

Procalcitonin and C-reactive protein as predictive biomarkers of anastomotic leak in colorectal surgery

Procalcitonina y proteína C reactiva séricas como biomarcadores predictivos de dehiscencia de anastomosis intestinal en cirugía colorrectal

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Abstract

Background: There has been recent interest in the seric levels of procalcitonin (PCT) and C reactive protein (PCR) as a marker of intraabdominal infection after a colorectal surgery, however, the actual literature remains inconclusive. **Objective:** To test if C-Reactive Protein (PCR) and procalcitonin (PCT) as predictive factors of anastomotic leak after colorectal surgery. **Method:** Retrospective cohort, of patients with ileostomy or colostomy who had intestinal transit restitution by general surgeons in our center, from march 2018 to march 2020. **Results:** We registered 4 (36.4%) anastomotic leaks. We compared median PCR and PCT between group 1 (without anastomotic leak) and group 2 (with anastomotic leak). Median PCT3PO was 4.86 ng/ml in group 1 vs 13.7 ng/ml in group 2, and PCT5PO was 1.3071 ng/ml vs 6.74 ng/ml (DS: 5.04 vs. 11.53 and 0.779 vs. 10.44). Median PCR3PO and PCR5PO was 194.7 mg/l in group 1 vs 100.97 mg/l in group 2, and 159.8 mg/l vs 65.67 mg/l, (DS: 88.78 vs. 82.01 and 94.77 vs. 58.009). **Conclusions:** Persistent higher levels of seric PCR and PCT at 3rd and 5th postoperative day could be an anastomotic leakage. This biomarkers might be added as additional criteria of discharge.

Keywords: Anastomotick leak. Procalcitonin. C-reactive protein. Positive predictive value.

Resumen

Antecedentes: La medición sérica de procalcitonina (PCT) y proteína C reactiva (PCR) como marcadores de infección intraabdominal posterior a la cirugía colorrectal ha tomado interés en los recientes años, sin embargo, la literatura que existe en la actualidad no es concluyente. **Objetivo:** Evaluar los biomarcadores séricos de inflamación procalcitonina (PCT) y proteína C reactiva (PCR) como factores predictores para dehiscencia de anastomosis (DA) en cirugía colorrectal. **Método:** Cohorte retrospectiva de pacientes con cirugía abdominal, con ileostomía o colostomía, que fueron protocolizados para restitución del tránsito intestinal por el departamento de cirugía general en un hospital de tercer nivel, de marzo de 2018 a marzo de 2020. **Resultados:** La DA ocurrió en 4 (36.4%) de 11 pacientes. Se comparó la media de dos grupos: el grupo 1 sin DA frente al grupo 2 que presentaron DA. Las concentraciones séricas de PCT3PO fueron de 4.86 ng/ml en el grupo 1 y 13.7 ng/ml en el grupo 2, y las de PCT5PO fueron de 1.3071 ng/ml y 6.74 ng/ml, respectivamente (desviación estándar [DE]: 5.04 vs. 11.53 and 0.779 vs. 10.44). Las concentraciones séricas de PCR3PO fueron de 194.7 mg/l en el grupo 1 y 100.97 mg/l en el grupo 2, y las de PCR5PO fueron de 159.8 mg/l y 65.67 mg/l, respectivamente (DE: 88.78 vs. 82.01 and 94.77 vs. 58.009).

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Conclusiones: La persistencia de valores elevados de PCR y PCT séricas al tercer y quinto día posoperatorios pudieran demostrar DA. Estos marcadores podrían agregarse como criterio de egreso.

Palabras clave: Dehiscencia de anastomosis. Procalcitonina. Proteína C reactiva. Valor predictivo positivo.

