($p < 0.001$). Age and symptom duration were negatively correlated with antioxidant parameters (albumin, NT, and TT) ($r = -0.321$, $p < 0.00$). C-reactive protein and WBC correlated negatively with albumin and antioxidant parameters and positively with disulfide ($r = 0.776$, $p < 0.001$; $r = 0.358$, $p < 0.001$),* **Conclusions:** *The oxidative stress markers in our study can be used to assist radiologic examinations in determining the severity of acute cholecystitis.*

Keywords: *Acute cholecystitis. Ischemia-modified albumin. Tokyo 2018 Guidelines. Thiol/disulfide.*

Resumen

Objetivo: *Según las directrices de Tokio 2018, los glóbulos blancos son los únicos marcadores utilizados en la estadificación de la colecistitis aguda. Nos propusimos investigar el papel del tiol-disulfuro y la albúmina modificada por isquemia, que se utilizan para el diagnóstico de enfermedades inflamatorias, en el diagnóstico y la gravedad de la colecistitis aguda.* **Método:** *Se midieron los niveles totales de tiol, tiol nativo y disulfuro, y de albúmina modificada por isquemia, en plasma de 108 pacientes con colecistitis aguda y 42 voluntarios sanos.* **Resultados:** *Se encontraron diferencias significativas entre los estadios de la enfermedad (I, II y III) y el grupo control en términos de marcadores inflamatorios y antioxidantes, edad y duración de los síntomas ($p < 0.001$). La edad y la duración de los síntomas se correlacionaron negativamente con los parámetros antioxidantes (albúmina, tiol nativo, tiol total) ($r = -0.321$; $p < 0.00$). La proteína C reactiva y los glóbulos blancos se correlacionaron negativamente con la albúmina y los parámetros antioxidantes, y positivamente con el tiol disulfuro ($r = 0.776$, $p < 0.001$; $r = 0.358$, $p < 0.001$).* **Conclusiones:** *Los marcadores de estrés oxidativo de nuestro estudio pueden utilizarse para apoyar a los exámenes radiológicos en la determinación de la gravedad de la colecistitis aguda.*

Palabras clave: *Colecistitis aguda. Albúmina modificada por isquemia. Directrices de Tokio 2018. Tiol-disulfuro.*

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Introduction

Gallbladder stones are detected in 60% of patients who apply to hospitals due to the right upper quadrant (RUQ) pain, and acute cholecystitis is seen as the main cause of related abdominal pain in approximately 50% of these patients[1]. Worldwide, gallbladder diseases are the most common and costly digestive disorders. Acute cholecystitis results from gallbladder stones permanently blocking the cystic duct in 95% of cases. Obstruction increases intraluminal pressure and gallbladder swelling. Without cystic duct patency, neutrophils penetrate the gallbladder wall, causing mucosal bleeding and necrosis[2].

The community incidence of acute cholecystitis in gallstone patients is unknown; however, 20% are diagnosed. About 20% of acute cholecystitis patients develop gangrenous cholecystitis (GC) and 10% have perforation. The acute-phase reactants white blood cell (WBC) and C-reactive protein (CRP) rise dramatically in these conditions[3].

Historically, the Murphy sign and Charcod's triad were the main exam findings for acute cholecystitis and cholangitis. The Tokyo 2018 Acute Cholecystitis and Cholangitis Treatment Guide (TR18) add new recommendations based on prospective studies. This guide advised field physicians to diagnose and treat probable acute cholecystitis or cholangitis to reduce morbidity and mortality[4].

In the patient with acute cholecystitis, the disease condition, which starts with only inflammation at first, may progress to ischemia and perforation in the gallbladder and then cause sepsis and multiple organ failure[5].

Increased inflammatory mediators in acute inflammatory diseases cause an increase in oxidants such as reactive oxygen groups. Oxidants, which are balanced by various antioxidant systems in the body under physiological conditions, reach levels that exceed the antioxidant system with the severity of inflammation. This situation is called oxidative stress. Thiol groups are antioxidants that take excess electrons from oxidants and form disulfide bonds. The increase in disulfide bonds in an environment where oxidants are abundant suggests that disulfide is a marker of oxidative stress. When oxidative stress decreases, disulfide bonds can be reduced back to thiol and, thus, establish the thiol-disulfide balance[6]. During ischemia, free oxygen radicals alter serum albumin structure and reduce heavy metal binding. Albumin changed by ischemia. Ischemia-modified albumin (IMA) was first used to diagnose emergency myocardial ischemia, according to literature. Recent investigations have connected IMA to infections, malignancies, and trauma[7].

In this study, we aimed to investigate thiol-disulfide balance and IMA levels in patients with acute cholecystitis, an acute inflammatory disease that we believe is caused by oxidative stress. Since these tests can be easily measured together with biochemical parameters and WBC is the only laboratory marker in the staging of acute cholecystitis according to the Tokyo 2018 guidelines, we aimed to determine whether oxidative stress markers can help radiological and clinical methods to determine the stage of the disease before hospitalization.

Method

Study design

In this prospective, multicenter descriptive study, a total of 168 individuals, including 126 patients consulted to general surgery with a prediagnosis of acute cholecystitis from patients admitted to the emergency departments of both centers between April 2019 and April 2020, and 42 adult volunteer patients with no organic pathology during their admission to the general surgery outpatient clinic, were included in the study. A total of 18 patients were excluded from the study because six patients did not meet the study criteria, four patients did not sign the consent form, five patients had hemolyzed blood samples, two patients were pregnant, and one patient had a history of malignancy. The remaining 108 patients were divided into Grade 1, Grade 2, and Grade 3 groups using the Tokyo 2018 acute cholecystitis treatment guideline criteria and routinely used WBC count, international normalized ratio (INR), CRP values, and ultrasound, computed tomography data were obtained from the hospital system. Demographic data of the patients and the control group were recorded prospectively by face-to-face interviews with the patients[4] (Fig. 1).

Patient selection

The study included treatment data for patients diagnosed with acute cholecystitis who were admitted to emergency departments or general surgery outpatient clinics across multiple centers. Eligible patients were those over 18 years old, not pregnant, and without a history of chronic disease or drug use. The exclusion criteria were as follows: patients under 18, pregnant women, individuals with chronic or autoimmune

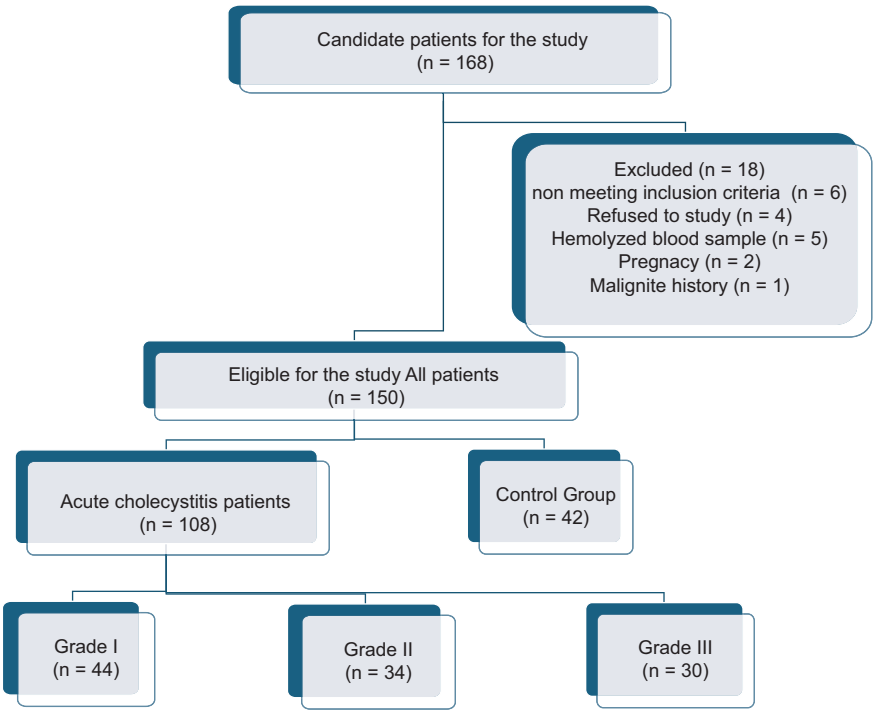

Figure 1. *Flow chart prospective multicenter descriptive study.*

diseases, those who did not sign the consent form, and patients with a history of past or active cancer.

This study was designed to evaluate the interactions between these markers and four different groups based on values obtained from the previous studies in patient groups with other diseases and published in international peer-reviewed journals. The power analysis was based on an effect size of 0.8 and was designed with 90% power and 5% probability of Type I error. The total sample size required for the study was calculated as 28. This sample size was determined to ensure that the study had sufficient statistical power.

Ethical approval

This scientific study Süleyman Demirel University Faculty of Medicine Clinical Research (dated March 05, 2019 decision no. 93) and Isparta Governorship Provincial Health Directorate Research and Development Commission (with document number 59222281-771 dated March 26, 2019) Ethics. It was initiated and carried out after receiving approval from the boards. The study was carried out by the Declaration of Helsinki.

Biochemical analysis

Patients with acute cholecystitis were diagnosed clinically and radiologically. Approximately 5 cc of blood was taken into a routine biochemistry tube before initiating antibiotic therapy, and the blood was centrifuged for 10 min at 3600 rpm at +4°C. The separated serum was placed in an Eppendorf tube and stored at −80°C. Thiol-disulfide and IMA parameters, thiol-disulfide homeostasis parameters, and IMA levels were analyzed. In the analysis of plasma thiol/disulfide homeostasis, Erel and Neşelioğlu the kits of the automatic method developed by him were used[8]. In IMA measurement, Bar-Or et al. the method developed by was used. Since IMA concentrations are not standard, they were given in absorbance units (ABSU)[9]. Native thiol (NT), total thiol (TT), disulphide (D) measurements, D/NT (index 1), D/TT (index 2), and NT/TT (index 3) ratios were evaluated in the biochemistry laboratory regarding the thiol-disulfide balance.

Statistical analysis

SPSS for Windows 25.0 (IBM Corp., Armonk, NY) was used to analyze study patient data. Kolmogorov–Smirnov and Histogram examined continuous variable normality assumptions, skewness and kurtosis coefficients, median, mode, and mean values, and Levene's Test examined variance homogeneities. Descriptive statistics for continuous variables included mean and standard deviation, and categorical variables included frequency (n) and percentage (%). Comparing three or

more levels was done with one-way analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for non-normal data that *post hoc* tests were used for continuous variables. Bonferroni correction was applied after ANOVA test. Mann–Whitney U-test was performed after Kruskal–Wallis test. X^2/Fisher exact analysis was used for categorical variables, Spearman (Spearman's rho) correlation analysis for continuous variables, and receiver operating characteristic (ROC) analysis for sensitivity and specificity. Relationship categorical variables were tested with Cramer's V. The results were statistically significant when $p < 0.05$.

Results

A total of 150 patients, the study had 42 control participants (28.0%) and 108 patients (72.0%). 40.7% of patients were in Stage I, 31.5% in Stage II, and 27.8% in Stage III. The control group averaged 52.14 years (range: 18-79), while the patient group averaged 56.77 years. The control group had 52.4% female and 47.6% male, while the patient group had 46.3% female and 53.7% male. The participants were split between Isparta City (42.6%) and Suleyman Demirel University Hospital (57.4%). Murphy sign was positive 78.7% of the time and negative 21.3%. About 88.9% of participants had RUQ tenderness, and 25.0% rebounded. RUQ palpable mass was absent in 81.5% and present in 18.5%. Fever was reported by 27.8% of patients and not by 72.2%. The characteristics of the patients are in table 1.

There are significant differences between different grades (Grade I, II, and III) and a control group. Significant differences were observed between groups in terms of WBC, CRP, albumin, IMA, index 1, index 2, index 3, INR, NT, TT, disulfide, age, and symptom duration ($p < 0.001$). WBC, CRP, IMA, index 1, index 2, and INR increased from stage I to stage III, whereas albumin, index 3, NT, and TT decreased numerically. The control group had the lowest mean values for CRP, IMA, index 1, index 2, INR, and symptom duration and the highest mean values for albumin, index 3, NT, and TT compared to the other patient groups (Table 2).

Our correlation analysis revealed complex relationships between age, symptom duration, inflammatory markers, and oxidative stress indicators in acute cholecystitis grading in the patient group. Age has a significant positive correlation with symptom duration ($r = 0.380$, $p < 0.001$), suggesting a role in disease progression. Age was positively correlated with inflammatory markers including CRP and WBC ($r = 0.355$, $p < 0.001$), but negatively correlated with antioxidant markers such as albumin, NT, and TT ($r = -0.321$, $p < 0.001$) (Table 3).

Symptom duration was positively correlated with CRP levels ($r = 0.776$, $p < 0.001$) and WBC count ($r = 0.358$, $p < 0.001$), indicating an inflammatory connection. Conversely, albumin ($r = -0.335$, $p < 0.001$) and antioxidant parameters (NT, TT, and index 3 ratio) showed negative correlations. Positive correlations were found between disulfide ratios (Index 1, index 2) and disease stage ($r = 0.809$, $p < 0.001$) (Table 3).

Table 4 shows the ROC analysis of NT, TT, index 3 ratio, disulfide, index 1 ratio, and IMA for oxidative stress diagnostics. Results showed significant discrimination for each parameter: NT showed an area under the curve (AUC) of 0.858 ($p < 0.001$), with an optimal

Table 1. Sociodemographic and clinical characteristics of the patients included in the study

Variable	n (%)
Group	42 (28.0)
Control group	108 (72.0)
Patient group	
Phase*	
Grade I	44 (40.7)
Grade II	34 (31.5)
Grade III	30 (27.8)
Age	
Control group	52.14 (18-79)
Patient group	56.77 (19-84)
Gender	
Control group	
Female	22 (52.4)
Male	20 (47.6)
Patient group	
Female	50 (46.3)
Male	58 (53.7)
Hospital (site)*	
Isparta City	46 (42.6)
Suleyman Demirel University Hospital	62 (57.4)
Murphy sign*	
Negative	23 (21.3)
Positive	85 (78.7)
Tenderness in the right upper quadrant*	96 (88.9)
Rebound examination finding*	27 (25.00)
SUC palpable mass*	
Negative	88 (81.5)
Positive	20 (18.5)
Fever*	
None	78 (72.2)
There is	30 (27.8)
*Only numbers and percentages in the patient group are given.	30 (27.8)

* For marked variables, only the numbers and percentages in the patient group are given. It does not include the control group.

Table 2. Comparison of BK, CRP, albumin, IMA, index 1, index 2, index 3, INR, native thiol, total thiol, disulfide, age, and complaint duration values between groups

Variable	Mean ± SD	Median (Min-Max)	F/χ^2	p
WBC*			59.491	< 0.001*
Grade I	9.15 ± 2.89	9.25 (3.30-14.50)		
Grade II	14.76 ± 3.92	14.05 (5.10-21.30)		
Grade III	15.98 ± 5.28	18.00 (3.80-22.20)		
Control	6.77 ± 1.22	6.45 (5.10-9.30)		
CRP**			91.955	< 0.001*
Grade I	8.16 ± 5.44	7.12 (0.28-21)		
Grade II	49.92 ± 34.73	38.50 (19.56-214)		
Grade III	181.27 ± 73.20	186.50 (51.29-56)		
Control	-	-		
Albumin**			65.033	< 0.001*
Grade I	3.09 ± 0.63	3.20 (0.73-3.87)		
Grade II	2.84 ± 0.77	3.00 (0.36-4.27)		
Grade III	2.36 ± 0.82	2.48 (0.53-3.52)		
Control	3.62 ± 0.27	3.61 (2.56-4.13)		
IMA**			31.470	< 0.001*
Grade I	0.81 ± 0.23	0.80 (0.45-1.53)		
Grade II	0.86 ± 0.22	0.83 (0.50-1.48)		
Grade III	1.14 ± 1.43	0.88 (0.42-8.46)		
Control	0.61 ± 0.19	0.59 (0.28-1.17)		
Index 1**			52.543	< 0.001*
Grade I	6.89 ± 5.21	5.26 (0.53-20.85)		
Grade II	10.55 ± 7.57	8.02 (1.08-34.21)		
Grade III	15.35 ± 11.22	10.40 (5.71-42.80)		
Control	4.39 ± 1.21	4.31 (2.18-9.73)		
Index 2**			52.553	< 0.001*
Grade I	5.73 ± 3.71	4.76 (0.53-14.71)		
Grade II	8.16 ± 4.62	6.91 (1.06-20.31)		
Grade III	10.79 ± 5.81	8.61 (5.12-23.06)		
Control	4.01 ± 1.03	3.97 (2.09-8.15)		
Index 3**			52.517	< 0.001*
Grade I	88.55 ± 7.42	90.49 (70.57-98.94)		
Grade II	83.68 ± 9.24	86.18 (59.38-97.88)		
Grade III	78.42 ± 11.62	82.79 (53.88-89.76)		
Control	91.98 ± 2.06	92.07 (83.71-95.83)		
INR**			10.900	0.004*
Grade I	1.21 ± 0.88	1.06 (0.91-690)		
Grade II	1.30 ± 0.95	1.14 (0.90-6.60)		
Grade III	1.34 ± 0.38	1.19 (0.98-2.20)		
Control	-	-		
Native thiol*			28.635	< 0.001*
Grade I	291.04 ± 74.19	295.97 (139.20-456.76)		
Grade II	253.89 ± 85.50	232.88 (85.38-440.60)		
Grade III	215.50 ± 83.45	216.81 (92.10-392.23)		
Control	369.07 ± 55.15	367.35 (229.58-527.63)		
Total thiol*			26.276	< 0.001*
Grade I	325.39 ± 67.05	318.10 (192.24-487.24)		
Grade II	296.72 ± 74.65	279.62 (143.79-459.18)		
Grade III	266.99 ± 77.28	271.75 (152.50-443.42)		
Control	400.82 ± 56.55	400.33 (261.84-566.58)		
Disulfide**			34.365	< 0.001*
Grade I	17.17 ± 9.10	15.77 (1.66-46.75)		
Grade II	21.42 ± 7.94	19.69 (4.46-38.89)		
Grade III	25.74 ± 9.15	21.46 (13.15-45.83)		
Control	15.88 ± 4.13	15.46 (8.75-36.60)		
Age*			24.829	< 0.001*
Grade I	54.98 ± 17.41	57.50 (22.00-86.00)		
Grade II	64.12 ± 17.79	66.00 (18.00-92.00)		
Grade III	71.60 ± 16.89	74.50 (24.00-91.00)		
Control	41.40 ± 10.46	42.00 (26.00-62.00)		
Symptoms (days)**			73.328	< 0.001*
Grade I	1.73 ± 0.45	2.00 (1.00-2.00)		
Grade II	5.06 ± 3.37	4.00 (1.00-20.00)		
Grade III	6.20 ± 2.34	5.50 (3.00-12.00)		

*Analysis of variance analysis was performed because the data met normal distribution assumptions.
**Kruskal–Wallis test was performed because the data did not meet normal distribution assumptions.
WBC: white blood cells; CRP: C-reactive protein; IMA: ischemia-modified albumin; INR: international normalized ratio.

cutoff value of 331.38, achieving 78.7% sensitivity and 83.3% specificity (95% confidence interval [CI]: 0.798-0.918). TT had an AUC of 0.849 ($p < 0.001$), a cutoff value of 363.58, a sensitivity of 79.6%, and a specificity of 81.0% (CI: 0.786-0.913). The index 3 ratio had an AUC of 0.784 ($p < 0.001$), with an optimal cutoff value of 91.20, 77.8% sensitivity, and 78.6% specificity (CI: 0.710-0.857) (Fig. 2).

Disulfide showed an AUC of 0.696 ($p < 0.001$), a cutoff value of 16.57, 65.7% sensitivity, and 66.7% specificity (CI: 0.612-0.779).

In addition, the D/NT ratio (Index 1) and D/TT ratio (Index 2) showed AUCs of 0.784 ($p < 0.001$) and 0.665 ($p < 0.001$), respectively, with optimal cutoff values of 4.82 and 4.395. Both ratios had 77.8% sensitivity and 78.6% specificity (CI: 0.711-0.858 and 0.710-0.857).

Finally, IMA showed an AUC of 0.791 ($p < 0.001$), a cutoff value of 0.655, and a sensitivity of 75.0% and specificity of 71.4% (CI: 0.709-0.872). The present findings suggest that the oxidative stress markers used in this study can be used as a laboratory test in addition to radiologic tests to distinguish between patients with acute cholecystitis and healthy people (Table 4 and Fig. 3).

Discussion

Significant changes in inflammatory and oxidative stress indicators were observed in patients with

Table 3. Correlation coefficients between age, duration of symptoms, CRP, WBC, albumin, IMA, Index 1, Index 2, Index 3, native thiol, total thiol, and disulfide in the patient group

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	-												
r	-												
p	-												
2. Symptoms (days)		-											
r	0.380	-											
p	0.000	-											
3. CRP			-										
r	0.355	0.776	-										
p	0.000	0.000	-										
4. WBC				-									
r	0.096	0.358	0.604	-									
p	0.325	0.000	0.000	-									
5. Albumin					-								
r	−0.321	−0.335	−0.358	−0.194	-								
p	0.001	0.000	0.000	0.044	-								
6. IMA						-							
r	0.157	0.119	0.106	−0.092	−0.032	-							
p	0.105	0.220	0.274	0.342	0.743	-							
7. Index 1							-						
r	0.320	0.351	0.391	0.356	−0.489	0.055	-						
p	0.001	0.000	0.000	0.000	0.000	0.569	-						
8. Index 2								-					
r	0.319	0.351	0.391	0.356	−0.489	0.056	1.000	-					
p	0.001	0.000	0.000	0.000	0.000	0.567	0.000	-					
9. Index 3				−0.355					-				
r	−0.320	−0.351	−0.390	0.000	−0.489	−0.055	−1.000	−1.000	-				
p	0.001	0.000	0.000		0.000	0.571	0.000	0.000	-				
10. Stage										-			
r	0.399	0.809	0.927	0.596	−0.396	0.082	0.441	0.441	−0.440	-			
p	0.000	0.000	0.000	0.000	0.000	0.399	0.000	0.000	0.000	-			
11. Native thiol											-		
r	−0.346	−0.266	−0.318	−0.247	0.613	−0.097	−0.858	−0.858	0.858	−0.355	-		
p	0.000	0.005	0.001	0.010	0.000	0.318	0.000	0.000	0.000	0.000	-		
12. Total thiol												-	
r	−0.341	−0.226	−0.275	−0.198	0.629	−0.109	−0.764	−0.764	0.764	−0.310	0.982	-	
p	0.000	0.019	0.004	0.040	0.000	0.261	0.000	0.000	0.000	0.001	0.000	-	
13. Disulfide													-
r	0.236	0.321	0.354	0.381	−0.324	−0.011	0.930	0.930	−0.930	0.398	−0.645	−0.513	-
p	0.014	0.001	0.000	0.000	0.001	0.914	0.000	0.000	0.000	0.000	0.000	0.000	-

WBC: white blood cells; CRP: C-reactive protein; IMA: ischemia-modified albumin; INR: international normalized ratio.

acute cholecystitis as the stage progressed. In particular, the increase in inflammatory indicators such as WBC, CRP, disulfide, and IMA and the decrease in antioxidant parameters such as albumin, NT, and TT are directly proportional to the stage of the disease.

Complex acute cholecystitis can lead to sepsis from gallbladder inflammation[2]. In 2018, the Tokyo Acute Cholecystitis Treatment Guideline was finalized after several updates to the timing of cholecystectomy and the selection of intensive care patients. WBC is the only laboratory marker used in disease staging by the Tokyo criteria[4].

WBC rises as a defense. Previous research describes acute cholecystitis WBC elevation up to 77%[10]. Our study found a statistically significant increase in all

Table 4. ROC analysis of oxidative stress parameters and confidence ıntervals

Test name	Zone	p	Cut off value	Sensitivity (%)	Specifity (%)	Confidence interval
Native thiol	0.858	< 0.001*	331.38	78.7	83.3	(0.798-0.918)
Total thiol	0.849	< 0.001*	363.58	79.6	81.0	(0.786-0.913)
(index 3)	0.784	< 0.001*	91.20	77.8	78.6	(0.710-0.857)
Disulfide	0.696	< 0.001*	16.57	65.7	66.7	(0.612-0.779)
(index 1)	0.784	< 0.001*	4.82	77.8	78.6	(0.711-0.858)
(index 2)	0.665	< 0.001*	4.395	77.8	78.6	(0.710-0.857)
IMA	0.791	< 0.001*	0.655	75	71.4	(0.709-0.872)

*For marked variables, only the numbers and percentages in the patient group are given. It does not include the control group.
ROC: receiver operating characteristic; IMA: ischemia-modified albumin.

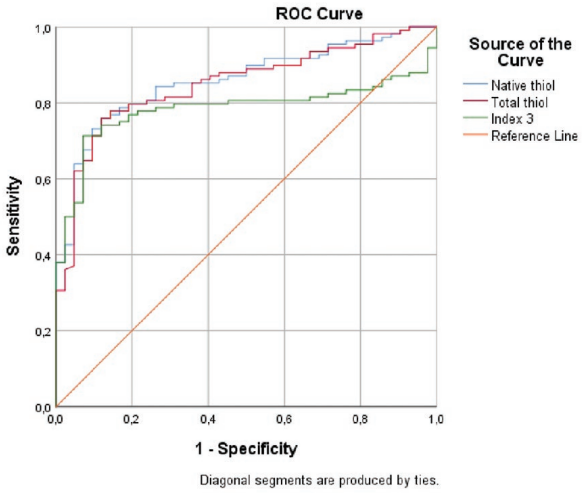

Figure 2. *Performance of native thiol, total thiol, and index 3 in differentiating acute cholecystitis form healthy controls.*

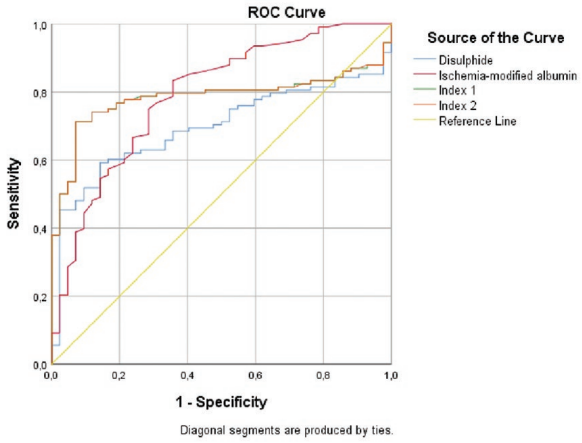

Figure 3. *Performance of acute ischemia-modified albumiin, disulphide, index 1, and index 2 in differentiating acute cholecystitis from healthy controls.*

patient groups compared to healthy individuals. Stages II and III had significantly more WBCs than Stage I, reflecting the progression of inflammation. Fagan et al. found that GC patients had significantly higher WBC counts than uncomplicated patients. Male gender and WBC counts above 15.000 microliter were risk factors for GC[11]. Our study found 14.700 and 18.000 microliter leukocyte counts in Stages II and III patients, consistent with previous research.

Acute-phase reactant C-reactive protein helps the body respond to trauma and inflammation. It should rise with inflammation. If pre-operative plasma levels were higher than post-operative CRP and WBC levels, post-operative complications, and conversion to open surgery increased[12]. Kabul Gurbulak et al. analyzed 682 patients retrospectively. They found that CRP levels rose as disease complexity increased in Tokyo 2013 guideline patients[13]. Despite the lack of studies, our study found that CRP levels increased significantly between groups as disease severity increased in all groups.

In mammals, albumin is the most common plasma protein. Oxidants may target plasma protein sulfhydryl groups. The unique free sulfhydryl group forms a sulfenic group in albumin for oxidation[14]. Albumin has many intracellular functions, but it is a negative acute phase reactant that participates in inflammation and decreases serum levels. High CRP and low albumin levels increase inflammatory disease mortality, especially in elderly patients[15]. Kaysen et al. found a negative correlation between CRP and serum albumin in hemodialysis patients[16]. All patient groups had significantly lower albumin levels

than the control group, and as disease severity increased, albumin levels decreased. Symptom duration increased with age, CRP, and disulfide.

This is the first study to compare thiol/disulfide homeostasis and IMA levels, which are thought to be markers of oxidative stress in acute cholecystitis patients, to inflammatory markers and disease grades according to the Tokyo 2018 guidelines.

IMA was initially approved by the Food and Drug Administration (FDA) for use in early prediction of myocardial ischemia in cardiac patients[17]. Later, studies used IMA to predict ischemia and necrosis in many diseases. Sinha et al. discovered that IMA preceded myocardial ischemia[18]. IMA can predict ischemia or severe disease in many diseases, including skeletal muscle ischemia, acute appendicitis, and mesenteric ischemia[19,20]. Sahin et al. found that acute pancreatitis severity increased IMA and corrected IMA levels[21]. Our study found a significant difference in IMA values between acute cholecystitis patients and healthy controls. The median ABSU values of all groups in our study were above 0.400 and 0.400 ABSU is considered as the threshold value for IMA and values above this value suggest ischemia[9]. The difference between Stage I and Stage III patients was statistically significant. In all stage groups, the median IMA level in patients was higher than in controls. Statistics showed that Stages II and III were significantly higher than the control group. Based on these results, IMA may be a marker for Grade II-III acute cholecystitis.

Thiols are sulfhydryl sulfide and hydrogen groups that participate in intracellular and extracellular antioxidant reactions. Plasma thiols are albumin or lower molecular weight cysteine-like protein thiols. Due to inflammation, free radicals increase, and the antioxidant system neutralizes them. Oxidative stress is caused by insufficient antioxidant defense during inflammation, but after antioxidant thiols become active, NTs decrease, and disulfide is expected to increase in response to free radicals[22]. In bacterial tonsillitis, Familial Mediterranean fever (FMF), tumors, and acute pancreatitis, serum thiol/disulfide values were in the disulfide direction[23]. FMF patients had higher disulfide and lower native and TT values than healthy people[24]. Bacterial tonsillitis patients had higher index 1 and index 2 ratios than controls[25]. Another study found that gallbladder perforation patients had higher median WBC, neutrophil count, disulfide, and IMA values than gallstone patients[26]. Researchers found that the healthy control group had significantly higher levels of native and TT ($p < 0.001$) compared to all other groups of patients with acute cholecystitis. The duration of symptoms, CRP value, disease severity, and disulfide were positively correlated, while total and NT levels were negatively correlated.

These findings showed that oxidative stress exposure increases with disease severity, inflammatory laboratory parameters, and antioxidants drop and oxidants rise. Since oxidative stress shifts the oxidant-antioxidant balance to the oxidant direction in inflammatory diseases, antioxidants may help treat them[27].

Conclusion

This study demonstrated that thiol-disulfide homeostasis and IMA can be used as a laboratory marker supporting radiologic and clinical parameters to differentiate between complex patient groups with severe acute cholecystitis and low-grade patient groups.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Volume status evaluation by IVC diameter and pleth variability index in spinal anesthesia

Evaluación del volumen mediante la IVC y el índice de variabilidad de pleth en anestesia espinal

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Abstract

Objective: *We aimed to predict the risk of hypotension due to spinal anesthesia (HSA) by measuring the diameter and area of the inferior vena cava (IVC-D, IVC-A) through ultrasound and pleth variability index (PVI) in patients who underwent endovenous radiofrequency ablation under spinal anesthesia (SA).* **Method:** *This cross-sectional, observational, and prospective study was completed with 64 patients. Before SA, PVI IVC-D, and IVC-A were measured. Patients were divided into two groups as hypotension group (Group 1) and patients who did not developed hypotension after SA (Group 2). Shapiro–Wilk normality test and student's t-test were used for statistical analysis.* **Results:** *The mean PVI of Group 1 was higher than Group 2, whereas the mean IVC-D and IVC-A in Group 2 was significantly higher than Group 1 ($p = 0.000$, $p = 0.000$, $p = 0.001$). Cutoff values for hypotension PVI > 15% and IVC-A ≤ 2.98 mm^2 ($p = 0.001$, $p < 0.05$).* **Conclusion:** *PVI and IVC-D and IVC-A measurements are effective and reliable methods that should be used to predict the risk of developing HSA in patients who will undergo surgery under SA.*

Keywords: *Spinal anesthesia. Hypotension. Pleth variability ındex. Inferior vena cava.*

Resumen

Objetivo: *El objetivo de nuestro estudio fue predecir el riesgo de hipotensión debido a la anestesia espinal (HSA) midiendo el diámetro y el área de la vena cava inferior (IVC-D, IVC-A) mediante ecografía y el índice de variabilidad de pleth (PVI) en pacientes sometidos a ablación por radiofrecuencia endovenosa bajo anestesia espinal.* **Método:** *Este estudio transversal, observacional y prospectivo se completó con 64 pacientes. Antes de la anestesia espinal (SA) se midieron los diámetros y áreas del PVI y la IVC. Los pacientes se dividieron en dos grupos: grupo de hipotensión (grupo 1) y pacientes que no desarrollaron hipotensión después de la SA (grupo 2). Se utilizó la prueba de normalidad de Shapiro-Wilk y la prueba t de Student para el análisis estadístico.* **Resultados:** *Este estudio transversal, observacional y prospectivo se completó con 64 pacientes. El PVI medio del grupo1 fue mayor que el grupo 2, que el IVC-D y IVC-A en el grupo 2 fueron mayores que en el grupo 1 ($p = 0.000$, $p = 0.000$, $p = 0,001$). Los valores de corte para la hipotensión fueron PVI > 15% y área de la VCI ≤ 2.98 mm^2 ($p = 0,00$; $p < 0.05$).* **Conclusión:** *Las mediciones del PVI, IVC-D y IVC-A son métodos efectivos y confiables que deben utilizarse para predecir el riesgo de HSA en pacientes que se someterán a cirugía bajo SA.*

Palabras clave: *Anestesia espinal. Hipotensión. Índice de variabilidad de pleth. Vena cava inferior.*

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Introduction

In addition to providing perioperative regional anesthesia, spinal anesthesia (SA) has many advantages such as controlling the sympathetic response that develops in response to surgical stress, post-operative analgesia, and shortening the recovery period with early mobilization followed by early discharge[1]. SA can be preferred for short-term surgeries, such as lower extremity venous insufficiency, where SA provides sufficient surgical comfort. With the development of technology, new surgical techniques such as laser and radiofrequency ablation have started to be preferred frequently in the treatment of lower extremity varicose veins[2]. Chronic venous insufficiency may cause not only cosmetic but also life-threatening consequences such as embolism. Therefore, early mobilization is important for the treatment processes.

On the other hand, hypotension due to SA (HSA) is a condition with a high incidence of 70%, impairing patient comfort and anesthesia quality and increasing morbidity[3]. It is thought that HSA develops due to a decrease in the preload as a result of vasodilation of veins and venous blood pooling due to a decrease in peripheral vascular resistance[4].

Patient's basic peripheral vasomotor-sympathetic tone and volume status are among the criteria determining the risk of developing HSA[5]. It is important to predict the risk of developing HSA and take precautions to ensure that the patient has a more stable surgery. For this purpose, existing parameters were evaluated and some invasive and non-invasive hemodynamic measurements were developed. Pleth variability index (PVI) is one of these measurements that automatically calculates respiratory variables in pulse oximetry amplitude and predicts fluid response. PVI is calculated by measuring the dynamic changes in the perfusion index, defined as the ratio of the non-pulsatile flow to the pulsatile flow in the capillary bed during a respiratory cycle[6].

$$PVI = \left[\frac{PI_{max} - PI_{min}}{PI_{max}} \right] x\ \%100$$

Another non-invasive method used to determine volume status is ultrasonography of inferior vena cava (USG IVC) diameter measurement[7]. The use of ultrasonography (USG) has advantages such as being simple, non-invasive, and reproducible.

The case of being able to predict HSA will give clinicians the opportunity to be prepared and take preventive measures. Therefore, in our study, we aimed to determine the predictability of the risk of developing HSA by measuring PVI and USG IVC diameter and area and the reliability of these methods in patients who underwent SA due to peripheral varicose surgery.

Method

After the approval of the Ethics Committee (date: 19 October 2018, number: 54132726-000-22167) and the informed consents of the patients were obtained, the study was conducted in the Department of Anesthesia and Reanimation of the Health Sciences University Ümraniye Training and Research Hospital between January 2019 and May 2019, as a cross-sectional, observational, and prospective study on the patients who were planned to undergo elective lower extremity varicose vein surgery under SA. It was chosen because it is short-them and would not affect the patient's volume status as there is no blood loss.

The patients who were between 18 and 65 years of age, with American Society of Anesthesiologists (ASA) physical status classification I-II, without cardiac disease, no contraindications for SA and no diagnosis of diabetes mellitus or hypertension were included in the study. Patients who did not give consent and/or gave up participating the study and patients whose SA procedure were unsuccessful were excluded from the study.

HSA was defined as a 25% decrease in systolic arterial pressure from the value measured before the SA or a decrease in systolic blood pressure (SBP) more than 90 mmHg within the first 10 min after SA. The patients who developed HSA were recorded as "Group 1" and the patients who did not develop as "Group 2".

The number of patients in Groups 1 and 2 was determined by taking the patients who met the study criteria in a certain time interval into account according to the power analysis performed in line with the sample study (n = 30 for group 1 and n = 34 for group 2).

All patients included in the study were administered 2 mg midazolam IV in the pre-operative care unit. Afterward, IVC diameter measurements were made in the supine position with USG and PVI values were recorded using Masimo Radical 7 pulse oximetry.

IVC measurements were made using Toshiba Istyle Aplio Xg ultrasound device, with a 4 MHz convex probe, using the liver window from the 7th intercostal

space on the anterior axillary line while the patient was in the supine position. In cases where a quality image could not be obtained from the 7th intercostal space, measurements were made from the 6th or 8th intercostal space. The widest IVC image in the interval between the left renal vein and hepatic vein pouring into the IVC was recorded at the end of the expiration and p wave, and anteroposterior, transverse diameters and area were measured. Measurements were made at the end of the expiration and by the same person using the device in all patients. PVI measurements were recorded on the Masimo Radical 7 monitor by attaching the pulse-oximetry probe to the index finger of the right hand in all patients.

After the measurements, the patients were taken to the operating room and 5 mL/kg 0.9% NaCl IV infusion was given in 30 min for hydration. Standard monitoring, pulse oximetry (oxygen saturation), non-invasive SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP) measurements, and three-lead precordial electrocardiogram monitoring were performed.

SA was administered to all patients in a sitting position under sterile conditions with a 26-gauge spinal needle and 15 mg 0.5% heavy bupivacaine intrathecally in L3-L4 interspace. Unsuccessful SA was defined as inability to enter the interspace after a maximum of 3 attempts, failure to achieve T10 block level within 10 min, and pain in the first 10 min intraoperatively. Patients who had unsuccessful attempts within these interspaces were switched to general anesthesia and these patients were excluded from the study.

Demographic data (age, gender, height, weight, body mass index [BMI], ASA, and additional diseases) of the patients participating in the study were recorded. SBP, DBP, and MAP values were recorded before SA, at the time of performing the SA (minute =0), and at the 5th, 10th, 15th, 20th, 25th, and 30th min after SA.

At the end of the operation, the patients were followed up in the post-operative recovery room for 20 min.

Statistical analysis

While evaluating the findings obtained in the study, IBM Statistical Package for the Social Sciences (SPSS) Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. The conformity of the parameters to the normal distribution was evaluated with the Shapiro–Wilk normality test and it was determined that all parameters were normally distributed. Student's t-test was used for the comparison of parameters between two groups and paired samples t-test was used for intragroup comparisons. Continuity (Yates) Correction was used to compare qualitative data. The most appropriate cutoff values were chosen based on the receiver operating characteristic (ROC) curve analysis. Statistical significance was evaluated at the $p < 0.05$ level.

The ROC curve is one of the most important evaluation criteria to control the performance of any classification model. When each value is accepted as the cut-off value for a positive result, sensitivity (sensitivity) and specificity (specificity) values are predicted for the diagnosis of the disease. At the end of the analysis, as the value indicated as area under the curve (AUC) approaches 1, the diagnostic value increases[8,9]. The diagnostic value of PVI and IVC diameter measurements for patients who developed SHA was evaluated with ROC curves and AUC.

Results

The study was conducted with a total of 64 patients (27 [42.2%] males and 37 [57.8%] females) aged between 22 and 65, with a mean age of 44.80 ± 10.74 years (Group 1= 30 [46.8%], Group 2 = 34 [53.1%]). A total of 73 patients who met the criteria were included in the study. Eight patients were excluded from the study because SA was unsuccessful for two patients, SA was switched to general anesthesia due to pain after the operation started for four patients sedation was given because the patient was incompatible for two patients, and one of them wanted to leave the study after SA was applied (Fig. 1).

Demographic data such as age, height, weight, BMI, gender distribution, and ASA scores of the patients were similar among the groups ($p > 0.05$; Table 1). Therefore, the patient's comorbidities did not affect our outcomes and findings.

The decrease in the measurements made at the 10th min and later in SBP and MAP, and only at the 15th min in DBP in Group 1 was statistically significant compared to Group 2 ($p < 0.05$); (Table 2 and Fig. 2). When PVI and IVC diameter (AP) and IVC diameter (transverse section), IVC area measurements were compared between the groups, the mean PVI was significantly higher in Group 1 compared to Group 2 ($p = 0.000$). IVC AP diameter, transverse diameter, and mean area were significantly higher in Group 2 than Group 1 ($p = 0.002$, $p = 0.000$, and $p = 0.001$, respectively); (Table 3).

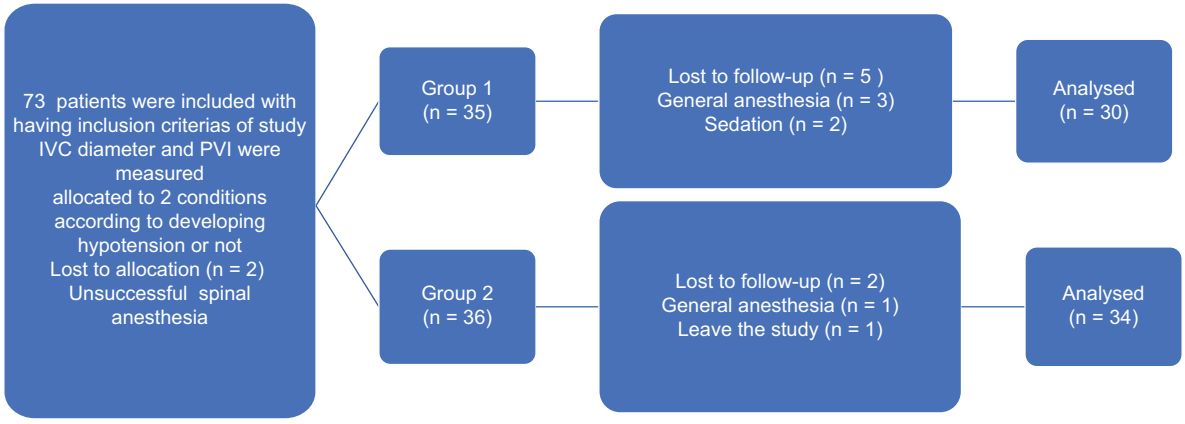

Figure 1. *Consort diagram.*

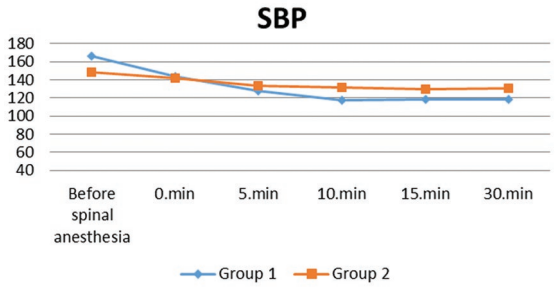

Figure 2. *Systolic arterial pressure change.*

The ROC curve including the AUC, cut-off, sensitivity, and specificity values drawn to evaluate the predictability of PVI, IVC AP diameter, IVC transverse diameter and BMI-IVC area measurements for the risk of developing hypotension are shown in Table 4.

AUC measurement values of all four parameters were found to be significantly >0.5. In our study, the threshold values predicting the development of hypotension were found to be > 15% for PVI, ≤ 18.7 mm for IVC diameter (AP), ≤ 18.8 mm for IVC diameter (transverse), and ≤ 2.98 mm^2 for IVC area, respectively ($p = 0.001$, $p < 0.05$); (Table 4, Fig. 3).

Discussion

HSA that develops during SA is an expected but undesirable side effect as it adversely affects perioperative morbidity and mortality[10]. Therefore, it is crucial to predict which patients may develop HSA during SA and to prevent it before developing. One of the most probable causes of HSA is hypovolemia. Hypovolemia may result from decreased systemic vascular resistance due to SA and/or the patient may already be pre-operatively hypovolemic. There are studies investigating the role of pre-operative volume status in predicting the development of HSA[4,11,12]. pulse index continuous cardiac output (PICCO) is a standard but invasive method to measure the volume status of patients. Alternatively, non-invasive measurements of PVI and IVC diameter and area have emerged.

In our study, as a primary outcome, we aimed to determine whether the measured PVI and IVC values through USG before the SA is performed are effective in predicting HSA and as a secondary outcome, if they are effective, we aimed to determine the cut-off values.

The study of Carpenter et al., reported advanced age (≥ 40 years) and high sensory block level as risk factors for hypotension after spinal block[13]. In our study, however, since there was no significant difference between the groups in terms of SA levels,

Table 1. Comparison of the groups in terms of demographic characteristics

Demographic Characteristics	Group 1	Group 2	p
	Mean ± SD	Mean ± SD	
Age (year)	46.87 ± 10.48	42.97 ± 10.79	0.149*
Height (cm)	1.8 ± 0.08	1.69 ± 0.08	0.764**
Weight (kg)	86.3 ± 17.59	81.79 ± 16.6	0.296*
BMI	30.65 ± 6.97	28.54 ± 4.86	0.171*
Gender	**n (%)**	**n (%)**	**p**
Male	13 (43.3)	14 (41.2)	1.000†
Female	17 (56.7)	20 (58.8)	
ASA	**n (%)**	**n (%)**	**p**
1	14 (46.7)	8 (23.5)	0.093†
2	16 (53.3)	26 (76.5)	

BMI: body mass index.
*Student t test; †continuity (yates) correction.

Table 2. Evaluation of the groups in terms of SBP, DBP, and MAP

SBP	Group 1	Group 2	p
	Mean ± SD	Mean ± SD	
Before spinal anesthesia	156.4 ± 26.37	148.18 ± 19.94	0.162
0 min	143.47 ± 31.88	142.26 ± 20.21	0.86
5 min	127.77 ± 23.56	133.59 ± 19.99	0.289
10 min	117.93 ± 20.71	131.26 ± 19.49	0.011*
15 min	118.2 ± 18.56	129.79 ± 16.15	0.010*
30 min	118.3 ± 15.07	130.71 ± 16.19	0.002*
DBP	**Group 1**	**Group 2**	**p**
	Mean ± SD	Mean ± SD	
Before spinal anesthesia	96.73 ± 18.34	92.74 ± 16.9	0.368
0 min	83.73 ± 19.51	85.82 ± 15.18	0.632
5 min	76.37 ± 20.72	82.91 ± 18.34	0.185
10 min	73.1 ± 20.41	80.53 ± 14.96	0.099
15 min	69.03 ± 17.83	78.18 ± 12.34	0.019*
30 min	71.1 ± 15.77	77.59 ± 11.91	0.066
MAP	**Group 1**	**Group 2**	**p**
	Mean ± SD	Mean ± SD	
Before spinal anesthesia	118.9 ± 22.34	113.03 ± 19.93	0.215
0 min	109.03 ± 25.8	107.41 ± 19.62	0.777
5 min	91.50 ± 21.39	99.65 ± 16.6	0.092
10 min	84.07 ± 18.59	96.59 ± 16.62	0.006*
15 min	85.93 ± 15.73	96.50 ± 17.0	0.013*
30 min	82.43 ± 14.60	95.97 ± 16.23	0.001*

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure. Student's t-test. *p < 0.05.

Table 3. Comparison of PVI and IVC diameters between groups

Parameters	Group 1	Group 2	p
	Mean ± SD	Mean ± SD	
PVI (%)	20.2 ± 3.09	14.24 ± 4.86	0.000*
IVC diameter AP (mm)	18.54 ± 2.05	20.19 ± 1.91	0.002*
IVC diameter Transverse (mm)	17.28 ± 2.23	20.22 ± 1.74	0.000*
IVC area (mm^2)	2.89 ± 0.72	3.60 ± 0.82	0.001*

PVI: pleth variability ındex; IVC: inferior vena cava; AP: anteroposterior. Student's t-test *p < 0.05.

age, gender, BMI, and ASA scores of the patients we compared in two groups according to hypotension and non-hypotension development, these parameters were not considered as risk factors for developing hypotension.

In a study conducted by Ceruti et al., HSA incidence decreased by 15% in patients who were given fluid therapy before SA after IVC diameter measurements by ultrasound[14]. In various studies conducted on trauma patients with hypovolemia or hemorrhagic shock in the intensive care unit, on patients receiving hemodialysis, or in healthy volunteers, ultrasonographic IVC diameter measurements were shown to be an effective method for evaluating the volume status of patients and their response to fluid therapy[15-19].

The fact that IVC is an elastic vessel, USG is an operator-dependent method, and the measurement quality varies depending on the device used, and the skill and experience of the operator may affect the measurements. This issue is the most important limitation of this method. To eliminate these factors in our study, the same device was used for the measurements made on each patient and all measurements were made by the same operator.

PVI is a new algorithm used to automatically calculate respiratory variables in pulse oximetry amplitude that predicts fluid response[5]. It is an easy-to-use, non-invasive method with the measurements made by the pulse oximetry probe that is independent of the operator using it. In a study of Yu et al. with 30 patients who underwent major abdominal surgery, it was observed that hemodynamic stabilization was achieved with a smaller amount of fluid replacement in patients whose fluid status was evaluated with PVI in addition to MAP, compared to patients evaluated with MAP alone[20]. A previous meta-analysis indicated that PVI is a reliable indicator of fluid response in the perioperative and critically ill patients, especially adults undergoing mechanical ventilation[21]. In the study of Kuwata et al., hypotensive states were reported to be able be defined with PVI and whether fluid loading is required in patients who breathe spontaneously and had undergone cesarean section under SA[3]. In our study, supporting these studies, hemodynamic stabilization was achieved with fluid replacement, and less HSA was observed.

Yokose et al., however, argued that PVI could not be a reliable indicator of intravascular volume in spontaneously breathing pregnant women during cesarean

Table 4. Comparison of ROC analyses for PVI, IVC diameter AP, IVC diameter transverse and IVC area

Parameters	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
PVI	0.848	> 15%	96.7	76.5
IVC diameter AP (mm)	0.719	≤ 18.7 mm	56.7	79.4
IVC diameter Transverse (mm)	0.873	≤ 18.8 mm	86.7	76.5
IVC area (mm^2)	0.765	≤ 2.98 mm^2	70	79.4

PVI: pleth variability index; IVC: inferior vena cava; AP: anteroposterior; ROC: receiver operating characteristic; AUC: area under the curve.

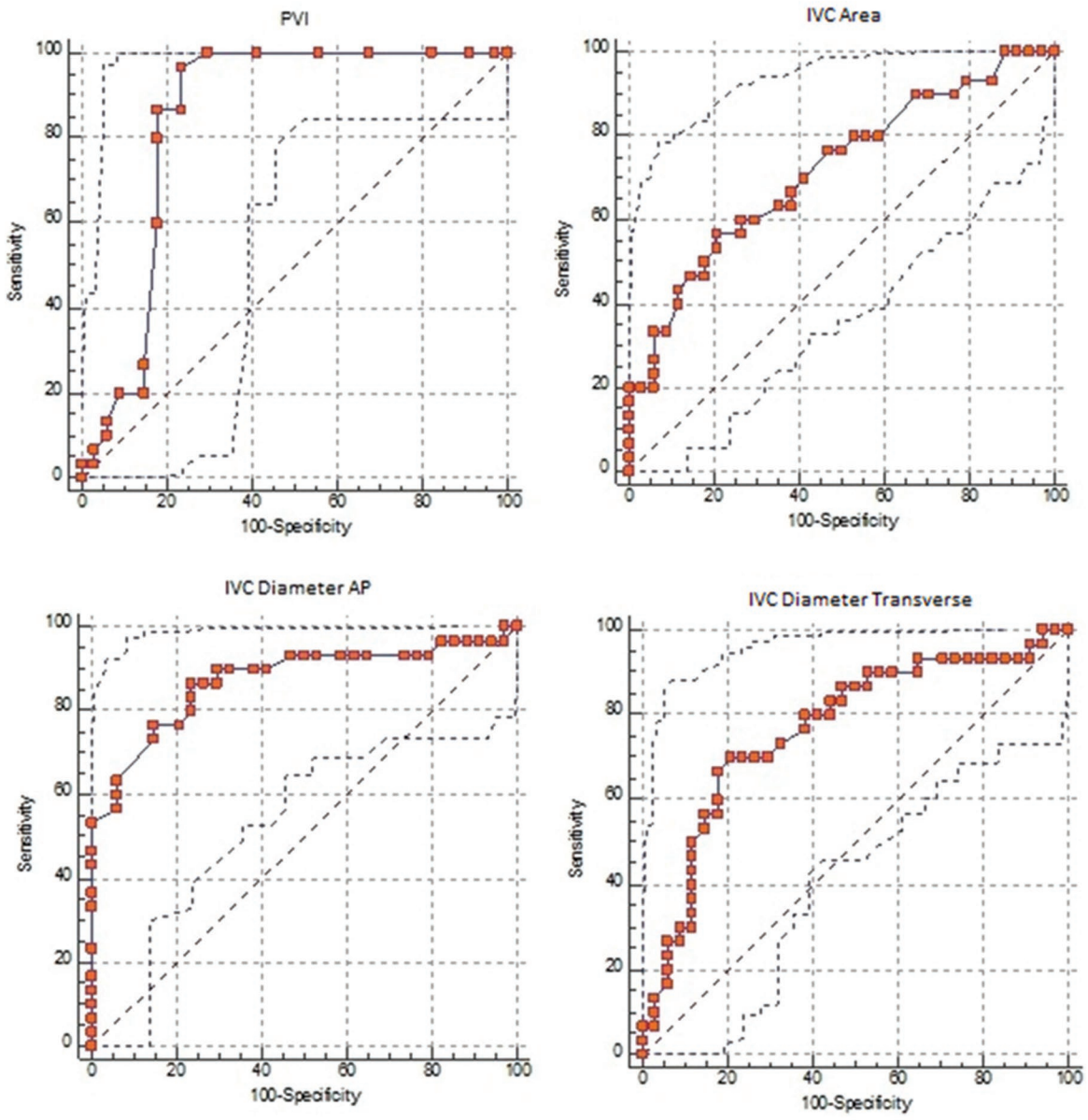

Figure 3. *Receiver operating characteristic curves for pleth variability index, inferior vena cava (IVC) diameter anteroposterior, IVC diameter transverse, and IVC area in the diagnosis of hypotension.*

section[22]. In our study, measurements were made after premedication with midazolam IV to minimize the effects of respiratory pattern on IVC and PVI measurements. Since IVC is also measured at the end of expiration in all patients, respiratory variability is eliminated.