Introduction

Anastomotic leak is the most feared complication after colorectal surgery, associated with an increase in mortality and length of hospital stay¹. It alters functional results and becomes a local recurrence factor in colorectal tumor cases², as it is considered a major postoperative complication with the highest severity of all complications³, with an occurrence ranging between 3% and 27%, depending on specific risk factors⁴. While the best approach is prevention, timely management after the leak occurs is considered the best way to decrease the severity of complications. The majority of infections associated with the re-installation of the intestinal tract are clinically evident between days four and six after surgery⁵. In some cases, the presentation is subtle, which can lead to delayed diagnosis⁶.

The purpose of this study is to test C-Reactive Protein (PCR) and procalcitonin (PCT) as predictive factors of anastomotic leak after colorectal surgery.

Method

The study was comprised of a retrospective cohort of patients admitted to the general surgery service, referred by any third-level service or any second-level care unit, with abdominal surgery and ileostomy or colostomy, who were registered for a restoration of the intestinal tract in a third-level hospital, within a hospitalization range between March 2018 and March 2020. The inclusion criteria were patients over 18 years of age, beneficiaries of the institution, with a variable etiology colostomy diagnosis and no active oncological abdominal condition, who had undergone intestinal tract restoration surgery in the same hospital. The non-inclusion criteria were patients under 18 years of age with chronic kidney disease in hemodialysis or with diabetes *mellitus* with poor treatment management (HbA1c > 7%), as well as loss of monitoring by the researcher. Both physical and electronic records were reviewed. The mean or median values as a central tendency were used, and the standard deviation (SD), as well as minimum and maximum values were employed as measure of dispersion.

Continuous variables were analyzed with the Student's t test or Wilcoxon test, depending on the parametric or non-parametric distribution of data. A $p \leq 0.05$ variable was considered statistically significant. The sensitivity and specificity of PCT and PCR for intestinal anastomosis dehiscence were determined, and the statistical significance and cut-off point were obtained through the ROC (*Receiver Operating Characteristic*), as well as the positive and negative predictive values.

Results

The study included 11 patients who underwent colorectal surgery between March 1, 2018 and March 1, 2020. The distribution by gender was 2 females (18.2%) and 9 males (81.8%). The average age of patients was 47.45 years (SD: 13.49), with a minimum of 21 years and a maximum of 63 years. Five patients (45.5%) underwent ileocolic anastomosis, and six patients (54.5%), colorectal anastomosis. Trans-surgical bleeding occurred at an average of 300 ml (SD: 228.035) with a minimum of 50 ml and a maximum of 750 ml. Concomitant conditions found in patients were systemic arterial hypertension in 4 (27.3%), diabetes *mellitus* under control in 1 (9.1%), systemic arterial hypertension and diabetes *mellitus* in 1 (9.1%), and previously healthy, 6 (54.5%). Anastomotic dehiscence was defined as a complication and it was present in 4 (36.4%) patients, and 7 patients did not develop said complication (63.6%). The average hospital stay length was 11.64 days (SD: 5.573), with a minimum of 5 days and a maximum of 20 days. Oral diet began at an average of 4.36 days (SD: 2.461), with a minimum of 2 days and a maximum of 10 days (Table 1).

The mean PCR and PCT before the surgical procedure and three and five days after surgery was analyzed. The results are shown on table 2.

The preoperative PCR and PCT values were evaluated, as well as those obtained three and five days after surgery, between patients with no anastomosis dehiscence (group 1) and those with it (group 2), and it was found that, in group 1, the average values for preoperative PCT was 0.614 ng/ml versus 0.055 ng/ml in group 2 (SD: 1.35 vs. 0.1; $p = 0.381$). The mean values for the

Table 1. Results for the mean, standard deviation, and minimum and maximum values of the age, trans-surgical bleeding, days of hospitalization, and days to beginning of oral diet variables for the total number of patients

	Age (years)	Trans-surgical bleeding (ml)	Days of hospitalization	Days to beginning of oral diet
Mean	47.45	300	11.64	4.36
Standard deviation	13.493	228.035	5.573	2.461
Minimum	21	50	5	2
Maximum	63	750	20	10