Cannesson et al. were among the first researchers of this method, and in their study of 25 patients undergoing coronary bypass surgery; they suggested that PVI > 14% was a variable that could evaluate fluid response[23]. In similar studies, threshold values were found between 10% and 16%[24-26]. In our study, IVC diameter was measured at the end of expiration in AP and transverse section and its area was calculated, and the cut-off point for PVI in the diagnosis of hypotension was found to be > 15%.

Similar to our study, in a study in which measurements of PVI and IVC diameter were made and compared together, measurements of PVI and IVC diameter were reported as the methods that can be used to evaluate fluid response in intubated patients followed up in the intensive care unit[27]. As a result of our study, the risk of developing HSA is high in patients with high PVI values (especially the cut-off values > 15%, which was found in our study) and/or low IVC diameter measurement (especially the cut-off values < 2.98 mm^2, which was found in our study), and we suggest that that pre-SA fluid resuscitation and perioperative follow-up should be done with caution.

Conclusion

In the light of the findings of our study, we suggest that PVI and IVC diameter measurement with the help of USG can be used as non-invasive methods to predict hypotension that may develop due to SA. Early and accurate prediction of HSA can improve the clinical decision process, modify therapeutic management, and may be helpful for appropriate early intervention. It should be noted that IVC diameter measurements provide more subjective data as they are device- and operator-dependent, while PVI measurements conducted with fingertip probes provide objective data. Although PVI is a method that has been studied frequently recently, a definite threshold value or reference range indicating the fluid status has not been defined as the studies are insufficient for such data. As the number of studies on PVI increase, it will be possible to determine the threshold value. The lack of samples can be considered a limitation of this study. Other studies with larger samples are needed to confirm the results in this study.

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Conflicts of interest

The authors declared that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Resultados de actores globales que influyen y convergen en el sector hospitalario

Results of global actors that influence and converge in the hospital sector

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Resumen

Objetivo: *Poner en práctica el método MACTOR (Método, Actores, Objetivos, Resultados de Fuerza) para identificar y analizar la convergencia de los objetivos en actores con mapas de influencia del poder estratégico sanitario.* **Método:** *Es un estudio analítico, muestra por conveniencia en tiempo y por accesibilidad a expertos en tres hospitales de alta especialidad con razonamiento deductivo, de alcance explicativo en correlación de objetivos estratégicos convergentes a los procesos de salud por medio de MACTOR.* **Resultados:** *Comprender la importancia de analizar y de entender la prospectiva en la toma de decisiones de los actores que impactan en esta investigación con lideres globales de la Organización Mundial de la Salud, la Organización Panamericana de la Salud, el comité CONACEM y el presidente del Consejo de Salud en su despliegue estratégico a la atención médica hospitalaria.* **Conclusiones:** *El análisis prospectivo de actores facilita evaluar a los líderes de salud de acuerdo con su influencia en razón a la convergencia o no a objetivos institucionales. MACTOR es relevante en pro de lograr visualizar el aporte a favor o en contra de alcance de esfuerzo con alineamiento estratégico en las instituciones hasta llegar a los hospitales y dar continuidad de los logros específicos en beneficio de la atención médica.*

Palabras clave: *Análisis estructural. MACTOR. Influencia de actores sanitarios. Objetivos convergentes de salud. Mapas y planos de actores de salud. Histogramas.*

Abstract

Objective: *Put into practice the MACTOR (Method, Actors, Objectives, Strength Results) method to identify and analyze convergence of objectives in actors with influence maps of strategic health power.* **Method:** *It is an analytical study, sampled for convenience in time and for accessibility to experts in three high specialty hospitals with deductive reasoning, of explanatory scope in correlation of strategic objectives convergent to health processes through MACTOR.* **Results:** *Understand the importance, analyze and understand the prospective in the decision making of the actors that impact this research with global leaders from the World Health Organization, the Pan American Health Organization, the CONACEM committee and the president of the Council of Health in its strategic deployment to hospital medical care.* **Conclusions:** *The prospective analysis of actors makes it easier to evaluate health leaders according to their influence due to the convergence or not of institutional objectives. MACTOR is relevant in order to visualize the contribution in favor or against the scope of effort with strategic alignment in institutions until reaching hospitals and continuing specific achievements for the benefit of medical care.*

Keywords: *Structural analysis. MACTOR. Influence of actors. Convergent objectives. Maps and plans. Histograms.*

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Introducción

Es de vital importancia implementar el despliegue estratégico sanitario de políticas públicas que integre la educación, prevención y la cobertura universal hospitalaria del proceso de salud global[1]. La prospectiva de la Organización Mundial de la Salud (OMS) cita un futuro inmediato en el que la ciencia y tecnología de respuesta a necesidades reales se tienen que enfrentar para adaptar modelos de salud eficientes[2] de acceso equitativo a los servicios de atención médica y como derecho fundamental[3]. La Organización Panamericana de la Salud (OPS) determina un lapso de tiempo inmediato de adaptación en las actividades de salud para implantar programas competitivos globales[4]. La Organización para la Cooperación y el Desarrollo Económico (OCDE) con la creación de cadenas de valor económico[5], que reside en el desarrollo capacidades para la acción social, solucionar problemáticas y conflictos, tomar decisiones y otorgar medios y recursos[6].

La Unión Europea analiza y argumenta el cambio a una economía circular que es de vital prioridad para la neutralidad en carbono al 2050 a la vez que fortalece el desarrollo sustentable y beneficio a la salud[7]. Se vincula la prospectiva como necesaria en Francia y EE.UU. en la planeación pública estratégica y competitiva[8] que aproxima el análisis estructural (AE) intelectual frente a cambios de variables identificadas en diversos escenarios para la analizar y reflexionar a los cambios del ámbito estratégico[9]. En el AE puesto en práctica en EE.UU. mediante *Global Trends 2030: Alternative Worlds* se realiza estudio de las tendencias mundiales de gran relevancia que tienen efecto para Latinoamérica y el Caribe (LAC)[10].

Se ha incrementado la población en LAC y la falta de competitividad de los servicios médicos hospitalarios globales[11]. En la República Mexicana la salud es un derecho del mexicano, pero hay decadencia en la atención médica en el sector público. La inversión y presupuesto en salud es insuficiente; en el sector privado existe un modelo de negocio de la salud[11], y hacer AE prospectivo es desafiante por el complejo sistema sanitario con resistencia a los cambios funcionales para garantizar un mejor futuro inmediato en salud[12]. Por lo anterior, el sector sanitario tiene la necesidad de dar respuesta y muy rápida a ¿cuáles son los actores globales que se identifican en la toma de decisiones de objetivos estratégicos y que resultan influyentes y convergentes en la atención médica hospitalaria?

Método

Objetivo

Aplicar el método MACTOR (Método, Actores, Objetivos, Resultados de Fuerza) para identificar y analizar la convergencia de los objetivos en actores con mapas de influencia del poder estratégico. Por medio del AE de actores para identificar la convergencia de objetivos y el apoyo político a los que se va a contraponer el proceso de despliegue y alineamiento de objetivos y estrategias para implantación del sector salud y hospitalario, se hace necesario el uso de metodologías que permitan la identificación y el análisis de la participación de los actores en los procesos de salud, en este estudio se utiliza la aplicación del conocimiento de MACTOR, así diseñar los medios e iniciativas estratégicas efectivas orientadas a intervenir sobre estos actores para incrementar la factibilidad política pública sanitaria.

Análisis de estrategias de actores

El AE da inicio del juego de actores, que se definen como personas que adoptan decisiones y toman posiciones determinadas en el entorno con trascendencia en el desempeño de los procesos con incidencia potencial en la toma de decisiones que lleva al análisis con el fin de entender el sistema de gobierno sanitario. Las personas defienden sus intereses, cada actor tiene justificadas razones para su actuar. A esta postura se le conoce como individualismo metodológico. El actor es individual-unipersonal o colectivo-colegiado y tratará de realizar todo lo que le favorezca para lograr sus finalidades, además, si hay coincidencia entre esos intereses se harán alianzas. Pero si existen divergencia de intereses, se dice que pueden darse conflicto por la diferencia de sus intereses. Es decir, el poder surgirá relativamente de los actores e incidirá en las características que favorezcan las alianzas o bien los conflictos[13].

Otro pensamiento es en el sistema potencial que los actores que corresponde al entorno donde se encuentran, el medio es determinante en la conducta de los actores. Cada individuo se comporta de acuerdo con a cómo se ha formado por la cultura social aprendida y cotidiana en el trayecto de su vida. Por lo cual tienen limitada libertad de acción, ya que dependen de los sistemas sociales. Sin embargo, en contraposición, si bien en el entorno suceden conflictos y

Tabla 1. Información para captura de matriz de actores del sector salud

Actores*	Código*	Descripción*	Objetivos
A1. Director General de la OMS	OMSDirect	Directivo a nivel global de la OMS consagrado en los Objetivos de Desarrollo Sostenible y para mejorar la salud y el bienestar de las personas en todo el mundo	La OMS señala al sistema de salud como un conjunto de bloques fundamentales que operan de manera interrelacionada para mejorar la salud de la población, disminuir las brechas en salud y alcanzar la protección social en salud[17]
A2. Director de la OPS	OPSLider	Líder para aumentar el acceso equitativo y fortalecer la capacidad de la región para producir medicamentos y otras tecnologías sanitarias	Proporciona cooperación técnica en salud a sus países miembros, combate las enfermedades transmisibles y ataca los padecimientos crónicos y sus causas, fortalece los sistemas de salud y da respuesta ante situaciones de emergencia y desastres[18]
A3. Presidente del CNS	CNS Presid	Preside la coordinación de la prestación de servicios de las entidades federativas y la Ciudad de México de la salud pública	Coordinar entre la Federación, las entidades federativas y la Ciudad de México lo necesario para consolidar el Sistema Nacional de Salud, para el análisis de la programación y presupuestación de la salud pública, la concertación de mecanismos de cofinanciamiento, y la evaluación de prestación de servicios[19]
A4. Secretario de Salud	SrioSalud	Secretario que establece las políticas de Estado para que la población ejerza su derecho a la protección a la salud[20]	Establecer las políticas de Estado para que la población ejerza su derecho a la protección a la salud[20]
A5. Comité normativo nacional de consejos de especialidades Médicas CONACEM Consejos de especialidades y profesionales de salud	CONACEMV comité	Comité que valida el conocimiento, evaluación de competencias, entrenamiento, habilidades, destrezas y calificación para la certificación de especialidades de la medicina	Validar el conocimiento, evaluación de competencias, entrenamiento, habilidades, destrezas y calificación de la pericia que se requieren para la certificación y recertificación de esta en las diferentes especialidades de la medicina reconocidas por el Conacem[20]
A6. Funcionarios de instituciones del sector público: Director General del IMSS	FunsSP	Funcionario que organizar y administra el Seguro Social que garantiza el Estado.	El objetivo institucional de organizar y administrar el Seguro Social, cuya finalidad es garantizar el derecho a la salud, la asistencia médica, la protección de los medios de subsistencia y los servicios sociales necesarios para el bienestar individual y colectivo, así como el otorgamiento de una pensión que, en su caso y previo cumplimiento de los requisitos legales, será garantizada por el Estado[21]
Director General del IMSS-BIENESTAR	Funcio IMSS-Bien	Funcionario que dirige servicios de salud a toda la población mexicana que no cuenta con seguridad social IMSS-BIENESTAR[21]	Brindar servicios de salud a toda la población mexicana que no cuenta con seguridad social por medio del programa IMSS-BIENESTAR
Director General de Salud del ISSSTE	Funcio ISSSTE	Funcionario que concreta la transformación del ISSSTE para otorgar el servicio médico garantizado	Concretar la transformación del ISSSTE: énfasis en la humanización de la atención, motivar al personal y dar herramientas necesarias para otorgar el servicio,; equipamiento y renovación de la infraestructura, cero corrupciones y garantizar insumos médicos[22]
Director General de Salud de PEMEX	Funcio PEMEX	Funcionario que garantiza el tratamiento temprano, adecuado y completo que contribuya con tu bienestar del paciente	Para garantizar que recibas de manera efectiva el tratamiento temprano, adecuado y completo que contribuya con tu bienestar, se han optimizado los procesos administrativos de surtimiento de medicinas e insumos médicos; además, se ha robustecido e innovado el catálogo de medicamentos[23]

(Continúa)

Tabla 1. Información para captura de matriz de actores del sector salud (*continuación*)

Actores*	Código*	Descripción*	Objetivos
Director General de Salud de SEDENA	FuncioSEDENA	Funcionario que contribuye al bienestar del personal que fortalezcan el otorgamiento de sus prestaciones sanitarias de igualdad, transparencia y eficacia	Contribuir al bienestar del personal de las tres fuerzas armadas y sus familias, por medio de acciones que fortalezcan el otorgamiento de sus prestaciones sanitarias, económicas y sociales, bajo principios de igualdad, transparencia y eficacia[24]
Director General de Sanidad Naval de SEMAR	FuncioSEMAR	Funcionario que administra el Sistema de Salud Naval, garantiza un manejo eficiente de los recursos para la promoción de la salud y la atención médica integral del personal naval y sus derechohabientes	Administrar el Sistema de Salud Naval, por medio de normas y políticas que garanticen un manejo eficiente de los recursos para la promoción de la salud y la atención médica integral, que satisfagan las necesidades y respondan a las expectativas del personal naval y sus derechohabientes[25]
A7. Directores de instituciones del sector privado de HAE:	DirsHAEPriv		
Hospitales Ángeles	DirecHAng	Director que trabaja para generar cambios y avances al interior del hospital y con gran nivel de calidad	Seguir trabajando para generar cambios y avances al interior del hospital y con ello llevarlo a un gran nivel de calidad[26]
Centro médico ABC	Direc ABC	Director que lidera la atención médica, que es de la más alta calidad, calidez y con los más elevados principios éticos	Uno de los objetivos institucionales relacionados con la atención médica es que esta sea de la más alta calidad y que al mismo tiempo sea cálida y con los más elevados principios éticos[27]
A8. Derechohabientes del sector salud del sector público	Derech/clie	Personas que derivan sus derechos del trabajador para tener acceso universal y gratuito a los servicios de salud	Tener acceso universal y gratuito a los servicios de salud y medicamentos de indistintos sectores de la población
A9. Pacientes: clientes, usuarios e interesados del sector privado y público	Pacient	El paciente es quien padece malestar y requiere la atención medica en tres prioridades: el cliente es quien paga el servicio para recibir la atención médica, el usuario es quien hace uso del servicio de atención médica y el interesado quien puede, si así lo decide, contar con la atención médica de su preferencia	El paciente es quien padece malestar y requiere la atención medica en tres prioridades: el cliente es quien paga el servicio para recibir la atención médica, el usuario quien hace uso del servicio de atención médica y el interesado quien puede, si así lo decide, contar con la atención médica de su preferencia
A10. Aseguradoras en atención médica	Asegura	Empresa que presta servicios de prevención de salud, ya sea: a) de forma directa con los propios recursos en sus instalaciones; b) mediante terceros, es decir, por medio de una red de médicos prestadores de estos servicios, o c) una combinación de ambos, en beneficio del asegurado	Es prestar servicios de prevención de salud, ya sea: a) de forma directa con los propios recursos en sus instalaciones; b) mediante terceros, es decir, por medio de una red de médicos prestadores de estos servicios, o c) una combinación de ambos, en beneficio del asegurado[28]
A11. Proveedores de infraestructura, suministros, equipo médico y farmacéuticos y tecnológicos	Provee	Empresa que da respuesta a la demanda de requerimientos y ofrecer insumos que proveen lo mejor en calidad precio e innovación	Cubrir la demanda de requerimientos y ofrecer insumos que proveen lo mejor en calidad, precio e innovación para dar respuesta a los requerimientos para situaciones diversas y múltiples

Con la información y captura en *software* Lipsor. Epita-MACTOR de anterior contenida en las diferentes columnas se procede a integrar 32 la matriz de actores o lista de actores con la captura de Actores* Código* y Descripción* para alimentar los primeros elementos en el *software* de MACTOR y enunciar y capturar los objetivos estratégicos Objetivo *corto*, *Objetivo largo* y *Metas*.

CNS: Consejo Nacional de Salud; CONACEM: Corporación Nacional Autónoma de Certificación de Especialidades Médicas; HAE: hospitales de alta especialidad; IMSS: Instituto Mexicano del Seguro Social; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; MACTOR: Método, Actores, Objetivos, Resultados de Fuerza; OMS: Organización Mundial de la Salud; OPS: Organización Panamericana de la Salud; PEMEX: Petróleos Mexicanos; SEDENA: Secretaría de la Defensa Nacional; SEMAR: Secretaría de Marina.

Tabla 2. Objetivos estratégicos en relación con las variables de mayor influencia de MICMAC

Variables determinantes y claves en MICMAC[30]	Objetivo corto	Objetivo largo	Metas
Visión y planeación de desarrollo de estrategia regional y global	O5 Vis-estr	Lograr el grado más alto de salud con equidad y bienestar para todas las personas a lo largo del curso de la vida, con acceso universal a la salud, sistemas de salud resilientes y servicios de salud de calidad	Preparar a los hospitales al 100% en atender a la población en general para el acceso universal
Calidad en mejor atención médica	Calidad	Satisfacer la carencia de procesos asistenciales cooperativos y de calidad para que estén alineados con las políticas coherentes de carácter global	Modelar los procesos y establecimiento de KPI en tableros de control para lograr la eficiencia del 80% de las políticas públicas en la atención hospitalaria
Tecnología e investigación para las políticas de salud pública	O1Tec-inv	Considerar apoyos económicos para eficiencia e innovación, en aumento al uso de las TIC que permita ejercer derechos y responsabilidades y la gestión del conocimiento dentro del sector salud	Interconectar para 2030 los tres niveles hospitalarios para optimizar recursos en atención hospitalaria de alta especialidad que puede ser atendida en los niveles 1.º y 2.º
Salud esencial	Saludesenc	Priorizar el aumento de la transparencia de los procesos y la información para la gestión de financiamiento y en la apertura de los gobiernos locales de apoyo a la salud esencial	Fortalecer los sistemas de salud y asignar un 8% del PIB para garantizar el acceso a todas las intervenciones y servicios de salud pública en el sexenio
Reformas de los sistemas de salud hacia la salud universal	Reforauniv	Integrar las dimensiones clave de sanitarias que permitan identificar y evaluar los distintos tipos de procesos de I+D para transformación de los sistemas de salud	Priorizar las necesidades para evaluar su implantación programadas con alineamiento local y municipal eficiente al 80% en los próximos 6 años

Se captura en *software* Lipsor. Epita-MACTOR Objetivo largo, su código y metas, que es la cuantificación del objetivo llevado en tiempo.
KPI: indicador clave de rendimiento; PIB: producto interior bruto; TIC: tecnologías de la información y la comunicación.

aparecen grupos que cuestionan al sistema. Estos actores propician los cambios y hacen evolucionar la realidad que evita este enfoque determinista en el ámbito social[14]. Por lo tanto, el entendimiento de la estructura de relaciones entre sus elementos da la pauta al conocimiento acerca del comportamiento del sistema y su cambio constante en donde la interconexión o red de relaciones entre elementos es primordial para entender[15].

- Etapas en el análisis de intervención y participación de actores para sus posibles efectos y consecuencias en los sistemas[16]:
  - Identificar y caracterizar descriptivamente los actores externos e internos que participan del sistema o su entorno.
  - Describir los objetivos, motivaciones e intenciones de cada actor, generando un cuadro en el que cada actor reconoce sus metas y estrategias en términos de maximizar su beneficio o desarrollar sus motivaciones (Tabla 1).

Ahora bien, en relación con las variables obtenidas en el cuadrante de mayor influencia de la matriz de impactos cruzados y multiplicación aplicada para una clasificación (MICMAC) resultado del análisis estructural con 17 factores globales y de salud. Se aplicó el coeficiente de alfa de Cronbach con la finalidad de evaluar la confiabilidad y consistencia de 1,314 cuestionarios, obteniendo un 0.9265 (alta confiabilidad), donde se obtienen las variables de prioridad[30]: variables determinantes que se ubicaron los factores de visión y planeación de desarrollo de estrategia regional-global y calidad en mejor atención médica que condiciona la dinámica del conjunto. Y variables clave o críticas, que se localizaron los factores de tecnología e investigación para las políticas de salud pública, salud esencial y reformas de los sistemas de salud hacia la salud universal grandes retos, inestables en la globalización y del sector salud que perturban la función normal del sector sanitario. Será entonces y que alrededor de estos se pueda ordenar una estrategia de gestión efectiva de salud para los hospitales que permita considerar como punto de partida la mayor relevancia global y regional de la dinámica hospitalaria (Tabla 2).

Tabla 3. Categorización de influencia de actores

Valor	Relación
0	Se asigna en razón a que no se tiene influencia del actor sobre otro, es decir que de la interacción no hay cambios en lo toma de decisiones y acciones de los actores ni consecuencias del cambio.
1	Indica una relación débil, y que el actor influyente modifica determinadas actividades o procesos en los que el actor desempeña.
2	Señala una relación de fuerza intermedia, donde el actor incide sobre otro con la posibilidad de cambiar proyectos completos o específicos del actor que recibe la influencia de otro.
3	Consigna a la relación de un actor sobre otro como fuerte. En esta modalidad, el primer actor influye de manera radical como para anular la razón de ser del otro actor. Las consecuencias son de alto impacto. La tarea asignable como misión del actor que recibe o repercute la interacción como comprometida.
4	Se da la ponderación por la influencia categórica de tal forma que amenaza la existencia del actor que la recibe e inclusive se manifiesta el riesgo de la integridad de los actores que reciben la influencia.

Con este criterio de ponderación y mediante el método DELPHI, que se utilizó con base a la disposición voluntaria de acuerdo con sus opiniones predictivas para ponderar y la captura de los directivos y mandos medios que se presenta para esta aplicación del conocimiento de esta investigación.
Adaptada de Godet, 1993[16].

Tabla 4. Valoraciones positivas (+) y (–) ante la actuación del actor en pro de los objetivos

Valor	(+) Objetivo (–)		Valor
+1	Primordial para el desarrollo de los procesos del actor	Riesgo de los procesos del actor	–1
+2	Prioritario para obtener los procesos y programas esperados del actor	Riesgo del éxito de los procesos y programas de actor	–2
+3	Indispensable en la misión del actor	Riesgo del cumplimiento de la misión del actor	–3
+4	Indispensable para la existencia y continuidad del actor	Riesgo de la existencia misma del actor	–4

Se aplican estas escalas para ponderar y se integra un cuadro de posiciones de los actores para cada objetivo estratégico. Esta información facilita la toma de decisiones de los responsables de la gestión de salud y permite entender alianzas u oposiciones posibles; finalmente el proponer estrategias con alineamiento y alianzas entre actores para atender las variables claves y los objetivos estratégicos asociados.

– Evaluar y ponderar las relaciones entre actores, esto es la influencia que cada actor (individual o colectivo), puede ejercer sobre el resto de los actores.
  Se lleva a cabo por medio de la matriz de influencia directas de actores (MID). Se obtiene el resultado que permite el entendimiento del rol y las interrelaciones de actores en el desempeño del proceso de gestión y gobierno. Ponderados por expertos para registro en la matriz de influencia de actores (Tabla 3 y Fig. 1).
– Conocer el posicionamiento de los actores respecto a los objetivos. Describir la actitud actual de cada actor respecto a cada objetivo (opuesto, neutro, indiferente o favorable). Representación matricial Actores x Objetivos.
  Esto se logra mediante la descripción matricial de alianzas potenciales a todas las posiciones de actores coincidentes o favorables respecto de algunos objetivos estratégicos determinados. De la misma forma, se interpretan como conflictivas las posiciones divergentes y opuestas entre diversos actores en razón a los objetivos estratégicos. Y, de igual manera, se observa de forma inversa o divergente la ponderación a los efectos de los objetivos sobre las intencionalidades de los actores.
  El mecanismo es por medio del cálculo de matricial, que se define a mediante el uso de la aplicación de MACTOR se distingue en las siguientes fases:
  - Asociar o correlacionar las preferencias identificadas que se da entre los actores y sus objetivos estratégicos del sistema o proceso.
  - Ubicar a los actores en razón a los objetivos o retos estratégicos en razón a la importancia de percibir si son aliados, o se ubican en conflicto, o bien son neutros.
  - Ponderar cuantitativamente la relación que se da, con la escala aplicable que registra distintos signos en las valoraciones de acuerdo con la actuación del actor respecto del objetivo, o a la inversa la incidencia del objetivo respecto de los intereses del actor. Con la distinción del signo en las escalas se verifica mediante valores neutros, positivos y/o negativos, de acuerdo con[29]:
    Valoración neutra (valor 0) y las valoraciones positivas (+) y (–) que se muestran en la tabla 4, ante la actuación del actor en pro de los objetivos y figura 2. Refleja que el actor es indiferente ante el objetivo y a su vez que los objetivos no cambian los intereses del actor.
– Conocer el grado de convergencia y de divergencia entre los actores y el plano de la distancia que existe entre los diferentes objetivos del

MID	OMSDirect	OPSLider	CNS Presid	SrioSalud	CONACEMV c	FuncloMSS	Directs Hs	Derec/clie	Pacient	Asegura	Provee
OMSDirect	0	3	3	4	3	3	3	3	3	3	3
OPSLider	3	0	3	4	3	3	3	3	3	3	3
CNS Presid	1	2	0	4	2	2	2	2	1	1	2
SrioSalud	2	2	4	0	4	4	4	3	3	3	3
CONACEMV c	0	0	1	3	0	1	1	1	1	1	1
FuncloMSS	0	0	1	3	1	0	3	0	0	0	3
Directs Hs	2	2	2	3	0	0	0	0	0	0	0
Derec/clie	1	1	1	3	1	1	1	0	3	3	0
Pacient	0	0	0	3	0	0	1	3	0	2	0
Asegura	1	1	0	3	0	0	4	4	4	0	2
Provee	4	3	3	4	3	3	3	3	3	4	0

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Figura 1. *Matriz de influencias directas. Se observa que se define la ponderación de acuerdo con el grado de influencia, cinco niveles de relaciones entre los actores: un actor tiene poca o ninguna influencia sobre otro (0), un actor puede poner en riesgo de forma limitada los procesos de otro actor (1), un actor puede poner en riesgo el éxito de los procesos de otro actor (2), el cumplimiento de sus misiones (3) o su propia existencia (4). Se ubica a los diferentes actores en un plano de influencia y dependencia. El análisis de las relaciones de fuerza pone de manifiesto las fortalezas y debilidades de cada uno de ellos, su capacidad de congelar una situación y circunstancias, entre otras. En resumen, con la ponderación se evalúan las influencias directas entre los actores con la categorización ponderada por medio de un recuadro de influencias mutuas a la que se llama matriz de actores x actores (MAA).*

2MAO	O1Tec-inv	O2 Met-KPI	O3 An-estr	O4 Crisis	O5 Vis-est
OMSDirect	3	3	3	3	3
OPSLider	2	2	2	2	2
CNS Presid	2	2	2	2	2
SrioSalud	1	1	1	1	1
CONACEMV c	1	1	1	1	1
FuncloMSS	-1	-2	-1	1	-3
Directs Hs	1	1	1	1	1
Derec/clie	2	2	2	2	2
Pacient	3	3	3	3	3
Asegura	-2	-1	-1	-1	-1
Provee	-1	-2	-2	-3	-3

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Figura 2. *Matriz de posiciones valoradas. Se aplican estas escalas para ponderar y se integra un cuadro de posiciones de los actores para cada objetivo estratégico (adaptada de Godet, 1993[16] en software Lipsor, Epita-MACTOR).*

sistema (Godet, 1990). Después del cálculo matricial de relaciones entre actores se obtiene un gráfico llamado plano o mapa que consta de dos ejes, ordenadas (Y) y abscisas (X), y como resultado se observan cuatro cuadrantes: actores dominantes (muy influyentes y poco dependientes en el proceso), actores enlace (muy influyentes y muy dependientes dentro del proceso), actores condicionados a resultados (poco influyentes como dependientes de los procesos), actores autónomos (ni influyentes ni dependientes en relación con el proceso analizado y que se presenta en resultados).

Resultados

Para terminar, en este estudio se visualizan los resultados de mayor importancia en la figura 3 y la implicación de actores (Fig. 4).

Discusión

Se innovó de forma especializada al presentar el desarrollo de metodología de aplicación en este estudio de análisis estructural prospectivo de actores sanitarios. Esta investigación parte y se da continuidad de variables en MICMAC[30] determinantes y seguimiento con la línea de investigación de análisis y construcción de mapas de actores en relación con el cumplimiento de objetivos estratégicos con el *software* MACTOR. Se podrán aclarar inquietudes al ver las diferentes decisiones estratégicas con los histogramas de la implicación de los actores sobre los objetivos y con ello tomar mejores decisiones en el ámbito de la salud en escenarios globales y regionales sanitarios. Además, la implicación de los actores tienen alineamiento estratégico global y regionalmente, los que sí están a favor o en contra de los objetivos específicos y de prioridad, donde se visualiza que de forma particular los HAE tienen necesidades que priorizar y dar respuesta además de lo que se pide globalmente, lo que complica sus capacidades de respuesta en el orden mundial, de acuerdo con el histograma de comportamiento de los actores en relación con los objetivos planteados de las variables estratégicas de visión de sus líderes, calidad, tecnología y reformas al sistema de salud del análisis de variables regionales en MICMAC. El análisis prospectivo de actores facilita evaluar a los líderes de salud

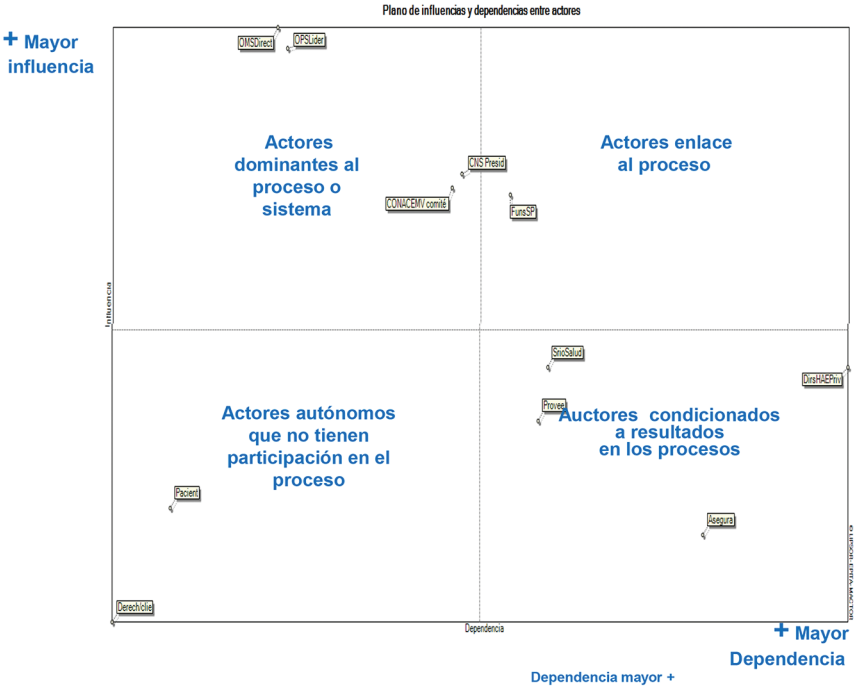

Figura 3. *Plano o mapa de influencias y dependencias entre actores. Este gráfico muestra los resultados que son la prioridad de actores en la toma de decisiones que impactan en el despliegue correcto en el sector salud, se obtiene en primera instancia y como información para la toma de decisiones el plano o mapa de influencias y dependencias de actores donde se ven actores dominantes a la OMS, OPS, CONACEM y CNS, sin embargo, las variables globales que le preocupan a los médicos y especialistas de los HAE para la atención médica hospitalaria que se identificaron en MICMAC[30] se visualiza que el mapa de influencia y dependencia de los actores consta de cuatro posiciones tipo: Actores dominantes. Muy influyentes y poco dependientes en el proceso sanitario se ubica los líderes de la OMS, OPS, CONACEM y el Presidente del Consejo de Salud. Actores de enlace. Muy influyentes y muy dependientes estos funcionarios del Sector público (Director General de IMSS, BIENESTAR, Director General de Salud del ISSSTE, Director General de Salud de PEMEX, Director General de Sanidad Militar- SEDENA Director General de Sanidad Naval- SEMAR). Actores condicionados a resultados. como dependientes de los procesos se localizan el Secretario de Salud al Secretario de Salud como actor ejecutor global sanitario y a los Proveedores de Suministros médicos-medicamentos, Directores de Hospitales privados y aseguradoras. Actores autónomos. Ni influyentes, ni dependientes en relación con el proceso analizado y qué se presenta el paciente y derechohabiente para recibir del sistema sanitario la atención medica hospitalaria (adaptada de Godet, 1993[16] en software Lipsor, Epita-MACTOR).*
CNS: Consejo Nacional de Salud; CONACEM: Corporación Nacional Autónoma de Certificación de Especialidades Médicas; HAE: hospitales de alta especialidad; IMSS: Instituto Mexicano del Seguro Social; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; OMS: Organización Mundial de la Salud; OPS: Organización Panamericana de la Salud; PEMEX: Petróleos Mexicanos; SEDENA: Secretaría de la Defensa Nacional.

de acuerdo con la influencia para la convergencia o no a sus objetivos de la razón de ser de sus responsabilidades en su manejo inteligente de administrar del conflicto de intereses políticos. MACTOR tiene relevancia en pro de lograr visualizar el aporte a favor o en contra de alcance de esfuerzo en objetivos en alineamiento estratégico en las instituciones de salud hasta llegar a los hospitales y dar continuidad de los objetivos en beneficio de la atención médica hospitalaria.

Conclusiones

El estudio por medio del análisis de actores es un aporte y su interpretación en MACTOR permite dar respuesta a la pregunta de investigación, donde sí se puede identificar a los actores globales y regionales que toman decisiones, así como el alineamiento estratégico hasta llegar a los directivos de los hospitales. Se valida la importante implicación de las variables objetivo con la utilización de los métodos de análisis de actores con el *software* de MACTOR y MICMAC que se puede aprenderse en el sector hospitalario para elaborar propuestas y estrategias disruptivas con este tipo de análisis y con ello los administradores de hospitales estén preparados para el diseño de políticas públicas futuras globales o regionales.

El análisis de actores se anticipa y visualiza en un mapa de priorización de actores, en el plano de acuerdo con su importancia y de poder estratégico

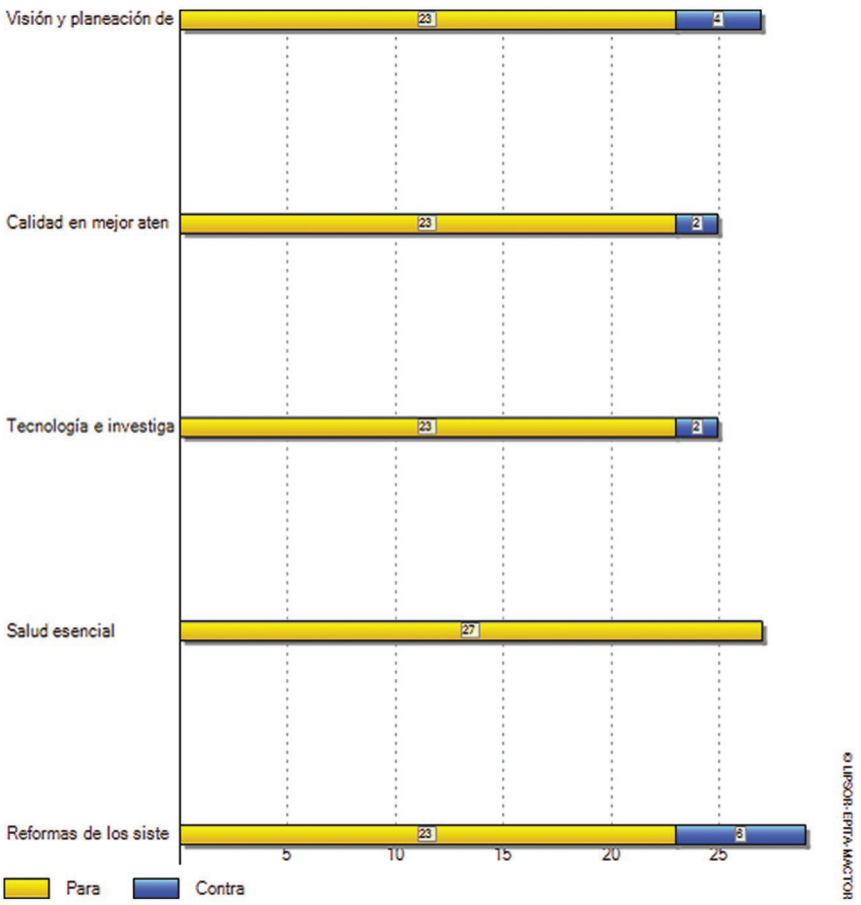

Figura 4. *Histograma de la implicación de los actores sobre los objetivos de MICMAC. Se puede distinguir la implicación de quienes están a favor y quienes en contra, además de que MACTOR presenta balance de posiciones a detalle por objetivo valorado en la competitividad hospitalaria que es importante consultar a detalle para escalar prioridades de los hospitales de alta especialidad. Además, visualiza cómo se comportan los actores en relación con los objetivos planteados de las variables estratégicas del MICMAC.*

que impactarán en un futuro a los hospitales que permite garantizar una visión de la atención médica hospitalaria eficiente, debido a los múltiples factores globales y actores líderes que a largo plazo impactarán a sector salud y el orbe.

Se sugiere tener alineamiento estratégico en sus niveles jerárquicos correspondientes, con el establecimiento e implementación de indicadores en metas de acuerdo con sus prioridades y alcance a sus objetivos y actividades con indicadores que permitan garantizar la misión, visión de objetivos estratégicos y en su caso implantar las líneas de acción, o iniciativas correspondientes en tiempo que permitan reivindicar acciones estratégicas hacia los resultados esperados en la producción de bienes y servicios médicos hospitalarios.

Es por el anterior análisis estructural prospectivo, que es preciso entender los sistemas de gobierno sanitario globales y señalar cuáles son los actores que apoyan o no los objetivos, requerimientos y cuáles no favorecen como se observa en el histograma de implicaciones de los actores; así como destacar en un plano o mapa de influencia y dependencia donde se prioriza la importancia de las relaciones e interacciones entre los sujetos que lo integran globalmente hasta que se perfila el alineamiento en los sectores y puntualmente en los HAE, por supuesto que el tiempo de decisiones permea de forma lenta hasta repercutir en la toma de decisiones y realización de objetivos por medio de la implementación estratégica en los HAE.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones 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, consentimiento informado y aprobación ética. El estudio no involucra datos personales de pacientes ni requiere aprobación ética. No se aplican las guías SAGER.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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REVIEW ARTICLE

Regenerative medicine in surgery: stem cells and exosome applications

Medicina regenerativa en cirugía: aplicaciones de células madre y exosomas

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Abstract

This review outlines the role of regenerative medicine in surgical applications, focusing on stem cells and exosomes. Among the most important features of stem cells are their unique ability to differentiate into various cell types, which make them stand out in regeneration and repair. Recent advances highlight the effectiveness of not only these cells themselves but also the exosomes, the nano-sized extracellular vesicles they produce, in this regeneration. On the other hand, exosomes assure additional advantages concerning low immunogenicity and high bioavailability but have raised problems in standardization and safety. In fact, the introduction of these stem cell and exosome technologies is changing the management of surgical pathologies and offering hope for diseases hitherto considered incurable. In this review, the use of stem cell therapies in various surgical diseases is categorized and examined, their clinical importance is emphasized, and the deficiencies in research studies are indicated. Therefore, the results are promising for treatments, but more standardized protocols and expanded research on long-term safety and effectiveness are needed.

Keywords: *Regenerative medicine. Stem cell. Exosomes. Clinical applications. Surgery.*

Resumen

Esta revisión describe el papel de la medicina regenerativa en aplicaciones quirúrgicas, enfocándose en células madre y exosomas. Entre las características más importantes de las células madre destaca su capacidad única de diferenciarse en diversos tipos celulares, lo que las hace sobresalir en regeneración y reparación. Los avances recientes resaltan la efectividad no solo de estas células en sí mismas, sino también de los exosomas (las vesículas extracelulares de tamaño nanométrico que producen) en estos procesos de regeneración. Por otro lado, los exosomas ofrecen ventajas adicionales relacionadas con baja inmunogenicidad y alta biodisponibilidad, aunque han planteado problemas en cuanto a estandarización y seguridad. De hecho, la introducción de estas tecnologías de células madre y exosomas está transformando el manejo de patologías quirúrgicas y

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ofreciendo esperanza para enfermedades hasta ahora consideradas incurables. En esta revisión se categoriza y examina el uso de terapias con células madre en diversas enfermedades quirúrgicas, se enfatiza su importancia clínica y se señalan las deficiencias en los estudios de investigación. Por lo tanto, los resultados son prometedores para los tratamientos, pero se necesitan protocolos más estandarizados y una investigación ampliada sobre la seguridad y efectividad a largo plazo.

Palabras clave: *Medicina regenerativa. Células madre. Exosomas. Aplicaciones clínicas. Cirugía.*

Introduction

Stem cells, which have the ability to differentiate into various cell types, play a crucial role in regenerative medicine, particularly in surgical applications. These cells can be classified according to their differentiation potential, ranging from totipotent, which can form all tissue types, to unipotent, which are limited to a single cell type[1]. Unique properties of stem cells, such as differentiation, self-renewal, and survival, make them invaluable for tissue regeneration and repair. In recent years, the importance of stem cell-derived exosomes in intercellular interactions has become more prominent, and their preference for use has also increased[1,2]. Exosomes carry proteins, lipids, and nucleic acids, making them potent tools for diagnostics and therapeutic interventions. The use of exosomes in clinical settings offers advantages such as reduced immunogenicity and improved bioavailability[2,3]. However, the lack of optimizations of fixed and worked protocols still brings some difficulties in terms of security. The integration of stem cell and exosome technologies is paving the way for innovative treatments in surgery, offering hope for patients with previously untreatable conditions[1-3].

This review aims to thoroughly analyze and examine the studies related to stem cell research conducted in various surgical diseases and within the broader context of surgical and medical sciences. By critically evaluating the methodologies and outcomes of these studies, we intend to provide a detailed understanding of their significance and potential clinical applications. The review seeks to shed light on the advancements in stem cell therapies specific to surgical conditions while also considering their implications for general medical practice. In addition, this analysis will identify existing gaps in the research and suggest directions for future studies, ultimately contributing to the advancement of stem cell-based treatments in both surgical and medical fields.

Stem cell system

Stem cells have the ability to transform into many cell types according to their source and differentiation potential. These cells have great potential for future therapeutic use in the fields of tissue regeneration and repair. Just like every cell has specific characteristics, stem cells need to have certain features to be stem cells. Among these features are self-renewal and differentiation[1]. Self-renewal refers to a cell's capacity to divide and create other cells with the same characteristics, while differentiation refers to the ability to create other cell types that perform different biological functions[2]. If we classify stem cells, we can divide them into four groups according to their developmental potential: totipotent, pluripotent, multipotent, and unipotent (Fig. 1). In this section, we will discuss the classification of stem cells. First, totipotent stem cells are differentiated cells capable of forming all tissues of the embryo and extra-embryonic tissues. These cells are obtained from the fertilized oocyte and the first blastomeres. They are also present in the early stages of the embryo and have a very broad differentiation potential[4]. Pluripotent stem cells are also having the ability to differentiate into the body's three germ layers: ectoderm, endoderm, and mesoderm. Pluripotent stem cells play a key role in disease models, drug release systems, cell therapy, and provide an important experimental platform[5]. There are several methods for the differentiation of pluripotent stem cells, including chemical activin A and the growth factor BMP-4[6]. Unlike totipotent cells, they cannot produce cells from extra-embryonic tissues. Multipotent stem cells, the most distinctive feature, are their ability to differentiate into a specific tissue. They are generally used for the regeneration of various body tissues. These stem cells have more limited differentiation abilities compared to other stem cells[6]. Finally, unipotent stem cells are groups of stem cells with limited capabilities, similar to multipotent stem cells. It can only differentiate into the cell type in their niche. For example, muscle stem cells can only lead to mature muscle cells[7]. Characterization of stem cells various factors affects stem cell cultures. These factors include cell density, density of feeder cells, growth factors, microbial contamination, and others. Techniques such as flow cytometry, karyotyping, fluorescence *in situ* hybridization, single-nucleotide polymorphism, immunocytochemistry, and western

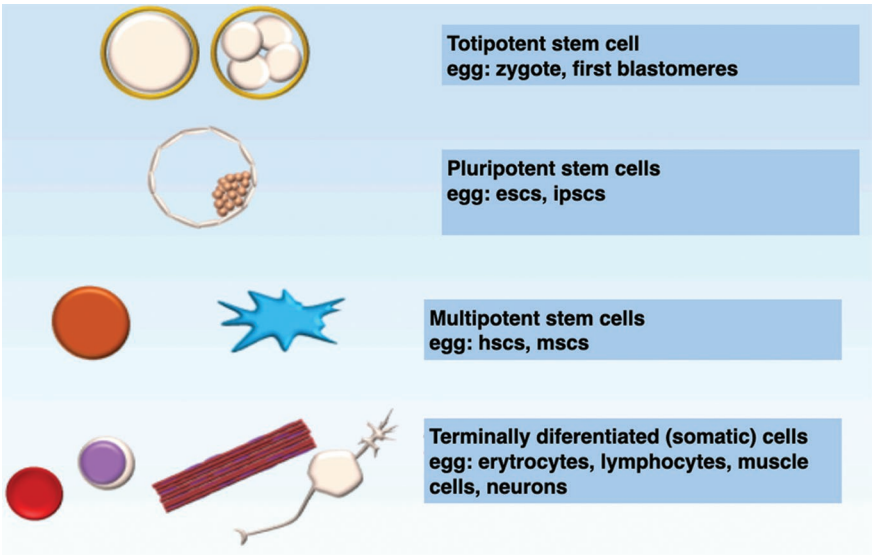

Figure 1. *Stem cell types.*

blot are preferred for the genetic characterization and analysis of stem cells. Some types of stem cells, especially pluripotent stem cells, are more prone to genetic instability and chromosomal changes and should be frequently observed. Stem cells express unique and specific combinations of transcription factors, cell surface proteins, and cytoplasmic proteins[8].

Exosomes technology: how does it work in clinical?

Exosomes are nano-sized extracellular vesicles naturally secreted by eukaryotic and prokaryotic cells, with diameters ranging from 30 to 150 nm and attracting intense interest in the field of biotechnology as they participate in intercellular communication[9]. Although the biogenesis mechanism of exosomes is controversial, in general, they are synthesized in early and late endosome stages of the cell and released outside the cell when these endosomes fuse with the plasma membrane[10]. Their biological functions and characteristics differ according to the cell types from which they are released and they carry a large amount of information due to their proteins, lipids, and nucleic acids. For this reason, they are considered as potential biomarkers to be used in the diagnosis and treatment of diseases. Animal-derived exosomes (ADEs) from mammals and plant exosomes, which have been increasingly studied in recent years, are the two main categories of naturally derived exosomes[11]. ADEs secreted by macrophages, mesenchymal stem cells (MSCs), dendritic cells, endothelial cells, and tumor cells play key roles in a variety of vital processes, including cell growth, proliferation, and differentiation, intercellular communication, angiogenesis, inflammation, immune responses, and tumor formation and development[11-13]. A study found that plant-derived exosome-like nanoparticles (PDENs) for the 1st time in carrot cells in 1967[14] and over time, studies have shown that nano-sized EVs obtained from plant cells have structures similar to mammalian exosomes[15,16]. Therefore, these EVs were called "plant-derived exosome-like nanoparticles"[17]. Since their discovery, PDENs have been studied for their pharmacological effects in various areas such as tumor, liver diseases, and skin wound healing[18]. Plant exosomes have a larger nanoparticle size and a complex content of small RNAs, proteins, lipids and other metabolites like mammalian exosomes[19]. The differences between the two forms of exosomes are detailed in table 1[19,20-28].

Although ACEs offer various benefits as therapeutic targets, diagnostic indicators, and drug delivery reporters, their clinical translation remains elucidated due to limitations such as possible toxicity, tissue-specific targeting issues, and low efficiency. PDENs have the advantages of not being detected by the immune system and having better bioavailability. They can also target specific organs, have fewer side effects, and dissolve faster[19,29]. Its use in the surgical field attracts attention in a wide range of areas, especially from wound studies to IVF, central nervous system applications to orthopedics[10,29].

Characterization techniques have been improved to the morphological and physicochemical properties of exosomes, as well as to distinguish and differentiate them from other extracellular vesicle subsets. There are three commonly used characterization methods for observing the morphology of exosomes: transmission electron microscopy, scanning electron microscopy, and atomic force microscopy[30]. While the advantage of these methods is that they require fewer samples, the disadvantage is that the preparation methods of the sample may cause shape changes. The most frequently used methods to determine the size distribution of exosomes are dynamic light scattering and nanoparticle tracking analysis (NTA). Fast and real-time observation makes the NTA method more advantageous. Western-blot and enzyme-linked immunosorbent assay methods are preferred for the determination of surface proteins of exosomes, while flow cytometry is used for exosomal biomarkers, allowing qualitative and quantitative analysis of exosomes. Flow cytometry offers high throughput and multi-channel analysis with few samples. The three approaches have the drawback of being arduous, complicated, and time-consuming[31].

Exosome biogenesis involves endocytosis, early endosome formation, multivesicular body (MVB) formation, and ultimately exosome release[32,33]. Exosome biogenesis begins with the accumulation of material taken up from the plasma membrane through endocytosis in the early endosomes[34]. At this stage, endocytic vesicles are detached from the plasma membrane and taken into the cell. Early endosomes are the first stop for molecules taken up from the cell surface for sorting and processing of materials[35]. At this stage, biomolecules, lipids, or proteins that are present on the cell surface and come from outside the cell are taken up by endocytosis and transported to early endosomes. Early endosomes mature into late endosomes. In this step, MVBs are formed[36]. MVBs are intraluminal vesicles (ILVs) containing large endosomal structures. ILVs are the precursors of exosomes and are formed by budding from the inner membrane of MVBs[33]. This process is critical for intracellular signaling and protein transport. MVB formation is an important step in intracellular transport and material processing. The formation of ILVs is regulated by the endosomal sorting complex required for transport (ESCRT) mechanism and ESCRT independent mechanisms[36]. ESCRT Mechanism: ESCRT-0 Complex (Recognizes and recruits ubiquitinated forms of surface proteins. This complex is the first step in the selective transport of proteins), ESCRT-I, ESCRT-II Complexes (Locates on the inner membrane of the MVB and creates a bend. These complexes play a key role in the budding step of ILVs), and ESCRT-III Complex (Completes membrane bending and ensures budding of ILVs into the MVB. ESCRT-III regulates the final closure of the membrane and the formation of ILVs)[37]. VPS4 ATPase: Ensures the separation of ESCRT complexes from the membrane and is effective in terminating the process[38]. ESCRT Independent Mechanisms: Tetraspanins, Crohn's disease (CD)63, CD81, and similar tetraspanin proteins play an critical role in ILV formation[39]. Tetraspanins promote ILV budding by forming membrane microdomains. Membrane microdomains are formed by local accumulation of lipids such as lipid raft and ceramides. These microdomains ensure membrane budding and ILV formation[40]. MVBs are transported intracellularly along cytoskeletal elements (microtubules and actin filaments). MVBs can follow two main pathways; lysosomal degradation and exosome secretion by fusion to plasma membrane MVBs fuse with lysosomes and digest the material inside them. The lysosomal degradation pathway is effective in recycling proteins and clearing intracellular waste. In the other pathway, MVBs go to the plasma membrane and fuse there, releasing the ILVs inside them as exosomes. This process allows the active material to be transported out of the cell and the exosomes to perform their biological functions[33]. Exosomes perform various biological functions after being released out of the cell (Fig. 2).

Transfer to humans: good manufacturing practices (GMP) conditions

They have a critical role as a safe and cell-free therapy in many immunological and degenerative diseases. Nonetheless, the isolation and translation to clinical applications might be restricted by insufficient large-scale manufacturing techonologies. There are many details and practices that need to be taken into consideration under GMP standards before applying it to the clinical trials[41-43]. It is important to evaluate cytotoxicity, hemolysis, and DNA damage of exosomes at the cellular levels and to test their effects at the animal levels including tissues, organs and their biodistribution[42]. Furthermore, it is crucial to test endotoxin levels, bacterial sterility, and mycoplasma detection and stored at (–80)°C until use[43].

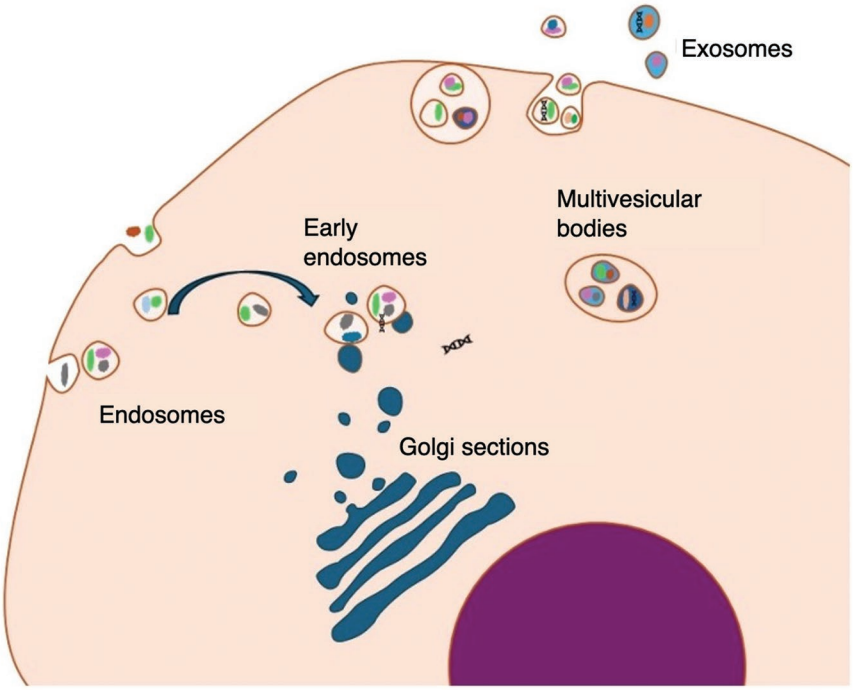

Figure 2. *Exosomes biogenesis.*

It must be applied in the methods including cell culture, exosome extraction, purification, and characterization for physical structure and bioactivity function under GMP condition. The ultracentrifugation is most critical in isolation of exosomes among these methods in the clinical trials. Exosome applications in clinical trials also have some challenges including non-homogenity, fast clearance from the body, and long-term preservation stability. To achieve clinical success, therapeutic doses and routes of administration need to be standardized[41].

Applying regenerative medicine in surgery

General surgery field

Liver failure resulting from portal vein thrombosis is a challenging and frequently encountered condition with difficult management and treatment. A systematic review by Stutchfield et al. Indicated that after the injection of stem cells isolated from peripheral blood mobilized with granulocyte colony stimulating factor or from the iliac crest bone marrow, induced pluripotent stem cells (iPSC), bone marrow MSCs (BMMSC), and adult stem cells (SSC) into the portal vein or hepatic artery, liver regeneration was observed[44]. Although it is believed that embryonic stem cells would also accelerate hepatic regeneration, studies on embryonic stem cells remain insufficient due to ethical concerns[44]. In cases of lymphedema following mastectomy and axillary dissection surgery for breast cancer diagnosis, a decrease in lymphedema and an increase in lymphangiogenesis were demonstrated following combined therapy with traditional decongestive treatment and intramuscular injection of adipose stem cells (ASC) containing MSC[45]. It is difficult to achieve positive results in surgery for complex perianal fistulas (CD or cryptoglandular type) in the short and long term. However, recent metaanalyses and clinical studies indicate that MSCs transplantation may be an effective and sustainable therapeutic method for the treatment of complex perianal fistulas in both short and long term[46-49]. For the treatment of pelvic organ prolapse, the use of autologous muscle-derived cells, fibroblasts, or MSCs added to bioresorbable, fragmentable, and potentially growth-promoting scaffolds is considered an alternative to traditional surgical reconstructive methods[50]. Proctitis is a complication frequently encountered as a result of radiation therapy in the treatment of various pelvic malignancies (rectal, gynecological, and urological cancers). The studies indicate that MSCs therapy can be considered as an

alternative treatment method in the management of this complication, in addition to treatment methods such as argon plasma coagulation, laser, radiofrequency ablation, and cryoablation. A study by Kim et al. on rats showed that stem cell application reduced fibrosis and increased new cell proliferation[51,52].

Gastroenterology and hepatology field

Liver is an important organ of human immune system. It is known that many liver diseases occur due to immune homeostasis imbalance[53]. MSCs are non-hematopoietic stem cell with self-renewal and differentiation capacity[53]. Studies have shown that they can re-establish the immune hemostasis, inhibit the activation of innate and adaptive immune cells, promote tissue regeneration, alleviate liver damage, and increase liver function[53-55]. MSCs exhibit these function mainly through their excreted extracellular vesicles (MSC-EV) and exosomes which are important component of these paracrine secretion. However, due to the breadth of the subject, this review will mainly focus on the clinical applications of MSCs. Different cell types with different delivery routes are used either allogenic or autologous. BMSCs were commonly used, followed by umbilical cord-derived MSCs and adipose-derived MSCs. Although there are reports with hepatic arterial and intrahepatic injection, peripheral intravenous line is the most commonly used delivery route[53]. *In vivo* studies demonstrated beneficial effect of MSC on certain liver diseases. It has been suggested that their beneficial effect is elicited through promoting anti-inflammatory M2 macrophage polarization and increasing IL-10 secretion in non-alcoholic steatohepatitis; increasing Treg/TH17 proportion in autoimmune hepatitis (AIH); activating of NLRP3 inflammasome and downregulating the Interleukin 6 (IL-6) signal pathway in acute liver failure, downregulating the tumor necrosis factor α (TNF-α) and Interleukin-1 β (IL1β) expression in liver fibrosis, downregulating CD154 expression, and enhancing the shift of TH17 toward Treg in ischemic liver disease. Focusing on different liver disease, autologous BMMSC transplantation revealed inconsistent results in non-viral etiology. A single-blinded controlled clinical trial performed with 27 decompensated cirrhotic patient including hepatitis C virus (HCV), hepatitis B virus (HBV), and AIH patients could not demonstrate any beneficial effect[54,55]. Another single-center randomized controlled study evaluated 9 grade 2-3 cirrhotic patients. They received 5 IV infusions of 1.0×10^6 cells/kg, BM-MSC twice a week for 2 week and another dose at 3rd week. Although MSC leads to significant improvement in Child-Pugh and model for end-stage liver disease (MELD) scores, 90-day survival rates were similar between the MSC and placebo groups[56]. Similarly, a randomized controlled clinical trial enrolling alcoholic cirrhotic patient reported no impact of BM-MSC on liver histology[57] Despite these disappointing results, studies with viral hepatitis and AIH seem more promising. In a prospective controlled randomized study, enrolling 110 HBV-related acute on chronic liver failure patient BM-MSC treatment decreased the severe infection rate and increased survival rate at the 24-week after transplantation[58]. Furthermore, in long-term follow-up, peripheral allogenic umbilical cord-derived MSCs (UC-MSC) therapy markedly improved liver function and reduced the volume of ascites in patients with HBV-related decompensated liver cirrhosis up to 75 month[59,60]. In another study enrolled with HBV infected cirrhotic patient, BM-MSC was given through hepatic artery injection and improvement of liver function was observed through downregulating TH17 and promoting Treg development, at 24 week follow-up[61]. Similar encouraging results are reported also in HCV infection-related liver disease. Peripheral vein infusion of autologous BM-MSC in HCV-related cirrhosis demonstrated improvement in liver function in a prospective randomized phase II clinical trial[62,63]. Regarding AIH, in fact, there are considerable amount of *in vitro* and *in vivo* studies related to the effect of stem cell on AIH[64]. However, clinical implications of these seem weak. The effect of allogenic MSC was evaluated in one study. The trail enrolled 26 patients with cirrhosis related to AIH. Patient received mainly UC- MSC through peripheral line. Although mean alanine transaminase level decrease was not significant at 6 month, and 2 years follow-ups, MELD score improvement was significant at 6 months[65]. There are also reports that allogenic BM-MSC safely improved quality of life and liver function in suboptimal ursodeoxycholic acid (UDCA) resistant primary biliary cirrhosis[66].

Another area where stem cell-based therapies have been suggested as promising source to improve disease state is inflammatory bowel diseases (IBD). Although the etiology of IBD has not been highlighted; completely, yet dysregulation of innate and adaptive immune pathways contributes to the development of aberrant inflammation[67]. Theoretically, stem cell transplantation can reset the dysregulated immune system, re-establish the immune homeostasis, and repair and

supplement intestinal epithelial cells leading to remission. To date, there have been numerous clinical studies on stem cell transplantation for the treatment of IBD utilizing different MSC origin. Nevertheless, most of these studies have confirmed the efficacy of MSCs in treating CD with desirable safety and seems highly promising approach for especially fistulizing perianal CD. However MSC, still less effective in luminal disease[68]. The application line of MSC has also been shown to be effective in achieving remission. For IBD treatment, intravenous, intraperitoneal, or local application is possible. Compared to peripheral or intraperitoneal injection, local applications have been found to be more effective in PFCD[67,68].

The clinical studies demonstrated encouraging results with adipose tissue-derived stem cell and darvadstrocel/Cx601 (Takeda) (allogeneic adipose-derived stem cells), which has already entered clinical treatment. A phase III multicenter randomized, double-blind placebo-controlled trail studied the efficacy of allogeneic ASC transplantation on treatment refractory CD with draining complex perianal fistula. The study comprised 212 patients who were assigned into treatment and placebo groups and received a single injection of Cx601 cells or placebo in addition with standard treatment. The study evaluated magnetic resonance imaging (MRI) proofed closure of all openings, and absence of draining fistulas termed as combined remission and clinical remission respectively at short term. At 24-week, a significantly greater proportion of patients treated with Cx601 versus placebo, achieved combined remission (51% vs. 36%, p = 0.021). Moreover, significantly less adverse event was observed in ASCT-(cx-601) treated group compared to placebo (17% vs. 29%, respectively). Same authors assessed the durable effect of Cx-601 in a second trail and observed that the efficacy and safety maintained for up to 52 weeks after treatment. A significant proportion of the treatment group compared to control group had combined remission at 52 weeks after treatment (56.3% vs. 38.6%, respectively)[67]. The authors concluded that Cx601 is an effective and safe treatment for patients with refractory, complex, and active perianal fistulas both in short and long term. Consistent with this result Barnhoorn et al. reported even longer durable clinical remission, fistula closure up to 4 years in previously BM-MSC transplanted treatment resistant perianal CD patients[68]. MSCs have also been reported as an effective and safe treatment for intractable intraluminal IBD. A randomized controlled trail enrolled 82 patients with refractory intracavitary CD. Forty-one of the patients were assigned to receive 1×10^6 UC MSCs/kg once a week. They injected a total of four peripheral intravenous infusions and assessed after 12 months of treatment. The clinical disease activity index decreased by 62.5 ± 23.2 in the intervention group compared to 23.6 ± 12.4 in the control group[69]. The studies on ulcerative colitis and MSCs therapy are also progressing. As in CD, local injection with colonoscope of MSCs has shown promising results also in ulcerative colitis[70]. In contrast, intravenous injection warrants further investigation. A single-center randomized controlled trail evaluated the efficacy and safety of Human Umbilical Cord MSCs in moderately active ulcerative colitis patient. The study included 70 patients who were randomly and almost equally assigned into treatment and control group (34 vs. 36 patients, respectively). The patient received MSC twice through peripheral vein. In addition to stable baseline 5ASA therapy, a third dose was administered through interventional catheterization into the superior mesenteric artery at a 7-day interval. The median Mayo score improved in the intervention group at 3 months after cell therapy and reached its lowest level at 6 months. It, then, continued or fluctuated slightly during the 24-month follow-up period. The clinical response rate was 85.3% in the intervention group and 16.7% in the control group. Interestingly, this study did not show any changes in mean plasma cytokine levels, including TNF-α, IL-6, and Interferon-γ. It failed to show any changes, which were shown to be significantly attenuated in the luminal Crohn's disease cohort treated with MSC culture in combination with AZA[71].

Pediatric surgery and pediatric urology field

Pediatric surgery is relatively the most recently established discipline within the field of medicine. Consequently, it is expected that pediatric surgery lags significantly behind other medical fields in terms of advancements in stem cell research. Indeed, while branches such as internal medicine and orthopedics lead the way in stem cell applications, discussions about the implementation of stem cell techniques in pediatric surgery have only just begun to emerge in recent medical conferences. Recently, the application of stem cell therapy in adults with liver cirrhosis has yielded promising results[72,73]. A study involving 12 children with BA who received stem cell transplantation showed mixed outcomes. Follow-up indicated decreased cholangitis and improved liver function in some patients, though five children succumbed to ongoing cirrhosis[74].

In 2011, Sharma et al. reported on how bone marrow cell transplants helped 11 patients with biliary atresia that had previously undergone the Kasai operation[75]. They found that patients who received stem cell therapy along with the Kasai operation showed improvements in their health compared to those who only had the Kasai procedure. Another study conducted by Nguyen et al., from 2017 to 2019 investigated the use of an autologous bone marrow cells (BMMNC) to treat liver cirrhosis caused by biliary atresia in children who had already undergone the Kasai operation[76]. The research involved 19 children, where bone marrow was collected and specific cells were separated. These cells were then infused into common hepatic artery twice over 6-month intervals. The study showed no overall side effects. Although one child passed away during the study period, the remaining 18 children demonstrated improvements in liver function, as evidenced by lower pediatric end-stage liver disease scores and improved biochemical markers. The research findings indicated that the use of BMMNC infusion could be a beneficial approach to improving liver function in children with biliary atresia. In addition, Nguyen et al. reported a significant decrease in the incidence of cholangitis following the administration of BMMNC. Before receiving BMMNC, all patients had experienced one or more episodes of cholangitis, but none of them experienced cholangitis after the treatment. Recently, some clinical trials on the application of stem cells in biliary atresia patients have been initiated. We also have an ongoing study where we are applying stem cell therapy in biliary atresia (NCT06564740)[77]. The protocol and infusion method for stem cell application in patients with biliary atresia are illustrated in figure. 3.

Stem cell therapy is also crucial in treating necrotizing enterocolitis (NEC)[78]. The recent emergence of stem cell therapy, which exhibits multi-directional differentiation capacity, self-renewing potential, and good abundance, has positively affected intestinal barrier function[79,80]. However, it can also lead to increased apoptosis in the presence of inflammatory reactions. These beneficial results have been studied recently for treating NEC diseases[78-80]. Yet, it is unknown whether the benefits of stem cells in NEC are preventive or protective, which might also determine the optimal time for delivery[81]. Experimental models simulating the condition of NEC suggest that stem cell therapy is effective. A full-term infant with NEC was operated on at Day 22 after birth and received intravenous UC-MSCs postoperatively. The circulation perfusion in the mesenteric area was remarkably improved. Stem cells in this case improved the prognosis of NEC and prevented short bowel in a critical infant[82].

Undescended testis is another diagnosis in pediatric surgery where there are significant future expectations for stem cell applications. It has been reported that BM-MSCs may differentiate into various types of cells at the site (and even locally fused with adjacent tissue), or act as chemoattractants to recruit local endogenous stem/progenitor cells to participate in compensating for damaged tissues[83-85]. One such study was conducted by Alhefnawy et al., using a single-dose intratesticular injection of MSCs in adult patients with non-obstructive azoospermia (NOA)[86]. In their study, out of 87 patients, 18 (20.7%) showed the presence of sperm in their semen at various times. As far as we know, there has not yet been published any article regarding stem cell applications in children for undescended testis. Undescended testis, a common condition in children, is an important cause of NOA. From this viewpoint, stem cell therapy may provide a promising option for patients undergoing surgery for undescended testis[87].

Musculoskeletal (MSK) system diseases

MSK disorders are a wide range of diseases and conditions that affect the muscles, bones, joints, and associated connective tissues. MSK disorders related disabilities can lead to loss of productivity, work absenteeism, early retirement, and increased healthcare costs[88]. MSCs, obtained from various autologous and allogenic sources, have promising effects on MSK pathologies, attributed to their ability for self-proliferation and multipotency. All clinical studies conducted today are based on the ability of mSCs to undergo osteochondrogenic differentiation, their ability to support stem cells in the bone marrow, their ability to suppress the immune system, and their trophic effects[89].

In MSK practice, MSCs are mostly used in cartilage lesions. MSCs create normal articular cartilage or mature hyaline-like tissue even in full-thickness cartilage defects through paracrine cell signaling[90-94]. In a study, autologous BMMSC found to be as efficient as autologous chondrocyte implantation[95]. In another study of patients with knee osteoarthritis divided into two groups, high tibial osteotomy was treated with autologous MSC injection or arthroscopy. It was observed that the chondral defects of the MSC injected group closed better, but no clinical difference was found[96]. Centeno et al.[97] examined the patients treated by high-dose or low-dose bone marrow aspirate concentrate (BMAC) injections.

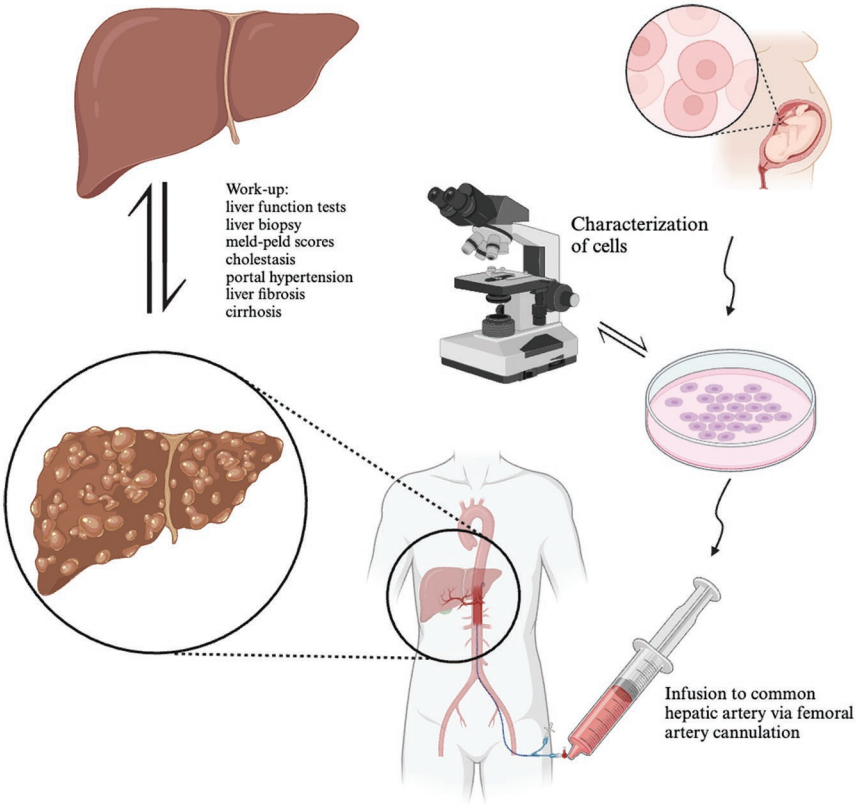

Figure 3. *Stem cell application model for biliary atresia patients (infusion to common hepatic artery through femoral arterial cannulation).*

In the evaluations made in terms of pain and functionality, positive and significant improvements were observed in both. Another study examined the efficacy of BMAC injections in knee and hip osteoarthritis (OA). Approximately 13 months after the injection, improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were seen[98]. In addition, long-term improvements in WOMAC scores have been reported in OA patients treated with platelet-rich plasma injections[99].

The inner 1/3 of the meniscus is a vascular. This area has no healing potential. Izuta et al.[100] reported avascular zone repair using mesenchymal tissue in the fibrin matrix in animal experiments of meniscal tears adipose tissue originated mesenchymal cells differentiate to menischal cells. Pak et al.[101] reported an increasing improvement in MRI of patients with Grade 2 meniscus tear after treated with autologous adipocyte-derived mesenchymal cells injection 3, 6, 12, and 18 months after the procedure. There is also a study suggesting that allogeneic MSCs have healing potential meniscus volume in some patients[102].

After the osteogenic potential of MSCs was demonstrated *in vitro*, studies showing their osteoblastic activities and contributions to bone formation *in vivo* were published[103-106]. Hidaka et al.[107] reported in a study that there was better union and fusion in the vertebral fracture area with the application of bone marrow cells.

Osteonecrosis may occur due to different causes or due to systemic steroid use. Abnormal proliferation of fat cells, fat accumulation in osteocytes, causes high intraosseous blood pressure and blood circulation disorders. This leads to osteonecrosis of the femoral head[108]. Treatment of osteonecrosis by MSC transplantation depends on the osteogenic effect of the transplanted cells on the femoral head[109,110].

MSC applications are also very promising in osteogenesis imperfecta by increasing type-1 collagen production, osteoblastic differentiation, and bone mineral density[111].

There are studies showing that MSC has effects on tendon and disc degeneration[112-119]. Awad et al.[112] have shown that MSCs promote healing in tendinopathy of rabbits. Chong et al.[113] showed that MSCs are

effective in the early phase of tendon healing on the rabbit Achilles tendinopathy. Hernigou et al.[114] revealed by ultrasound and MRI that all 45 patients who underwent MSC injection during arthroscopic rotator cuff repair recovered within 6 months, and 67% of the 45 patients (30 patients) who did not undergo MSC recovered within 6 months, and they reported that the rate of rerupture decreased over time. Selek et al.[115] reported that MSC application increased tendon strength due to antiapoptotic effects. The cell-based therapies have entered the literature as a highly suitable treatment strategy for patients with intermediate stages of intervertebral disc degeneration. The clinical studies have shown the potential impact of allogeneic BMSCs in terms of safety and feasibility[116,117]. Regression of vacuum phenomenon in MRIs of patients with intervertebral disc degeneration 2 years after MSC therapy has been reported[118]. In a pilot study, autologous BM-MSCs were incorporated in the nucleus pulposus and reported an increase in disc height and water content of NP, improvement in LBP, and disability at 12 months of injection[119].

Effect of exercise on stem cells

It is a widely accepted view that regular exercise has a regenerative and protective effect on the human body. This includes cardiac regeneration, neural regeneration, bone development, and muscle regeneration[120,121]. Exercise training is considered safe, simple and has extensive health effects[122]. In a study published in 2024, Takegaki et al.[123] discovered that the intramuscular injection of MSCs activated the transcription of insulin-like growth factor 1 and muscle protein synthesis 72 h after three bouts of resistance exercise. In addition, the injection of MSCs was found to increase protein ubiquitination, suggesting that basal muscle protein turnover may be augmented following consecutive resistance exercise. Guerci et al.[124] showed that serum response factor, a ubiquitous transcription factor expressed in muscle, can regulate the synthesis of IL-6, an event necessary for satellite cell proliferation in response to mechanical exercise in rodents. Taken together, these studies suggest an important role for the paracrine factor milieu in satellite cell activation after exercise. Finally, in a review by Song (2022)[121], current evidence suggests that mechanical loading is beneficial for better callus properties and faster bone regeneration. The clinical studies in elderly fracture patients have shown improved healing and MSK function[125].

Neurosurgery field

The stem cell studies in the field of neurosurgery also include the principles of tissue engineering. Peripheral and central neuroengineering include stem cell and exosome transport systems, conduit scaffolds, and graft discs[126-130]. These studies face various difficulties in translating from the clinic to practice. The studies on nerve damage with exosomes, compared to stem cells, may be more efficient in terms of ethical issues and controllability of toxicity, with lower immunogenic, teratogenic, and tumorigenic capacity. It is hopeful that nanomedical practitioners can transform the laboratory and clinical studies conducted so far into more practical applications in the future[129]. In particular, in traumatic brain injury and some ischemia studies, exosome and stem cell therapies target neuroinflammation by preventing cell death. Gao and colleagues have shown that exosomes from reprogrammed neuronal stem cells used in stroke stimulate both neuroinflammation and neurogenesis[131]. In another study, it was discovered that neuronal stem cell exosomes added to the medium with stress with H_2O_2 increased cell survival[132]. It has been demonstrated that exosomal miR-146a-5p derived from umbilical cord MSC can improve the activation and neuroinflammation of microglia cells *in vitro* and *in vivo*[133].

In a clinical study published in 2024, four cerebral palsy patients who were unable to stand or walk without external support were administered UC-MSCs intrathecally, intravenously, and intramuscularly at 1×10^6/kg 6 times allogeneically and measured using the Modified Ashworth Scale (MAS). A significant change was seen in MAS measurements on both sides, but no significant change was found in cognitive functions[134]. Especially in peripheral nerve injuries, combination therapies that include tissue-engineered neural conduits, scaffolds, stem cells, or exosomes are among the most current areas of nerve tissue engineering. In complete nerve transection injuries, compared to stem cell/exosome applications alone, stem cell/exosome applications carried as combination therapy in the scaffold significantly increase nerve terminal integration and neural stem cell differentiation efficiency[127,135].

In a peripheral nerve injury study conducted at the clinic and published in 2024, microvesicles of 5 billion MSCs were applied in conjunction with sural autograft for repair in a case example of left radial nerve damage. At the 10th week, findings were obtained that the nerve was reinnervated. It was shown electroneurophysiologically that the patient still maintained regeneration at the

end of the 6th month[136]. Bioink forms can be produced by combining gel systems with various biomaterials that trigger neuronal differentiation, such as graphene. The cells or exosomal structures to be carried in these injectable systems are promising, especially in surgical applications such as nerve ending bonding[128].

In a study conducted by Giovannelli et al. in 2023, after creating a mouse and neuron traumatic brain injury model, it was observed that after mesenchymal exosomal treatment, mitophagy was activated by mediating the putative kinase protein 1/Parkinson protein 2 E3 ubiquitin-protein ligase pathway. Thus, it was observed that it reduced neuronal cell death and suppressed apoptosis, pyroptosis, and ferroptosis[137]. The use of exosomes in drug delivery systems is also a topic of interest, especially in neurology. When exosomes were loaded with dopamine and compared with control groups on cells in the *in vitro* 2D and 3D Parkinson's disease model, it was observed that EXO/DOP formulations improved proliferation, increased survival and neuroprotective activity[126]. Its activity was tested, and its neuroprotective activity was interpreted by artificial intelligence. As can be understood from here, the production of exosomes of approximately 100 nm size obtained from WJ-MSCs has become the focus of attention with their neuroprotective activities and ability to cross the blood-brain barrier[130,138].

Urology field

Erectile dysfunction (ED) affects sexual function and the capacity to sustain an erection[139]. To effectively treat ED, it is crucial to use a therapeutic strategy that fosters blood vessel growth, safeguards nerves, and supports tissue regeneration[140]. Various medications have been employed to manage this condition, with phosphodiesterase type-5 inhibitors being the most frequently prescribed by healthcare professionals[139,140]. Stem cell technology shows promise in treating ED. Specifically, MSC secretome therapy leverages the paracrine effects of stem cells, eliminating the risk of tumor formation and offering a minimal immune response. This method presents a significant potential solution for ED treatment, overcoming limitations of traditional therapies[141]. In 2010, Bahk et al. conducted the first human clinical trial using allogeneic umbilical cord MSCs to treat ED in patients with diabetes mellitus[142]. The study included seven men, aged 57-83, who received an intracavernous injection of 1.5×10^7 cells. Within 1 month, most participants experienced a return of spontaneous morning erections, and these improvements were sustained throughout the 6-month follow-up period[142]. Yiou et al. demonstrated that a single intracavernous injection of autologous BMMSCs was both safe and effective in treating vasculogenic ED[143] In a randomized controlled trial (RCTs), Mirzaei et al. demonstrated that an intracavernous injection of autologous MSCs ($5\text{-}6 \times 10^7$) significantly improved sexual function in the majority of diabetic patients[144]. Protogerou et al. developed a technique that integrates adipose tissue-derived MSCs (AT-MSCs) with components of the stromal vascular fraction[145]. They administered cultured AT-MSCs suspended in platelet lysate plasma and observed significant improvements in erectile function at 1, 3, and 6 months post-treatment, with no reported adverse effects.

Recent advances in understanding the pathology and molecular mechanisms of urinary incontinence have opened the door to exploring stem cell therapy as a potential solution for restoring continence[146]. Over 30 prospective single-center and multicenter studies, including follow-up assessments, have been conducted to evaluate the feasibility, safety, and efficacy of cell therapy in treating female stress urinary incontinence (SUI)[147]. Mahboubeh et al. reported that periurethral injections of autologous adult mucosa-derived stem cells were not inferior to the less invasive mini-sling procedure. The stem cell group experienced shorter intervention times, reduced hospital stays, and fewer complications. This pilot randomized trial demonstrated that stem cell therapy and mini-sling surgery produced comparable results in medium-term follow-up[148].

Approximately 1% of all males and 10-15% of infertile men are affected by azoospermia, a condition characterized by the complete absence of sperm in the ejaculate, as determined through the analysis of centrifuged semen samples[149]. In a study, a single intratesticular injection of pure MSCs was administered to treat patients[86]. Among the 87 azoospermia patients treated, 18 (or 20.7%) exhibited the presence of sperm in their semen at various intervals post-treatment. In a phase I clinical trial, an innovative treatment approach using autologous BMMSCs was developed for NOA (87). The study included 80 patients, 40 receiving BM-MSC therapy and 40 undergoing hormone therapy. BM-MSCs were transplanted into the testicular network using microTESE. After 6 months, improvements in hormone levels and sperm concentration were observed. Notably, 9 patients (22.5%) with secondary infertility and azoospermia showed successful outcomes with this treatment. The protocol and infusion method for stem cell application in patients with azoospermia are

illustrated in figure. 4. Stem cell therapies, particularly those involving mesenchymal MSCs, offer promising advancements in treating conditions such as ED, SUI, and NOA in urology area. These approaches demonstrate significant potential by improving outcomes and addressing limitations of traditional treatments, with minimal side effects.

Ophthalmology field

The studies on stem cells and exosome application in areas such as age-related macular degeneration (AMD), corneal damage and diseases, diabetic retinopathies, glaucoma, and various autoimmune eye diseases have become quite current and interesting. There are still controversial points regarding the dosage applications, toxicity status, and standardization of target-oriented transport systems of exosomes produced for these areas[150].

It has been stated that human exosomes of MSCs alleviate retinal ischemia by preventing retinal thinning against oxygen-induced retinopathy induced in mouse models[151]. MicroRNA-126-transferred MSC exosomes were shown to effectively suppress hyperglycemia-induced retinal inflammation both at the gene expression level and by retinal immunohistochemical section examinations[152].

There are studies suggesting that exosomes released from retinal astroglial cells that form the blood-retinal barrier can reduce retinal vascular leakage and that they contain anti-angiogenic components, which are a new treatment model for age-related macular degeneration. Recently, periocular injection models have been developed by taking more advantage of the anti-inflammatory properties of exosomes[153].

In a study, the neuroprotective and neuritogenic effects of BMMSCs-derived exosomes were investigated in a rat optic nerve crush model after weekly intravitreal application. It was observed that exosomes provided regeneration of retinal ganglion cells and preservation of axonal integrity[154].

Corneal damage, one of the causes of visual impairment, is identified by corneal opacity. In a study conducted in 2022, exosomes obtained from iPSCs were loaded onto time-release heat-sensitive chitosan hydrogels and both miRNA release profiles and regional cell regeneration were examined[155].

In another study, it was reported that in a mouse model of retinal ischemia-reperfusion injury, exosome-loaded degradable polymeric biomaterial poly(lactic-co-glycolic acid) microcapsules caused retinal thickness to return to a level close to the healthy retina control group with prolonged release[156].

In addition, topical applications can also be used. Spray products with nano-sized exosomes, cellular or biomaterials, increased area of effect and long-term release can be produced. The important advantages of these products are that they prevent infection formation and reduce the need for intravitreal or extraocular injections. It is thought that the use of these new generation regenerative products with high added value will increase, especially in common diseases such as glaucoma.

Previous studies have explored various routes for stem cell administration, including subretinal, suprachoroidal, and intravitreal approaches[157-162]. For instance, Both Oner et al. and Limoli et al. utilized adipose tissue-derived stem cells (ADSCs) delivered through the suprachoroidal route[161,162]. Öner et al. reported significant improvements in best-corrected visual acuity (BCVA) at the 6-month follow-up[161]. Importantly, no adverse effects, such as proliferation, rejection, or severe ocular or systemic complications, have been documented in these ocular applications[161-163]. Patients with dry AMD demonstrated improvements in BCVA at 6 and 12 months post-stem cell therapy compared to baseline, indicating its potential efficacy[163]. Subgroup analyses revealed variable BCVA outcomes based on stem cell types, such as human embryonic stem cell-derived retinal pigment epithelium, ADSCs, and CD34+ bone marrow-derived stem cells[163]. A meta-analysis of RCTs further supports the potential of SCT to enhance BCVA in patients with dry AMD[163].

Cardiovascular diseases field

Ischemic heart disease (IHD), also known as coronary heart disease or coronary artery disease, is one of the major causes of heart failure (HF), especially in developed countries[164-166]. Various strategies are being pursued to protect the injured myocardium and to prevent adverse cardiac remodeling[167-169]. Surgical revascularization has been shown in several studies to be an effective and preferred treatment strategy for patients with IHD[170]. Song et al. demonstrated that autologous bone marrow stem cell transplantation, in combination with coronary artery bypass grafting (CABG), improves left ventricular function compared to CABG alone[170,171]. In these patients, stem cells can be administered either intramyocardially (IM) or intracoronarily (IC)[172,173]. Qi et al. performed bypass surgery using the saphenous vein and injected approximately

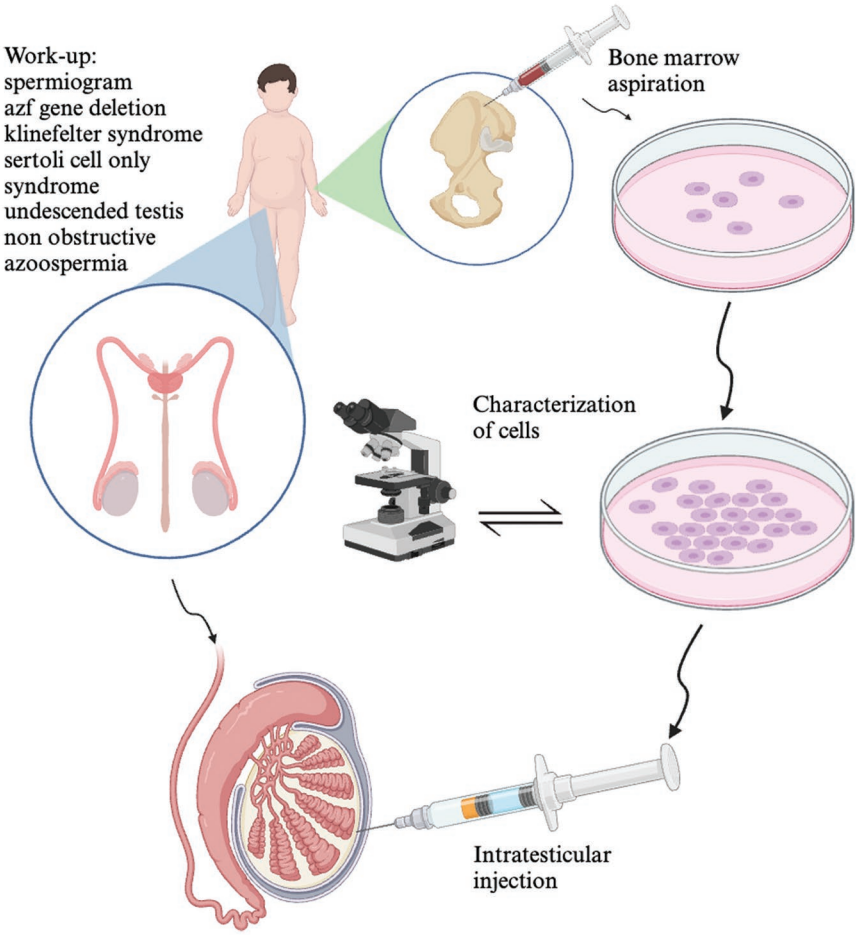

Figure 4. *Stem cell application model for azoospermia patients (injection into testicular parenchyma).*

Table 1. Differences in composition and size between ADEs and PDENs

Paramaters	Animal-derived exosomes	Plant-derived exosome-like nanoparticles	References
Size (nm)	30-150	50-500	9,20
Proteins	Membrane transporters (Fusion proteins, chaperones, cytoskeletal proteins) MVB synthesis proteins (tetras panin proteins, cell adhesion molecules, MHC molecules)	Cytosolic proteins (actin, proteolysis enzymes) membrane transporters (aquaporin, chloride channels)	21-23
Lipids	Cholesterol sphingomyelin glycosphingolipid phosphatidylserine	Phosphatidic acid phosphatidylethanolamin phosphatidylcholine digalactosyl monoacylglycerol digalactosyl diacylglycerol monogalactosyl diacylglycerol	24,25
Nucleic acids	DNA mRNA miRNA mtDNA lncRNA	DNA mRNA miRNA non-coding RNA	26-28

ADEs: Animal-derived exosomes; PDENs: plant-derived exosome-like nanoparticles; MVB: multivesicular bodie; MHC: major histocompatibility complex.

10^7 autologous BMMNCs through IC through a 1-min infusion during the procedure[172]. This method resulted in a greater improvement in the left ventricular dyssynchrony compared to CABG alone. On the other hand, Ulus et al. administered 70 × 10^7 autologous BMMNCs to one group and 25 × 10^6 allogenic

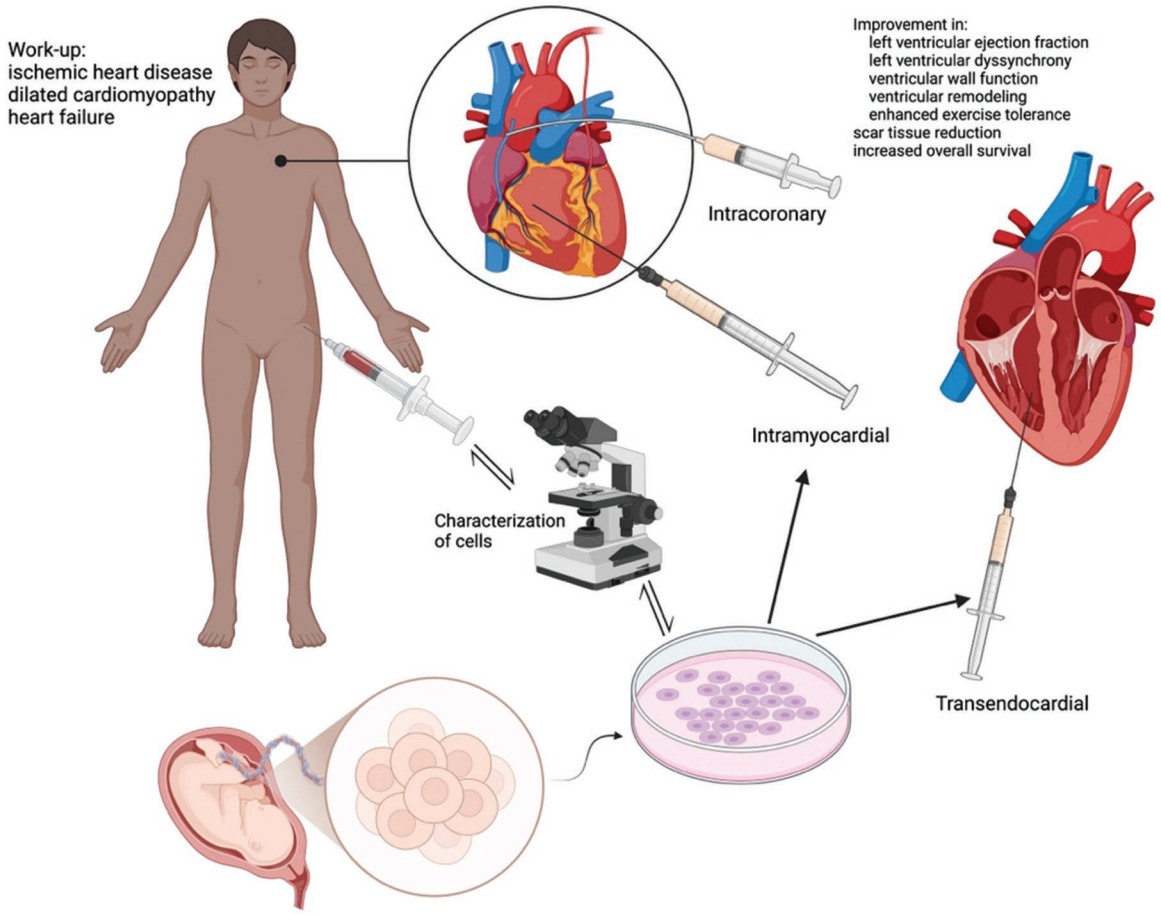

Figure 5. *Stem cell application model for cardiovascular disease (injection route: intracoronary, intramyocardial, transendocardial, and intravenous).*

UC-MSCs to another, both through IM injection into ischemic areas[173]. They observed that IM administration of UC-MSCs combined with CABG resulted in greater scar tissue reduction and improved ventricular wall function compared to autologous BMMNCs. However, the administration route and dose of stem cells remain controversial, requiring further research to its their efficacy and safety[171].

Despite advances in pharmacological treatments and implantable cardiac devices, clinical outcomes for HF patients remain suboptimal, highlighting the need for innovative therapies[174-176]. Various types of stem cells have been increasingly utilized in recent years to enhance clinical outcomes in HF patients[177]. A meta-analysis of 36 RCTs concluded that both BMMNCs and MSCs effectively improve left ventricular ejection fraction (LVEF) in patients with heart failure, with no significant difference observed between the two cell types[177]. Stem cell injection routes included intracoronary, intramyocardial, transendocardial, and intravenous. All routes significantly improved LVEF, while transendocardial injection showed superior outcomes for reducing major adverse cardiac events[177].

Although, some RCTs in patients with dilated cardiomyopathy (DCM) indicated that stem cell therapy did not significantly improve left ventricular function in cases of non-ischemic DCM[178-182], on the other hand, a systematic review and meta-analysis of 11 RCTs involving 637 patients indicated that stem cell therapy may have a beneficial effect on the prognosis of patients with non-ischemic DCM[183]. Another RCT involving 55 patients demonstrated that IC stem cell administration improved ventricular remodeling, enhanced exercise tolerance, and increased overall survival rates in patients with DCM[184]. The optimal type and quantity of stem cells, along with the most effective route of administration, remain contentious issues in the field of regenerative medicine for cardiovascular diseases. It is

important to note that these challenges highlight the need for further research, more detailed analyses, and large multicenter studies to establish reliable and effective therapeutic strategies. The methods of stem cell administration in cardiovascular diseases are illustrated in figure 5.

This review highlights the promising potential of stem cells and exosomes in regenerative medicine and surgical applications, yet certain limitations must be addressed. The heterogeneity in study designs, including variations in cell types, dosages, and administration routes, complicates the establishment of standardized protocols and hinders the comparability of findings. While initial results are encouraging, robust long-term safety and efficacy data remain scarce, limiting clinical translation. Furthermore, the lack of consensus on the optimal stem cell type, quantity, and administration route adds complexity to defining effective therapeutic strategies. Ethical concerns, such as equitable access and cost considerations, are also underexplored. To address these challenges, future research must focus on multicentric RCTs with standardized methodologies to ensure safe and effective integration into clinical practice.

Conclusion

Stem cell-based therapies have demonstrated significant success and acceptable safety profiles with in various used surgery to date. The advances in MSCs therapies, particularly those involving genetic modifications such as gene transfer or transduction, have shown promise in enhancing therapeutic outcomes. For example, strategies leading to overexpression of anti-inflammatory cytokines or inhibition of pro-inflammatory cytokines as well as modifications such as addition of pro-inflammatory cytokines to the culture medium have been effective in optimizing the therapeutic potential of MSCs. In addition, techniques to improve the homing ability of stem cells or exosomes, including the addition of surface markers, have further amplified their efficacy. Despite these promising developments, there are still challenges that may impede the widespread clinical translation of these therapies. Potential therapeutic risks, such as tumorigenesis and the high costs associated with these advanced treatments, remain significant concerns. Future clinical trials should therefore prioritize addressing these risks by focusing on strategies to minimize heterogeneity, determining the optimal routes of infusion, and establishing standardized protocols for dosage and infusion frequency. In addition, there is a need for the production of stem cells and exosomes under GMP conditions, their effective and safe application in the clinic, optimization of production and application protocols, and support with RCTs. The studies examined in this review include studies emphasizing the safety and efficacy of these treatments in comprehensive and diverse patient populations. Such studies are very important for determining therapeutic strategies and ensuring the safe integration of innovative exosome and stem cell-based therapies into standard clinical practices.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASO CLÍNICO

Identificación anatómica de la vía biliar por iluminación intrínseca en colecistectomías difíciles: dispositivo Prometeo

Anatomical identification of the bile duct by intrinsic illumination in difficult cholecystectomies: Prometheus device

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Resumen

La lesión biliar sigue siendo una de las complicaciones más temidas después de una colecistectomía. El dispositivo Prometeo, mediante iluminación intrínseca, facilita la identificación anatómica intraoperatoria de estructuras biliares. En un caso de colecistitis, se utilizó durante una colecistectomía convencional, avanzándolo por la bolsa de Hartmann hasta la confluencia con el hepático común, iluminando las estructuras biliares y mejorando la visión crítica de seguridad. Este dispositivo demostró ser un método seguro y accesible, con potencial para su uso en la mayoría de los centros de salud.

Palabras clave: *Colecistectomía. Laparoscopia. Colangiografía. Experimental. Indocianina.*

Abstract

Bile duct injury remains one of the most feared complications after cholecystectomy. The Prometheus device, through intrinsic illumination, facilitates intraoperative anatomical identification of biliary structures. In a case of cholecystitis, it was used during a conventional cholecystectomy, advancing it through Hartmann's pouch to the confluence with the common hepatic duct, illuminating the biliary structures and enhancing critical view of safety. This device proved to be a safe and accessible method, with potential for use in most healthcare centers.

Keywords: *Laparoscopic. Cholecystectomy. Cholangiography. Investigational. Indocyanine.*

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Introducción

La colecistectomía es actualmente el procedimiento quirúrgico más común realizado por cirujanos generales, siendo el estándar de tratamiento para la litiasis vesicular[1,2]. Desde los trabajos de Mühe en 1985, y posteriormente los de Mouret, Dubois y Perissat, la colecistectomía laparoscópica ha evolucionado en términos de precisión y seguridad[2]. Los pacientes sometidos a un procedimiento laparoscópico se benefician de una recuperación precoz, menos dolor y menor riesgo de infección del sitio quirúrgico[3].

Una de sus complicaciones más temidas es la lesión de vía biliar, con una tasa del 1-2% después de una colecistectomía laparoscópica, y sus complicaciones relacionadas a corto y mediano plazo, con una tasa del 9.84%[4]. Los estudios epidemiológicos sugieren una incidencia del 0.4-0.6%, con reportes recientes que hablan de una incidencia similar a la de la cirugía abierta[5]. La lesión de la vía biliar aumenta el riesgo de mortalidad por todas las causas de un 8.8% a un 20%[4], con un aumento en la mortalidad a 1 año de hasta seis veces[6]. Las consecuencias de una lesión de la vía biliar no solo repercuten en la calidad de vida del paciente, sino también en la del cirujano. En Inglaterra, los litigios por mala práctica después de una lesión de la vía biliar cuentan por la mayoría de las demandas contra cirujanos, el 16% de las lesiones de la vía biliar terminan en demanda, y en los Estados Unidos de América el 20-30%[4,7].

La cultura de la «colecistectomía segura» ha permeado en la práctica diaria de los cirujanos en todo el mundo. Diversos autores han ideado métodos para disminuir este riesgo basados en herramientas técnicas, imagenológicas y clínicas, siendo de los más importantes los trabajos de Strasberg[8] y el empleo de la «visión crítica de seguridad», para de esta manera disminuir el riesgo de lesión de la vía biliar relacionada con la mala identificación anatómica, presente en aproximadamente el 71% al 97% de los casos[8,9].

Por lo anterior, la identificación anatómica de la vía biliar es crucial para el éxito del procedimiento. Cuando no se logra la visión crítica de seguridad en casos de colecistectomía difícil, el cirujano puede valerse de métodos de imagen e intrínsecos, como lo son la fluorescencia con verde de indocianina o la colangiografía transoperatoria. Las desventajas principales de estos métodos son el precio, la necesidad de dispositivos especiales, la radiación ionizante y el medio de contraste necesario[9-14].

El dispositivo Prometeo trata de evitar las desventajas principales de los métodos descritos, ya que no requiere aparatos especiales (únicamente una fuente de luz) ni someter al paciente a agentes que causen lesiones asociadas, como la radiación ionizante y el medio de contraste, siendo posible utilizarlo en pacientes con comorbilidad sin riesgos agregados.

Método

Se describe un caso de colecistitis aguda tratado en nuestro centro en el que se utilizó el dispositivo experimental Prometeo, con el fin de evaluar su utilidad y confiabilidad en la identificación de la anatomía biliar. Se realiza una revisión de la literatura actual en las principales bibliotecas digitales con los términos “colecistectomía difícil”, “lesión de vía biliar”, “colecistectomía laparoscópica”, “colangiografía transoperatoria” y “colangiografía fluorescente”, tomando en cuenta los artículos relevantes para nuestra investigación.

Acude a nuestro centro un paciente de 41 años con un cuadro confirmado de colecistitis aguda leve TG18. Se realiza colecistectomía laparoscópica a su ingreso, previo consentimiento informado. Se realiza el neumoperitoneo a 14 mmHg con técnica cerrada con aguja de Veress. Se colocan dos puertos de 12 mm y dos de 5 mm (Fig. 1). Se realiza la disección inicial de la vesícula biliar hasta descubrir el infundíbulo, antes de obtener la visión crítica de seguridad. En este momento realizamos una incisión de 3 mm en la cara anterior de la bolsa de Hartmann. Introducimos el dispositivo experimental Prometeo por el puerto de 12 mm, el cual se conecta previamente a un adaptador hacia una fuente de luz externa (Fig. 2). Se introduce la punta de la fibra óptica del dispositivo en la incisión descrita en dirección distal hacia la vía biliar común, sin forzar su entrada al encontrar resistencia (Fig. 3). Una vez dentro, se enciende la fuente de luz del dispositivo y se disminuye la intensidad de la fuente principal hasta lograr un contraste adecuado (Fig. 4). Introducimos y retiramos levemente la fibra óptica hasta lograr una visualización satisfactoria del conducto cístico y su confluencia con la vía biliar común (Fig. 5). Verificamos los hallazgos con una colangiografía transoperatoria (Fig. 6). Ya que se corrobora la identificación anatómica exitosa, se procede a disecar el triángulo hepatocístico hasta obtener la visión crítica de seguridad y terminar el procedimiento de manera convencional.

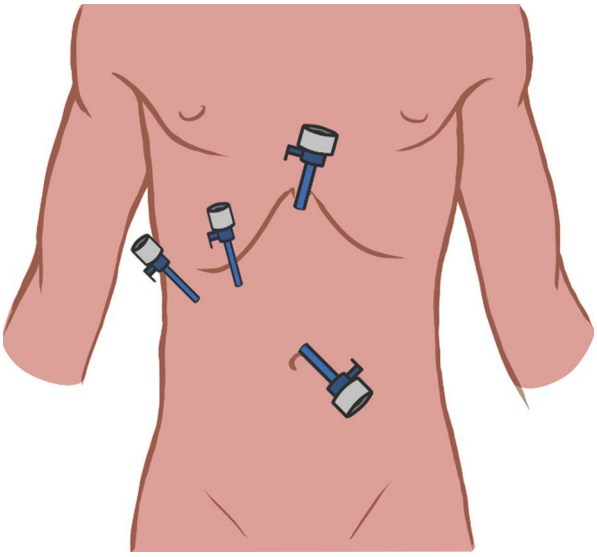

Figura 1. *Esquema de la colocación de los puertos.*

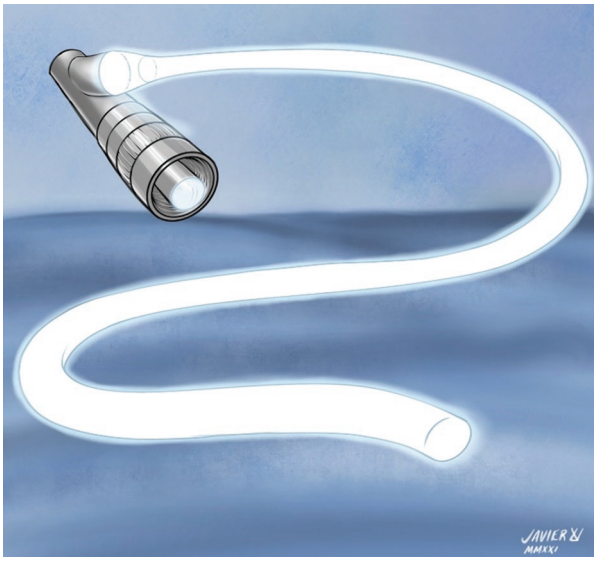

Figura 2. *Representación de la propuesta inicial para el dispositivo Prometeo.*

Resultados

Durante el posoperatorio el paciente no presenta complicaciones relacionadas con la patología de base ni con el procedimiento, y con una evolución clínica adecuada se decide su egreso al día siguiente del evento quirúrgico. Durante el procedimiento se logró identificar la totalidad del conducto cístico, siendo inicialmente este el objetivo al idear la técnica descrita. Sin embargo, durante la introducción de la fibra óptica a la vía biliar logramos identificar de manera preliminar la confluencia del conducto cístico con la vía biliar común (Fig. 5).

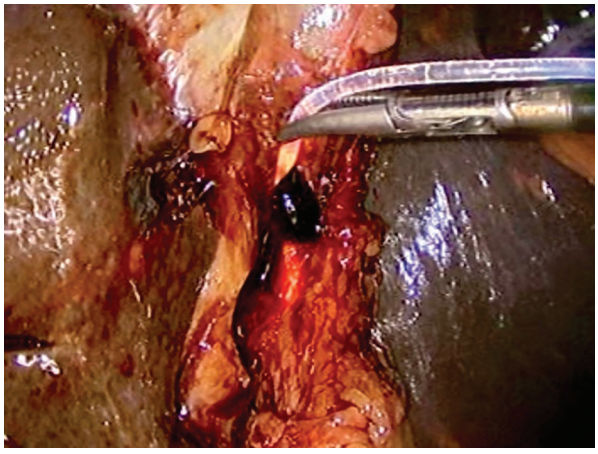

Figura 3. *Introducción del dispositivo por la incisión realizada en la cara anterior de la bolsa de Hartmann.*

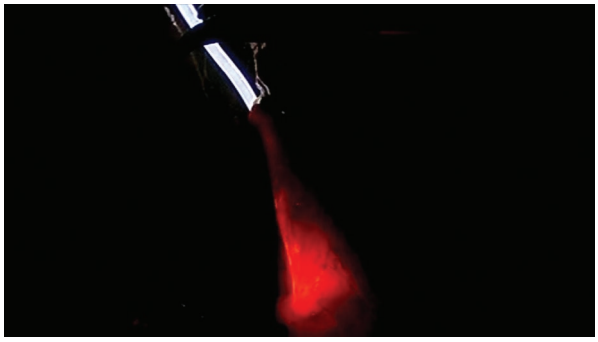

Figura 4. *Iluminación intrínseca. En este momento se atenúa la fuente de luz principal para lograr un adecuado contraste.*

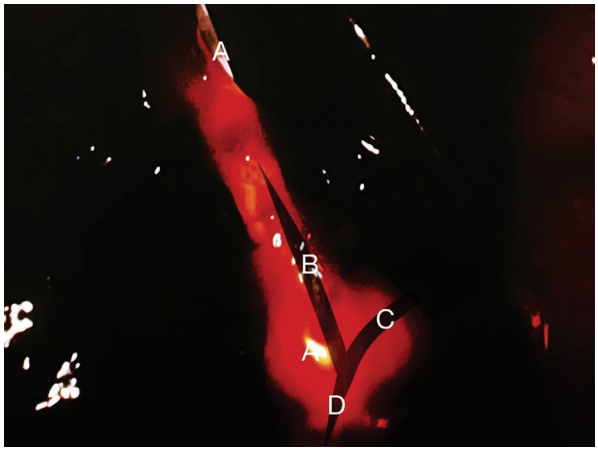

Figura 5. *Imagen intraoperatoria en la que se observan, iluminados por la fibra óptica* **(A)**, *el conducto cístico* **(B)**, *el conducto hepático común* **(C)** *y la vía biliar común* **(D)**.

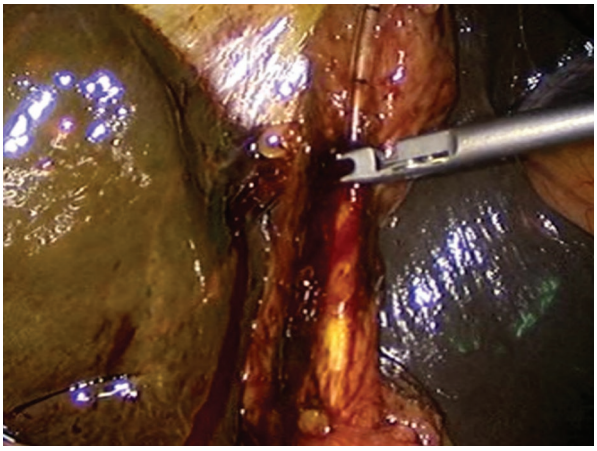

Figura 6. *Introducción de la sonda para realizar la colangiografía transoperatoria.*

Discusión

La identificación del triángulo hepatocístico resulta compleja en casos de colecistectomía difícil. En la actualidad no existen unos parámetros objetivos a partir de los cuales el cirujano deba valerse de un método externo para asegurarse de tener la visión adecuada. Nassar et al.[15] trataron de llegar a un método objetivo para delimitar este punto de corte mediante imágenes transoperatorias asociadas a «dificultad», en el cual, a diferencia de otros *scores* intraoperatorios, una calificación alta está relacionada con un aumento en la tasa de complicaciones, y no únicamente predice la tasa de conversión a procedimiento abierto[16]. El conocimiento previo a la cirugía de una posible colecistectomía difícil es esencial para una planeación adecuada. Los factores asociados a dificultad pueden ser transoperatorios o preoperatorios. Se han estudiado parámetros clínicos, imagenológicos y químicos. La edad, el sexo masculino, la colecistitis crónica o aguda, la obesidad, la cirrosis, el cáncer, la colangiopancreatografía retrógrada endoscópica o las cirugías previas, la colecistectomía después de 2 semanas del cuadro inicial de pancreatitis aguda[17-19], el engrosamiento de la pared, el líquido pericolecístico y la estriación de la grasa en los estudios de imagen, los parámetros inflamatorios como la proteína C reactiva elevada, la leucocitosis, el fibrinógeno[20-22] y los factores durante el procedimiento, como la dificultad para la tracción vesicular y la retracción hepática, el cístico corto o ancho, las adherencias, los litos enclavados en la bolsa de Hartmann, la gangrena, el piocolecisto y el síndrome de Mirizzi, entre otros[16,23], aumentan el riesgo de colecistectomía difícil y falla en la obtención de la visión crítica de seguridad. Otros factores, como el volumen de procedimientos (alto volumen: más de 50-85 casos por año), la experiencia y la intervención de un cirujano hepatopancreatobiliar se relacionan con la morbimortalidad en una colecistectomía difícil[24].

Un 10-15% de las colecistectomías se catalogan como difíciles. El grado de dificultad se relaciona con la falla en la obtención de la visión crítica de seguridad y, por lo tanto, con la lesión de la vía biliar. Para evitar este desenlace podemos valernos de procedimientos de rescate, como la colecistostomía, un abordaje *fundus first,* la colecistectomía subtotal laparoscópica y la conversión a cirugía abierta[2]. El uso de procedimientos como la colecistectomía subtotal laparoscópica ha aumentado en los últimos años y ha disminuido la tasa de conversión con la modificación de los programas de entrenamiento y la disponibilidad de nuevas tecnologías[25-27].

La elección del procedimiento más seguro y eficaz dependerá de la identificación anatómica disponible. Diversos métodos se han estudiado para lograr este cometido. Entre los más utilizados se encuentra la colangiografía transoperatoria, que consiste en administrar medio de contraste mediante un catéter en una zona segura en el infundíbulo. Tiene la ventaja de la visualización directa del árbol biliar, además de la detección de litos, los cuales se encuentran en el 8-15% de los casos, con una sensibilidad del 97% y una especificidad del 99%[28]. Dentro de sus desventajas más notorias se encuentra la necesidad de administrar un medio de contraste que puede ser nefrotóxico. Además, Lehrskov et al.[11] encontraron que en uno de cada seis pacientes en que se utilizó la colangiografía transoperatoria el conducto cístico no era permeable.

La colangiografía fluorescente con indocianina fue descrita en 2009 por Ishizawa[29] y consiste en la administración de un bolo de 0.2 mg/kg de indocianina previo a la cirugía (aunque la dosis y el tiempo no estan estandarizados), la cual se metaboliza en el hígado, con lo que se logra, mediante la proyección directa con un espectro de luz cercano al infrarrojo, la visualización de la anatomía biliar en tiempo real[29]. Las desventajas son la necesidad de un aparato especial para la detección de la fluorescencia y su utilidad limitada en pacientes con obesidad, adherencias e inflamación grave, ya que la penetración de la luz cercana a la infrarroja es de aproximadamente solo 1 cm[10,12].

Nuevos métodos, como el ultrasonido laparoscópico, definen de manera más exacta las estructuras (sensibilidad del 92-100%), con el beneficio agregado de la detección de litiasis con unas elevadas sensibilidad y especificidad (76-100% y 96-100%, respectivamente), que puede ser utilizado antes de la disección, y es rápido e inocuo; sin embargo, requiere aparatos especiales y una mayor curva de aprendizaje[13].

Dentro de las ventajas teóricas de la identificación anatómica por iluminación intrínseca se encuentran la visualización en tiempo real del conducto cístico y la unión crítica con el conducto hepático común, y no requerir contraste, radiación ionizante ni medicamentos que puedan causar reacciones adversas, además de una curva de aprendizaje menor y prescindir de equipos especiales. En 2020, Vidrio et al.[29] describieron un método de transiluminación con una lente de 5 mm y 30° conectada a una fuente de luz, la cual colocaban de manera directa en la zona a disecar. En este estudio retrospectivo se logró identificar las estructuras anatómicas (sin reportar cuáles) en 2 de los 10 pacientes estudiados; en el resto fue necesaria la disección previa del peritoneo con el riesgo de lesión de la vía biliar. Por lo anterior, los autores llegaron a la conclusión de que era necesario realizar más estudios y la búsqueda de un dispositivo diferente[30].

Conclusiones

La identificación anatómica por iluminación intrínseca con el dispositivo Prometeo resulta un método seguro y eficiente, de bajo costo y que puede ser utilizado en la mayoría de los centros en que se realicen procedimientos laparoscópicos. Es necesario llevar a cabo ensayos clínicos aleatorizados y multicéntricos que evalúen su costo real, así como el impacto en la disminución del riesgo de lesión de la vía biliar.

Financiamiento

Los autores declaran no haber recibido financiamiento para este estudio.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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Apendicitis complicada con perforación vesical manejada por vía laparoscópica: reporte de caso

Complicated appendicitis with bladder perforation treated with laparoscopic surgery: case report

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Resumen

El retraso en el diagnóstico y en el tratamiento de la apendicitis aguda aumenta el riesgo de complicaciones secundarias al efecto de la perforación visceral. La perforación apendicular hacia la vejiga es una complicación anecdótica, pero probable, cuyo tratamiento generalmente consiste en laparotomía con apendicectomía y reparación de la pared vesical. El abordaje laparoscópico es una opción viable en cuadros de apendicitis complicada, incluso en escenarios clínicos complejos. El objetivo de este trabajo es presentar un caso clínico de apendicitis con perforación vesical tratado de manera exitosa por vía laparoscópica mediante hemicolectomía derecha y cierre de la pared vesical.

Palabras clave: *Apendicitis. Perforación vesical. Laparoscopia. Fístula apendicovesical.*

Abstract

Misdiagnosis and delay in the treatment of acute appendicitis increases the risk of complications secondary to visceral perforation. Appendicular rupture into the bladder is an uncommon complication, but possibly to happen; treatment generally consists of a laparotomy with appendectomy and repair of the bladder wall. The laparoscopic approach is a viable option in cases of complicated appendicitis, even in complex and infrequent clinical scenarios. The aim of this paper is to describe a case of complicated appendicitis with bladder perforation, treated with a laparoscopic right hemicolectomy, terminal ileostomy and closure of the urinary bladder wall.

Keywords: *Appendicitis. Bladder perforation. Laparoscopy. Appendicovesical fistula*

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Introducción

La apendicectomía es el procedimiento quirúrgico de urgencia más frecuentemente realizado. Se estima que el riesgo de padecer apendicitis durante la vida es del 7 al 9%.

En los adultos, las escalas como la de Alvarado y los marcadores inflamatorios por sí solos no son capaces de predecir el diagnóstico en todos los pacientes con apendicitis aguda. El rastreo por ultrasonido (US) es el método de imagen más utilizado, pero la tomografía computarizada (TC) es la técnica de referencia, con una especificidad del 98%. El uso escalonado de US y TC aumenta la certeza diagnóstica[1]. El retraso en el diagnóstico de apendicitis aguda puede llevar a perforación y un aumento de la morbilidad, con resultados adversos para el paciente[1].

La perforación se presenta en aproximadamente el 20% de los casos de apendicitis. Varios estudios han mostrado que el riesgo de perforación se relaciona con el tiempo de evolución, y que el retraso en el tratamiento quirúrgico se asocia a peores resultados. Además, el tiempo quirúrgico, así como la estancia hospitalaria posquirúrgica, se incrementan significativamente con mayores intervalos de tiempo desde el inicio de los síntomas hasta la cirugía[2].

La perforación del apéndice se puede manifestar con síntomas localizados en el cuadrante inferior derecho o con una perforación libre con diseminación de pus y materia fecal intraperitoneal. En ocasiones puede manifestarse con presentaciones clínicas inusuales, como abscesos retroperitoneales, fístulas enterocutáneas, abscesos hepáticos por diseminación hematógena, oclusión intestinal o incluso trombosis venosa portal séptica (pileflebitis). Las complicaciones de la apendicitis aguda son ampliamente variables y la mayoría son secundarias a los efectos de la perforación visceral[3]; existen algunas muy poco frecuentes, pero probables, como la perforación vesical y la fístula apendicovesical. Debido a la presentación variable de síntomas y a la incapacidad de los estudios de imagen para detectar esta rara patología, es difícil hacer un diagnóstico temprano. La TC, el método de referencia, muestra la pared vesical engrosada y fecalitos cerca de la vejiga como principales hallazgos, y en algunos casos se puede observar el trayecto fistuloso del intestino a la vejiga[4]. Para esta complicación no existe un tratamiento estandarizado, pero generalmente incluye apendicectomía y reparación de la pared de la vejiga[3,4].

El manejo de la apendicitis perforada depende del estado del paciente. Cuando la perforación está contenida, con absceso localizado, puede ser inicialmente no quirúrgico con antibióticos por vía intravenosa y drenaje percutáneo, con posterior apendicectomía, o con apendicectomía inmediata[5]. En los pacientes hemodinámicamente inestables con peritonitis generalizada se requiere una exploración quirúrgica de urgencia. Actualmente se ha comprobado que la vía laparoscópica conlleva menor riesgo de infecciones del sitio quirúrgico, una estancia intrahospitalaria más corta y menos tiempo hasta el reinicio de la vía oral, con un tiempo quirúrgico ligeramente más largo respecto a la abierta, y sin incrementar el riesgo de formación de abscesos intraabdominales[6,7]. Aun en pacientes considerados de alto riesgo, con ASA 3-4, la laparoscopia en la apendicitis complicada presenta las mismas ventajas, con mayor frecuencia de complicaciones leves, pero menos graves, que la cirugía abierta[8].

El objetivo de este trabajo es presentar un caso clínico de apendicitis con perforación vesical tratado de manera exitosa por vía laparoscópica mediante hemicolectomía derecha y cierre de la pared vesical.

Caso clínico

Mujer de 70 años con antecedentes de diabetes *mellitus* tipo 2 e hipertensión arterial sistémica de larga evolución, así como enfermedad renal crónica de 6 meses de diagnóstico sin terapia de sustitución renal; como quirúrgicos, una cesárea y salpingooforectomía bilateral hace 22 años, sin complicaciones; ginecoobstétricos: gesta 3, partos 2, cesárea 1.

Al inicio de su padecimiento, 2 semanas previas a su ingreso, se presentó con dolor pélvico bilateral y fiebre que no cedió con el uso de analgésicos y antipiréticos, diarrea y vómito, sin síntomas urinarios. Fue llevada a atención hospitalaria en otro centro, el US reveló litiasis vesicular y la TC simple mostró litiasis bilateral, con deterioro de la función renal. Se egresó de manera voluntaria después de 1 semana y fue trasladada a nuestro centro médico, donde ingresó con datos de urgencia dialítica. Tras la colocación de un catéter para hemodiálisis presentó deterioro de la función respiratoria, requiriendo manejo avanzando de la vía aérea. En su hospitalización se diagnosticó con choque séptico de probable foco urinario, necesitando apoyo aminérgico. Se interconsultó a cirugía general, encontrando en la exploración física plastrón

en la fosa iliaca derecha y gasto fecal por sonda de Foley.

Los estudios de laboratorio mostraron leucocitosis de 45,000 con neutrofilia, tiempos de coagulación prolongados, lesion renal aguda y acidosis metabólica. La TC reportó líquido libre de predominio en la corredera parietocólica derecha, colección intraabdominal paracecal en proximidad con la vejiga, gas en la cavidad, ligero engrosamiento de la pared vesical y una zona de interfaz entre el ciego y la vejiga (Fig. 1). Se diagnosticó como probable apendicitis aguda complicada con perforación vesical secundaria.

Se decidió realizar exploración quirúrgica de urgencia por abordaje laparoscópico, encontrando material intestinal y purulento libre en la cavidad (Fig. 2), con el ciego perforado hacia la vejiga, observándose el globo de la sonda transuretral (Fig. 3). Se realizó hemicolectomía derecha (Fig. 4) con ileostomía terminal, cierre primario de la perforación vesical en tres planos (Figs. 5 y 6) y colocación de drenaje. La paciente se mantuvo en vigilancia posoperatoria en terapia intensiva, resolvió el cuadro de sepsis abdominal y fue egresada al sexto día a piso para continuar su recuperación a cargo de los servicios de nefrología y cirugía general. En el día 15 de posoperatorio se evidenció una nueva colección intraabdominal en la corredera parietocólica derecha, la cual se trató mediante drenaje percutáneo y antibiótico por vía intravenosa, resolviéndose sin complicaciones. Continuó con evolución tórpida por sus patologías de base, requiriendo múltiples sesiones de hemodiálisis, y finalmente falleció por complicaciones asociadas a la enfermedad renal.

Discusión

La apendicitis aguda todavía es subdiagnosticada con frecuencia. La proporción de apendicitis subdiagnosticadas oscila entre el 20 y el 40%[1]. La complicación más frecuente de la apendicitis es la perforación. Desde hace muchos años se han realizado esfuerzos para reducir esta complicación, buscando discernir mejor entre los pacientes que requieren o no exploración quirúrgica. Actualmente, la TC brinda mucha información precisa y se utiliza para detectar los casos dudosos; sin embargo, algunas veces no proporciona datos suficientes para diagnosticar la apendicitis aguda[9]. En nuestro caso, a la paciente se le realizó una TC previamente a su ingreso en nuestro nosocomio, que no reportó datos de proceso apendicular, lo que contribuyó al diagnóstico tardío y las consecuentes complicaciones. De acuerdo con Sosner et al.[10], una de las causas comunes de falsos negativos por TC ante la sospecha de apendicitis aguda es que la inflamación periapendicular puede estar oculta, por ejemplo, por ascitis secundaria a comorbilidad, algo acorde a la situación de nuestra paciente con enfermedad renal.

El retraso en el diagnóstico y en el tratamiento de la apendicitis aguda aumenta el riesgo de perforación, según diversos estudios. Saar et al.[2], en 2016, demostraron que la gravedad según la *Disease Severity Score* (DSS), así como la gravedad de las complicaciones evaluadas por el *Comprehensive Complication Index* (CCI), incrementan proporcionalmente con el tiempo desde el inicio de los síntomas hasta la cirugía[2]. Por otro lado, en un metaanálisis de 45 estudios realizado por Van Dijk et al.[11] se encontró que no existe un incremento significativo en el riesgo de apendicitis complicada con un restraso de la apendicectomía de 24-48 h desde el ingreso del paciente a la unidad hospitalaria, proponiendo que la apendicitis perforada es una afección distinta de la apendicitis no complicada, en lugar de ser el siguiente paso en la evolución natural de la enfermedad.

La perforación apendicular hacia la vejiga es una complicación anedóctica, que puede ser producida por el proceso inflamatorio entre el apéndice y la vejiga, causando fusión y necrosis[12]. El primer caso fue descrito por Percy Allan en 1900[13] y hasta hoy se han reportado alrededor de 115 casos de perforación vesical y fístula apendicovesical por apendicitis, y apenas algunos en la literatura reciente[3,4,9,12,14,15], todos asociados a una apendicitis aguda no evidenciada de manera temprana.

En dos de los casos revisados, los síntomas de infección de vías urinarias persistente fueron los que llevaron a los pacientes a buscar atención médica; en ambos casos hubo antecedentes de dolor en el hemiabdomen derecho y fiebre sin tratamiento[4,14]. En otro de los casos, los síntomas urinarios precedieron al dolor abdominal migratorio, la fiebre, las náuseas y la anorexia[9]. En los otros dos, los pacientes se presentaron con historia de dolor abdominal, fiebre y náuseas en los 4 a 10 días previos a su ingreso, sin síntomas urinarios asociados[3,12]. La diarrea con o sin sangre y el vómito estuvieron presentes en casi todos los casos. En la exploración física, la presencia de una masa en el cuadrante inferior derecho con hiperestesia fue una constante. En los estudios de laboratorio, la leucocitosis y el examen urinario patológico,

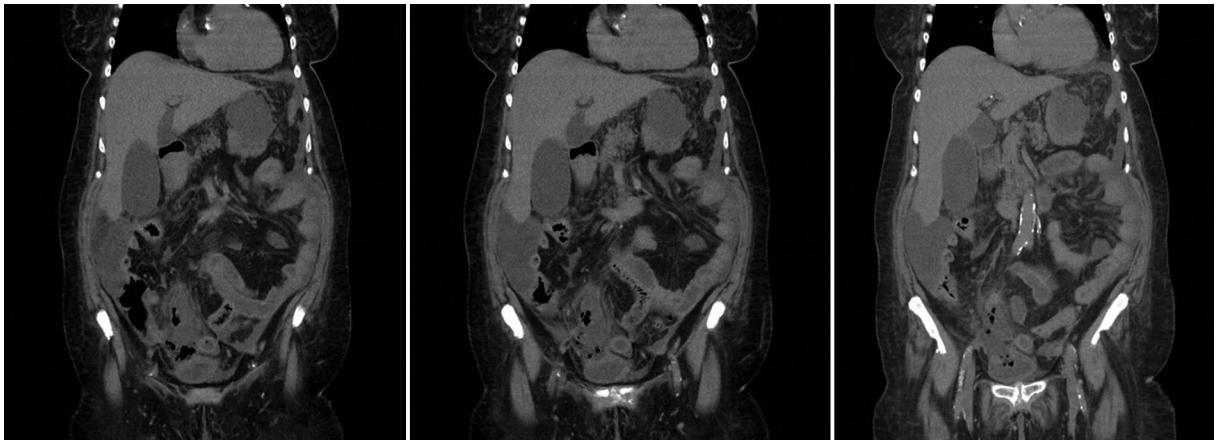

Figura 1. *Hallazgos de la tomografía computarizada abdominal contrastada, vista coronal.*

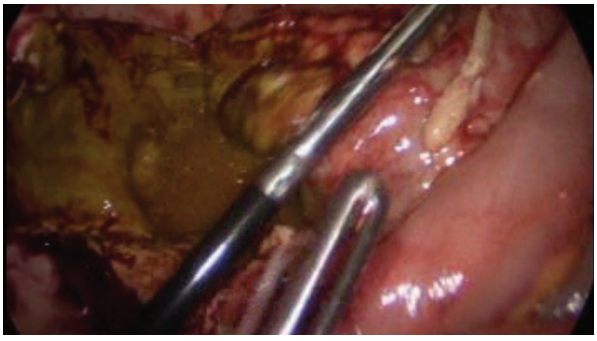

Figura 2. *Visión laparoscópica del absceso pélvico secundario a la perforación.*

Figura 4. *Resección laparoscópica del colon con engrapadora.*

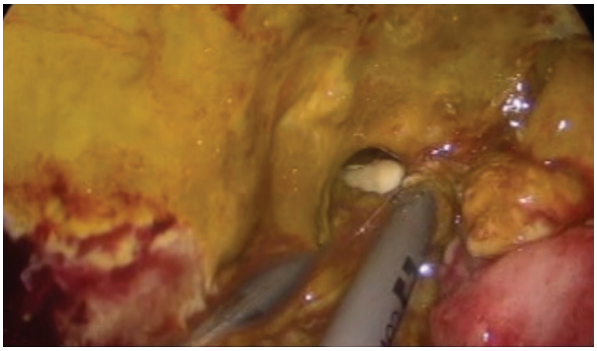

Figura 3. *Visión laparoscópica del globo de la sonda transuretral en relación a la perforación vesical.*

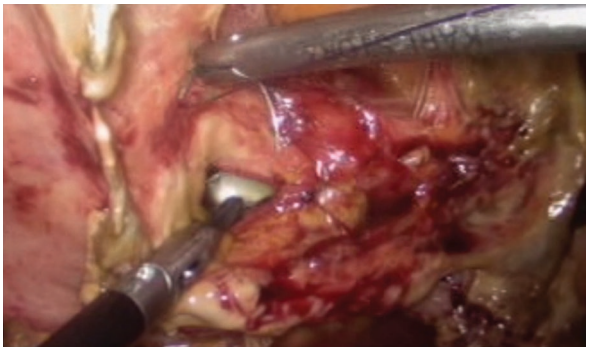

Figura 5. *Cistorrafia laparoscópica por planos.*

con leucocituria, piuria o fecaluria, estuvieron presentes en todos los casos; en uno de ellos, se evidenció lesión renal aguda[3]. La sospecha diagnóstica se hizo por TC con contraste y los hallazgos más consistentes con perforación vesical secundaria a proceso inflamatorio apendicular fueron la presencia de una colección líquida periapendicular en proximidad con la vejiga, cambios inflamatorios en la grasa periapendicular y perivesical, engrosamiento apendicular y engrosamiento de la pared de la vejiga[3,4,9,12,14].

En nuestro caso, la presentación clínica, las analíticas de sangre y orina, así como los hallazgos por TC, fueron similares a lo descrito en los casos revisados. Sin embargo, nuestra paciente se presentó

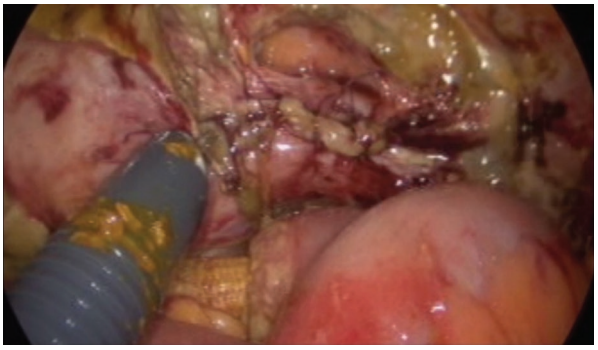

Figura 6. *Visión laparoscópica del cierre de la pared de la vejiga terminado.*

con datos de choque séptico e inestabilidad hemodinámica.

Históricamente, la laparotomía exploradora ha sido la pieza clave para el diagnóstico y el tratamiento definitivo de esta patología. En los casos que revisamos, todos menos uno fueron tratados por esta vía, mediante laparotomía, apendicectomía con o sin hemicolectomía derecha, y cierre de la pared de la vejiga o cistectomía parcial[3,4,9,12,15]. Solo en el caso descrito por García-Muñoz et al.[14] en 2013 se realizó el abordaje por vía laparoscópica, llevando a cabo la apendicectomía y la resección de la fístula apendicovesical, egresando a la paciente a las 48 horas de la intervención. Como este, se han reportado algunos otros casos de reparación de fístula apendicovesical por vía laparoscópica, pero secundarios a apendicitis crónica u otras causas, y con la intervención realizada de manera electiva.

De acuerdo con la literatura revisada, el caso que presentamos es el primero con una perforación aguda de la vejiga secundaria a apendicitis complicada y con datos de choque séptico, que se trató, posterior a la reanimación preoperatoria, por vía laparoscópica, completándose la hemicolectomía derecha y el cierre de la pared de la vejiga sin complicaciones. Sin embargo, la paciente tuvo un desenlace fatal, debido a la agudizacion de fallos orgánicos de base a pesar de la resolución del proceso séptico primario.

Conclusiones

La apendicitis perforada continúa siendo un reto diagnóstico y terapéutico; algunas complicaciones tardías no tan estudiadas, como la perforación de estructuras periapendiculares, conllevan una alta tasa de morbimortalidad.

La cirugía de mínima invasión es una opción viable, diagnóstica y terapéutica definitiva, en cuadros de apendicitis complicada, incluso en escenarios clínicos complejos y poco frecuentes como la perforación vesical.

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CASO CLÍNICO

Reparación laparoscópica de hernia ilíaca tras la obtención de injerto óseo autólogo de la cresta ilíaca

Laparoscopic repair of iliac hernia after obtaining autologous bone graft from iliac crest

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Resumen

El injerto de cresta ilíaca es la fuente ideal de injerto óseo autólogo. Es un procedimiento que se asocia con pocas complicaciones, siendo la hernia ilíaca una complicación rara que aparece especialmente cuando se toman injertos de espesor completo. Es más frecuente en el sexo femenino y el principal síntoma es el dolor en la zona del injerto. El tratamiento quirúrgico es el recomendado por el riesgo de incarceración, pues estas hernias pueden contener vísceras abdominales. No existe un tratamiento estándar para estas hernias.

Palabras clave: *Hernia ilíaca. Complicación de injerto óseo. Hernia laparoscópica.*

Abstract

The iliac crest graft is the ideal source of autologous bone graft. It is a procedure that is associated with few complications. Iliac hernia is a rare complication that appears especially when full-thickness grafts are taken. It is more common in females and the main symptom is pain in the graft area. Surgical treatment is recommended due to the risk of incarceration as these hernias may contain abdominal viscera. There is no standard treatment for these hernias.

Keywords: *Iliac hernia. Bone graft complication. Laparoscopic hernia repair.*

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Introducción

El injerto óseo es un procedimiento común realizado en ortopedia. Los injertos autólogos son seguros y siguen siendo un tratamiento estándar en el mundo[1]. El injerto de cresta ilíaca es la fuente ideal de injerto óseo autólogo[2]. Es un procedimiento que se asocia con pocas complicaciones; la frecuencia varía del 2% al 49%[3]. Las complicaciones asociadas van desde un simple dolor óseo hasta una hernia «deslizante», en especial cuando se toman injertos de espesor completo[4].

Caso clínico

Mujer de 79 años con antecedentes de hipertensión arterial, dislipidemia, síndrome miofascial cervical e intervenida de fractura de codo izquierdo con injerto monocortical de cresta ilíaca izquierda, tras lo que comienza con dolor en la cadera izquierda. La resonancia magnética informa hernia de pared lateral izquierda con salida de contenido mesentérico adyacente a la zona del injerto de cresta ilíaca (Fig. 1).

Se realiza una laparoscopia y se identifica una hernia de pared de 3 cm donde se tomó el injerto óseo (Fig. 2). Se coloca una malla de polipropileno titanizado de 4 × 4 cm en el espacio preperitoneal, fijada con *tackers* reabsorbibles (Fig. 3). La intervención duró 20 minutos y transcurrió sin incidentes. La paciente recibió el alta al día siguiente.

Discusión

En 1945, Oldfield describió por primera vez la hernia a través del defecto óseo de la cresta ilíaca[5]. Es una complicación muy rara. Algunos autores han descrito una incidencia del 5% y del 9%[6]. Es más frecuente en el sexo femenino, con un inicio de síntomas que oscila entre 24 días y 15 años después de la obtención del hueso[7]. El paciente suele presentar molestias en la zona del injerto. El contenido de estas hernias incisionales puede ser asas de intestino delgado o colon, y hay descrito un caso de herniación hepática[8]. El diagnóstico definitivo se puede hacer con una tomografía computarizada que muestre la hernia y su contenido[9].

No existe un tratamiento estándar para estas hernias. Se han publicado casos de reparaciones primarias, uso de colgajos de tejido y mallas, incluidos abordajes laparoscópicos, transabdominales y retroperitoneales[10].

Conclusiones

Las hernias ilíacas son raras y ocurren después de la extracción de un injerto óseo ilíaco. Es un hecho aceptado que una reparación de hernia exitosa requiere la colocación adecuada de una malla y su fijación apropiada. La fijación de la malla en la corrección de este tipo de hernias es técnicamente difícil. Estos defectos a menudo tienen poca o ninguna fascia para colocar la malla. Además, la retracción muscular y fascial no permite el cierre del defecto. La reparación laparoscópica requiere menos tiempo de cirugía y posibilita una recuperación más rápida y menos dolorosa.

Agradecimientos

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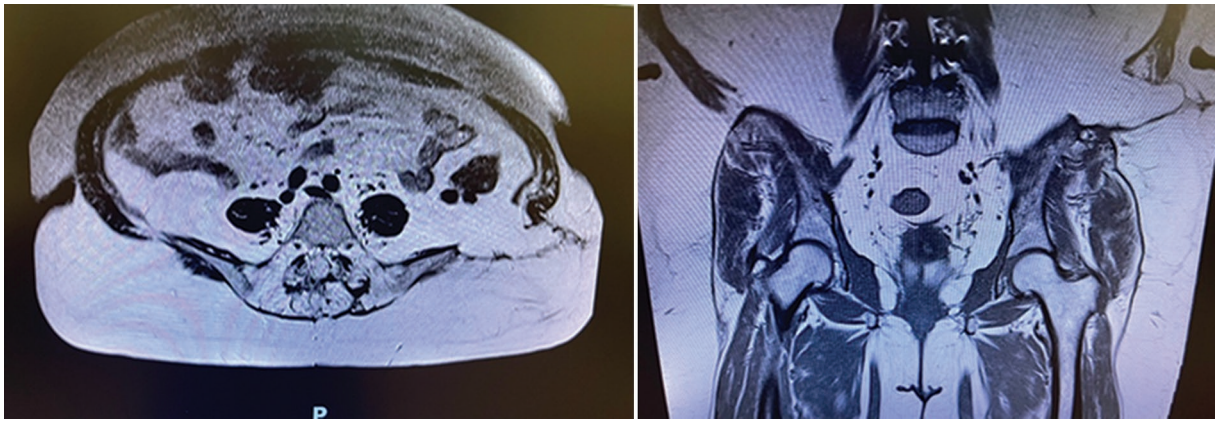


Figura 1. *Imágenes de resonancia magnética en la que se aprecia una hernia de pared lateral izquierda con salida de contenido mesentérico adyacente a la zona del injerto de cresta ilíaca.*

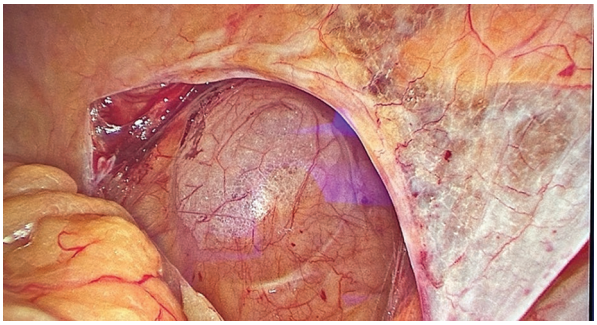
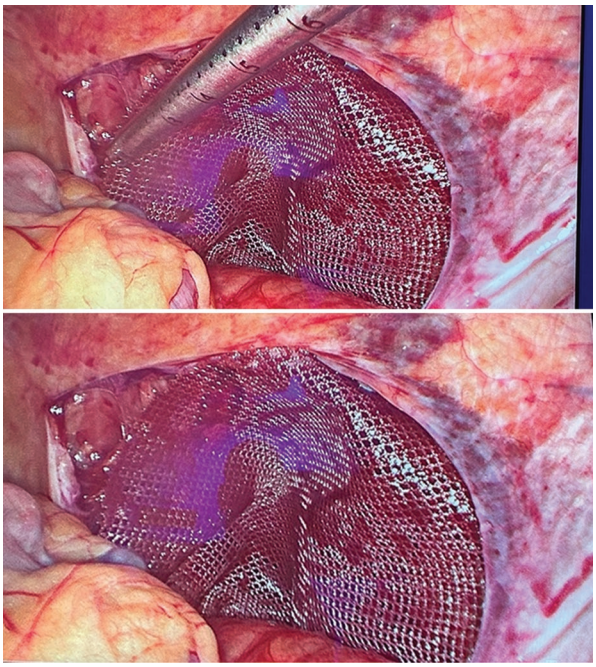


Figura 2. *Imagen de la intervención quirúrgica en la que se aprecia una hernia de pared abdominal de 3 cm donde se tomó el injerto óseo.*



Figuras 3. *Imágenes de la colocación de la malla de polipropileno titanizado de 4 × 4 cm en el espacio preperitoneal fijada con tackers reabsorbibles.*

Financiamiento

Los autores declaran no haber recibido financiamiento para este estudio.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

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Malrotación intestinal en el adulto, causa de oclusión intestinal. Reporte de caso

Intestinal malrotation in adults, cause of intestinal obstruction. Case report

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Resumen

La malrotación intestinal es una rotación incompleta del intestino primitivo alrededor del saco vitelino o la arteria mesentérica superior. Comúnmente es evidente en los primeros días de vida extrauterina o como hallazgo incidental en la etapa adulta con eventos recurrentes de oclusión intestinal. Presentamos un caso de malrotación intestinal en un adulto, el cual fue sometido a exploración quirúrgica abdominal urgente.

Palabras clave: *Malrotación. Oclusión intestinal. Abdomen agudo. Procedimiento de Ladd.*

Abstract

Intestinal malrotation refers to the incomplete rotation of the primitive intestine around the vitelline sac or superior mesenteric artery. It is frequently found on the first days of extrauterine life or in adult life, as an incidental finding or with obstructive symptoms. We present a case of intestinal obstruction due to intestinal malrotation in a male adult, who underwent urgent surgical abdominal exploration.

Keywords: *Malrotation. Intestinal obstruction. Acute abdomen. Ladd procedure.*

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Introducción

La malrotación intestinal es una entidad clínica caracterizada por una rotación incompleta o anómala durante el desarrollo embriológico del intestino primitivo. En pacientes pediátricos suele aparecer en los primeros días de vida en un 80% de los casos, en la vida adulta puede llegar a ser un hallazgo incidental durante algún estudio radiológico o causar síntomas obstructivos recurrentes. El diagnóstico se realiza con sospecha clínica y confirmación mediante estudios de imagen, el método de referencia es el tránsito intestinal con medio de contraste hidrosoluble. El tratamiento definitivo es quirúrgico y el procedimiento de Ladd es la técnica de elección; si es practicada en la infancia puede llegar a recurrir en la vida adulta, ameritando reintervención quirúrgica.

Reporte de caso

Presentamos el caso de un paciente de 29 años que acude al servicio de urgencias por presentar un cuadro clínico caracterizado por dolor abdominal intenso de 48 horas de evolución, generalizado, asociado a distensión abdominal y evacuaciones diarreicas en más de cinco ocasiones, así como náuseas y emesis de contenido gastroalimentario en cuatro ocasiones.

Como antecedentes de importancia, presentó dos eventos de oclusión intestinal previos en la infancia que fueron tratados quirúrgicamente. El primero de ellos a los 15 años, refiere el paciente, una laparotomía exploradora, donde se desconoce el procedimiento quirúrgico realizado y posteriormente a los 22 años fue reintervenido para lisis de adherencias.

A la exploración física con evidente distensión abdominal y dolor a la palpación media y profunda, peristalsis hipoactiva y percusión timpánica generalizada, se encuentra afebril, sin taquicardia y normotenso. Los estudios auxiliares de laboratorio sin alteraciones.

Al ingreso se inició la hidratación intravenosa con solución Hartmann y se decidió la colocación de sonda nasogástrica, con la cual se recolectaron 1,025 cc de contenido gastrointestinal, lo que condicionó mejoría parcial de los síntomas. Se realizó una tomografía computarizada (TC) de abdomen con contraste oral hidrosoluble e intravenoso, la cual reportó distensión de asas de íleon, así como sitio de transición en íleon distal, diámetro incrementado de aproximado de 40 mm con niveles hidroaéreos en el interior, a nivel de válvula ileocecal se identifica «signo de remolino» con inversión de la vena y arteria mesentérica superior (AMS) (Fig. 1), por lo que se decide su ingreso a quirófano para realización de laparotomía exploradora.

Se realiza incisión en línea media, evidenciando dilatación de asas intestinales sin datos de sufrimiento intestinal, con líquido y gas en el interior, con adherencias asa-asa y asa-pared, a nivel de la válvula ileocecal. Se encuentra vólvulo del mesenterio en sentido horario (Fig. 2), se liberan adherencias laxas con corte frío y fibrosas con energía monopolar, se exteriorizan las asas intestinales, se libera vólvulo y se decide la pexia del colon ascendente a la corredera parietocólica derecha, encontrando como hallazgo apendicectomía previa (Fig. 3), y se introducen asas intestinales de nuevo a la cavidad mediante la técnica de Noble. Se cierra la pared abdominal y se concluye la cirugía sin eventualidades.

Posteriormente se retira la sonda nasogástrica al 3.er día y se inicia vía oral con líquidos y hielo frappé, cursa posteriormente con íleo postquirúrgico, se decide colocación de catéter venoso central yugular derecho guiado por ultrasonido para inicio de nutrición parenteral total de aproximadamente 1,800 kcal. Al 7.º día de estancia intrahospitalaria se inician líquidos vía oral con adecuada tolerancia, se progresa dieta paulatinamente hasta lograr tolerancia de dieta normal. Es egresado asintomático al 10.º día postoperatorio.

Discusión

La malrotación intestinal se caracteriza por una anomalía en el desarrollo embriológico, donde la rotación del intestino primitivo es incompleta o aberrante alrededor de la arteria vitelina o AMS[1].

Los pacientes que presentan esta entidad inician los síntomas en los primeros meses de vida, con vómito biliar, dolor abdominal y en casos más graves con hematoquecia y peritonitis, llegando al diagnóstico durante el primer año de vida en un 75-85% de los casos[1].

Durante la rotación embriológica del intestino, si el asa cecocólica regresa al abdomen antes que el resto del intestino proximal, el colon ascendente carece de una adecuada fijación y el intestino medio ocupa su lugar del lado izquierdo, consecuentemente el duodeno desciende directamente a lo largo del trayecto de la AMS[2].

Cuando se presenta un paciente sintomático es recomendable iniciar el abordaje diagnóstico con radiografía simple de abdomen. En muchas ocasiones se identifica patrón radiográfico normal, algunos hallazgos sugerentes de malrotación incluyen asas

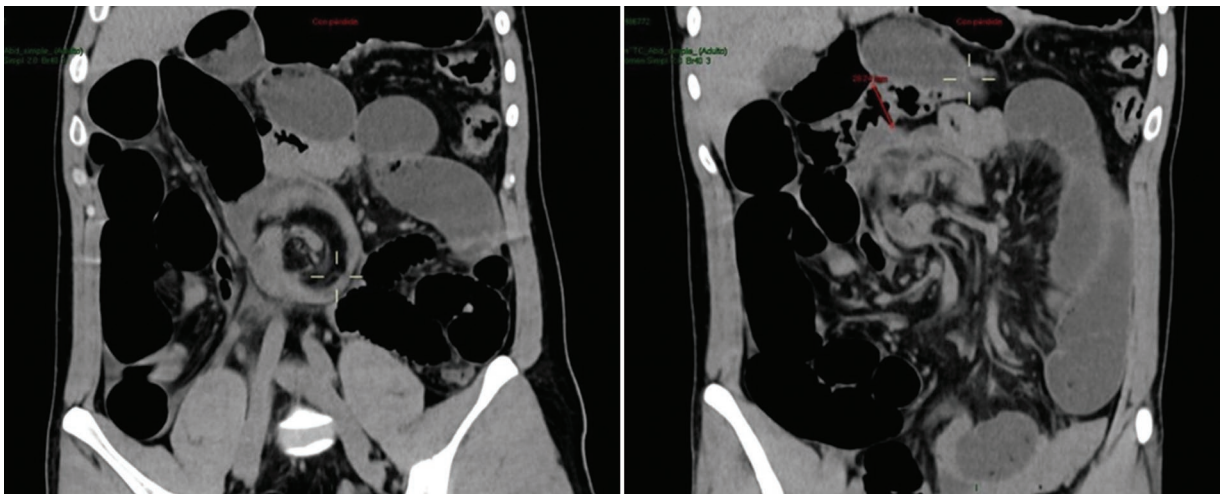

Figura 1. *Tomografía computarizada. Asas de íleon y colon ascendente dilatadas en hemiabdomen derecho y con ocupación líquida en hemiabdomen izquierdo, «signo del remolino» con inversión de arteria y vena mesentérica (flecha blanca).*

Figura 2. *Rotación mesentérica en sentido horario con posición anómala del ciego, localizado en hipocondrio derecho.*

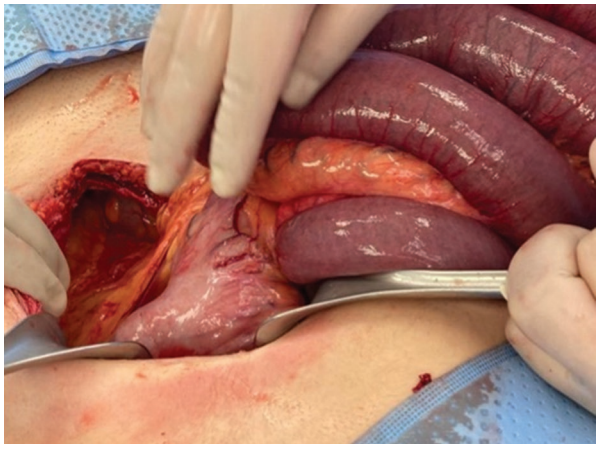

Figura 3. *Dilatación de asas intestinales, al realizar la exploración intestinal se observa posición anómala del duodeno, el cual discurre hacia fosa ilíaca derecha.*

yeyunales neumatizadas en hemiabdomen derecho y colon en hemiabdomen izquierdo[3].

La prueba diagnóstica de elección es el tránsito intestinal con contraste oral hidrosoluble, con sensibilidad del 96% para malrotación y 54% para vólvulo[4].

La malrotación intestinal puede presentar síntomas en la etapa adulta, con una incidencia aproximada del 0.2-0.5%. La rareza de presentación en la vida adulta hace que el diagnóstico sea incidental durante el abordaje de oclusión intestinal[1,3,5].

En el adulto es común el diagnóstico como hallazgo incidental durante la realización de TC o resonancia magnética[1,3].

El tratamiento en pacientes sintomáticos con hallazgo incidental de esta entidad aún es tema de discusión, existen alternativas conservadoras y quirúrgicas de las cuales se considera de elección el procedimiento de Ladd, que consta de cinco pasos secuenciales, comenzando por la disección de bandas de Ladd (fijaciones peritoneales anómalas del ciego a los distintos segmentos intestinales), destorsión del segmento intestinal malrotado, separación del mesenterio, reposicionamiento del intestino delgado y el ciego con pexia en el correcto sitio anatómico y apendicetomía[6].

Los pacientes sometidos a procedimiento de Ladd en la infancia son propensos a padecer episodios recurrentes de oclusión intestinal secundaria a vólvulos, por lo que es de vital importancia conocer este antecedente y evitar consecuencias letales[2,4].

Conclusión

En la vida adulta, la malrotación intestinal es un reto diagnóstico. La oclusión intestinal en el adulto es causada en su mayoría por adherencias, hernias internas o neoformaciones. El hecho de que esta entidad clínica sea casi exclusiva de la infancia provoca que en el paciente adulto el diagnóstico sea incidental. La sospecha diagnóstica inicia en el contexto de un paciente con cirugía abdominal en la infancia, de predominio en etapa neonatal, que posteriormente cursa con eventos repetitivos de oclusión intestinal.

El abordaje diagnóstico se encuentra bien definido, siendo los estudios radiológicos el pilar del descubrimiento de esta patología. Durante el tratamiento quirúrgico los hallazgos transoperatorios son vitales en la toma de decisiones, el procedimiento de Ladd se considera el tratamiento definitivo, pero puede estar sujeto a modificaciones durante esta toma de decisiones. Ante un abdomen reintervenido o como en nuestro caso, con dos antecedentes quirúrgicos de cirugía abdominal previa, se realizó una modificación, realizando pexia del ciego a la corredera parietocólica derecha, respetando los pasos anteriores en la descripción de la técnica original.

El seguimiento posquirúrgico del paciente juega un papel fundamental, debido a la posibilidad de cursar con íleo posquirúrgico, ameritando nutrición parenteral y así garantizar el adecuado estado metabólico general. A pesar de ser un reto diagnóstico y terapéutico, en manos expertas el paciente puede cursar con adecuada calidad de vida.

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Consideraciones éticas

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Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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CARTA AL EDITOR

Detección clínica y descripción de las características sociodemográficas de la variante SARS-CoV-2 ómicron en población de la Sierra Sur de Oaxaca

Clinical detection and description of the socio-demographic characteristics of the SARS-CoV-2 omicron variant in the population of the Sierra Sur of Oaxaca

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Señor Editor:

Ómicron es una variante preocupante del SARS-CoV-2 que tiene un curso clínico leve[1,2]. Presentamos un estudio transversal en 628 pacientes con infección por la variante ómicron, diagnosticados por RTq-PCR *(real time quantitative polymerase chain reaction)* multiplex con sondas Taqman específicas de clado, enrolados de enero a abril de 2022, originarios de la Sierra Sur de Oaxaca (Tabla 1). El 100% presentaban cefalea vascular, tos seca, artralgias, mialgias, astenia, adinamia y congestión nasal. El 80% tenían diarrea de 1 o 2 días, el 98% presentaban fiebre solo de cabeza y cuello con saturación del 92-95%, el 28% presentaban parestesias en miembros superiores e inferiores, acompañadas de hormigueo y sensación de ardor, y el 12% presentaron vómito durante 1 o 2 días o en los primeros 5 días de inicio. Como hallazgos no descritos, el 80% tenían una vasculitis en todo el paladar. El paladar anterior se encontró de coloración salmón o rosa pálido (Fig. 1), y el posterior de color violáceo con un enantema vesicular difuso. En el 10.03% había petequias en la orofaringe acompañadas de enantema vesicular difuso en el arco faríngeo y la base de la lengua. En el 10.03% se observó un paladar y una orofaringe exudativa ulcerativa con petequias en la cavidad oral. Se detectaron tres fenotipos: uno leve, similar a un cuadro gripal (linajes BA.2 y BA.2.12.1), en el 20.06%; otro moderado, con macroangiopatía (linajes BA.2.12 y BA.2.9), en el 60.01%; y otro grave (linajes DeltaAY.4/ÓmicronBA.1 [deltacron], BA.5, BA.4 y BA.1), con daño microangiopático (neuropatía periférica, nefropatía e insuficiencia venosa) y macroangiopático (telangiectasias oculares), en el 19.90%. La variante deltracron fue exclusiva del grupo de 11-68 años de edad. El 79.93% respondieron al protocolo con OM-85 1 cada 12 h por 21 días, dobesilato de calcio 500 mg cada 12 h por 2 meses, ibuprofeno 800 mg cada 12 h por 10 días y dexametasona intramuscular 8 mg en dosis única. Solo el 20.03% requirieron antihistamínicos, cefalosporina con bromhexina, por tener agregada una infección bacteriana. En los diabéticos se usaron hipoglucemiantes orales.

Este es el primer estudio que muestra las características clínicas de las variantes ómicron del SARS-CoV-2.

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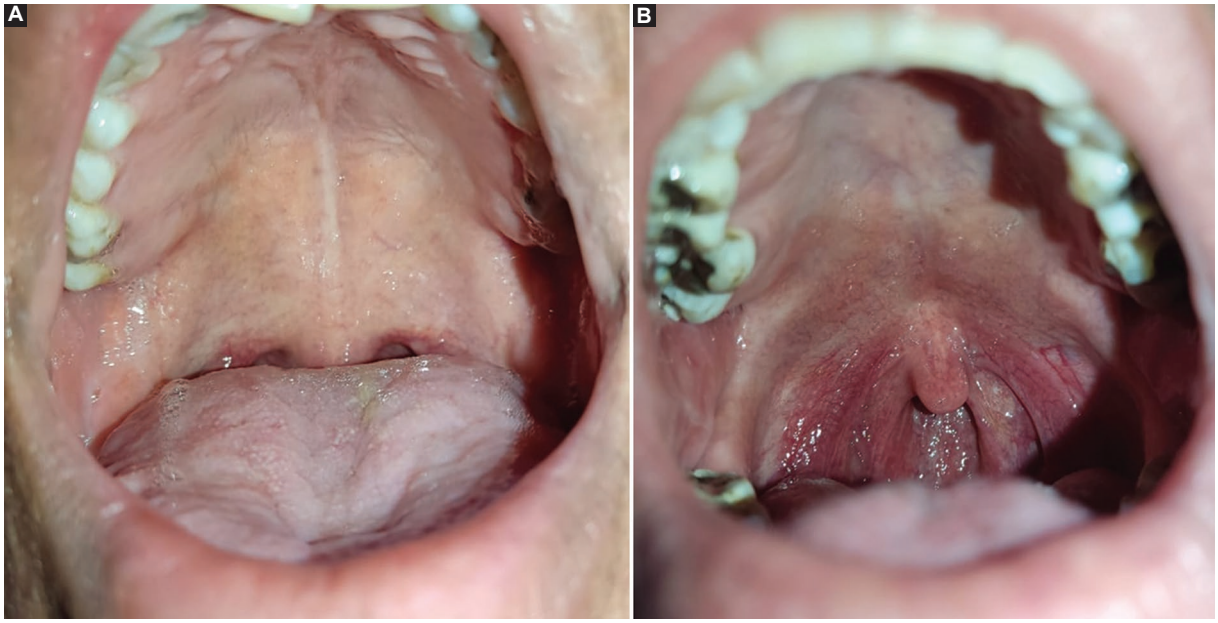

Figura 1. A: *proliferación vascular en el paladar posterior, con una coloración salmón con enantema vesicular.* **B:** *el velo del paladar posterior tiene un color violáceo, acompañado de un enantema vesicular palatofaríngeo difuso muy característico de los pacientes diabéticos con ómicron.*

Tabla 1. Variables sociodemográficas y clínicas de la variante SARS-CoV-2 ómicron en población de la Sierra Sur de Oaxaca

Variables sociodemográficas y clínicas	Porcentaje	Número de sujetos
Edad		
0-10 años	10.98%	69/628
11-68 años	89.02%	559/628
Sexo		
Hombre	23.89%	150/628
Mujer	76.11%	478/628
Vivienda		
Rural	79.94%	502/628
Urbana	20.06%	126/628
Vacunados contra SARS-CoV-2	96.97%	609/628
Escolaridad		
Sin estudio	2.07%	13/628
Jardín de niños	9.87%	62/628
Primaria	46.97%	295/628
Secundaria	17.03%	107/628
Bachillerato	24.04%	151/628
Educación superior	0%	0/628
Hospitalizados	0%	0/628
Manejo ambulatorio	100.00%	628/628
Comorbilidad		
Obesidad	2.07%	13/628
Diabetes mellitus de tipo 2	46.97%	295/628
Hipertensión arterial sistémica	17.04%	107/628
Asma y problemas alérgicos	24.04%	151/628

Se destaca que se puede detectar clínicamente con una exploración de la cavidad oral y que sus subvariantes no son benignas, ya que los pacientes presentan daño microangiopático y macroangiopático.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki. Los procedimientos fueron autorizados por el Comité de Ética de la institución.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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Comment on SARS-CoV-2 genome and spike protein, COVID-19, and efficacy of vaccines

Comentario sobre el genoma y la proteína de la espiga del SARS-CoV-2, COVID-19 y la eficacia de las vacunas

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Dear Editor:

We would like to share ideas on the publication "Importance of the SARS-CoV-2 genome and spike protein in the immunopathogenesis of COVID-19 and in the efficacy of vaccines[1]". The SARS-CoV-2 pandemic is currently a significant global health issue, according to Jiménez-Morales et al.[1]. According to Jiménez-Morales et al. suggest that the virus's ability to propagate, escape the immune system, and reduce antibody neutralization is due to many mutations in the receptor binding domain (RBD). According to Jiménez-Morales et al., recent research indicates that individuals who have already contracted one variant or subvariant will have a significant likelihood of reacquiring that variant[1]. This highlights the importance of developing new vaccines and completely immunizing the global populace.

A number of factors need to be taken into account to fully understand the results. It is impossible to make a connection between asymptomatic COVID-19 and the absence of symptoms without the required laboratory tests. Without extensive laboratory testing, asymptomatic COVID-19 and the lack of clinical symptoms could be incorrectly diagnosed. A silent COVID-19 must be ruled out if neither the most recent clinical signals nor the most recent clinical markers are present[2]. In addition, genetic variations seem to affect how a particular person's immune system responds to COVID-19[3]. Before the results can be confirmed, more clinical study will be needed.

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The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CARTA AL EDITOR

Factores asociados a la calidad de vida en los pacientes con diabetes tipo 2

Associated factors with poor quality of life in patients with type 2 diabetes

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Sr. Editor:

En el artículo de Velázquez-López et al.[1] se han estudiado varios factores en pacientes con diabetes tipo 2 (DM2) para evaluar su calidad de vida, como el control glucémico, el perfil lipídico, el ejercicio, la presión arterial y más. Sin embargo se considera que faltan otros factores importantes que también podrían influir en este contexto médico.

La intervención en factores modificables como la dieta, los niveles de triglicéridos y colesterol, la terapia farmacológica y la adherencia a programas preventivos puede mejorar el control de pacientes en atención primaria; especialmente en hombres menores de 65 años con más de cinco años de evolución de DM2. La inclusión de estas variables puede mejorar el entendimiento de los factores relacionados con la calidad de vida en estos pacientes[2].

Entre otras comorbilidades, Carrillo-Larco y Bernabé-Ortiz[3] resaltaron la importancia de describir la interacción de la DM2 con otras enfermedades infectocontagiosas que son un problema en Sudamérica. Por ello, se debe prestar atención a la relación de la DM2 con tuberculosis o malaria, pues no está bien estudiado el impacto de la interacción de estas patologías sobre la calidad de vida de los pacientes.

Es entendible que no siempre es posible recolectar todos los datos necesarios en una investigación, por ello sugerimos que para próximas investigaciones se puedan considerar estas variables para mejorar el entendimiento de los aspectos relacionados con la calidad de vida en pacientes con DM.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Consideraciones 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, consentimiento informado y aprobación ética. El estudio no involucra datos personales de pacientes ni requiere aprobación ética. No se aplican las guías SAGER.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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