Table 2. Results for the mean, standard deviation, and minimum and maximum values of the age, trans-surgical bleeding, days of hospitalization, and days to beginning of oral diet variables for the total number of patients

Variable	Group 1 (n = 7)	Group 2 (n = 4)	p
Age	42.8 (SD: 4.34)	55.5 (SD: 7.724)	0.142
Trans-surgical bleeding	250 ml (SD: 180.27)	387.5 ml (SD: 303.795)	0.566
Preoperative PCT	0.614 ng/ml (SD: 1.35)	0.055 ng/ml (SD: 0.1)	0.381
PCT on 3 rd day	4.86 ng/ml (SD: 5.04)	13.7 ng/ml (SD: 11.53)	0.089
PCT on 5 th day	1.3071 ng/ml (SD: 0.779)	6.74 ng/ml (SD: 10.44)	0.257
Preoperative PCR	17.9 mg/dl (SD: 37.54)	13.35 mg/l (SD: 16.58)	0.680
PCT on 3 rd day	194.7 mg/l (SD: 88.78)	100.97 mg/l (SD: 82.01)	0.059
PCR on 5 th day	159.8 mg/l (SD: 94.77)	65.67 mg/l (SD: 58.009)	0.131
Start of oral diet	4 days (SD: 2)	5 days (SD: 3.367)	0.561
Days of hospital stay	10.14 days (SD: 4.741)	14.25 days (SD: 6.65)	0.154

SD: standard deviation; PCR: C-reactive protein; PCT: procalcitonin.

PCT determination values three and five days after surgery were 4.86 ng/ml in group 1, and 13.7 ng/ml in group 2, and 1.3071 ng/ml and 6.74 ng/ml, respectively (SD: 5.04 vs. 11.53 and 0.779 vs. 10.44; $p = 0.089$ and $p = 0.257$, respectively).

The mean values of preoperative PCR for group 1 were 17.9 mg/l versus 13.35 mg/l for group 2 (SD: 37.54 vs. 16.58; $p = 0.680$). The mean values for the PCR determinations three and five days after surgery

were 194.7 mg/l for group 1, and 100.97 mg/l for group 2, and 159.8 mg/l and 65.67 mg/l, respectively (SD: 88.78 vs. 82.01 and 94.77 vs. 58.009; $p = 0.059$ and $p = 0.131$, respectively).

The average age of patients in group 1 was 42.8 years, and 55.5 years in group 2 (SD: 4.34 vs. 7.724; $p = 0.142$). The mean trans-surgical bleeding value for group 1 was 250 ml versus 387.5 ml for group 2 (SD: 180.27 vs. 303.795; $p = 0.566$). Oral diet was started on average after 4 days in group 1 versus 5 days in group 2 (SD: 2 vs. 3.367; $p = 0.561$). Average hospital stay length was 10.14 days for group 1 and 14.25 days for group 2 (SD: 4.741 vs. 6.65; $p = 0.154$).

The sensitivity and specificity of PCT and PCR for anastomotic dehiscence three days after surgery were 75% and 72%, respectively, when values exceeded 4.18 ng/dl, as shown in figure 1.

The sensitivity and specificity of PCT five days after surgery for anastomotic dehiscence were 75% and 86%, respectively, when the values exceeded 1.73 ng/dl, as shown in figure 2.

The sensitivity and specificity of PCR three days after surgery for anastomotic dehiscence were 50% and 30%, respectively, when the values exceeded 3.26 mg/l.

The sensitivity and specificity of PCR five days after surgery for anastomotic dehiscence were 75% and 15%, respectively, when the values exceeded 30.75 mg/l.

Discussion

This study compares preoperative PCR and PCT value with those obtained three and five days after surgery. The diagnostic usefulness of PCR after colorectal surgery has been established by other authors. Depending on the methodology of each study, PCR serum concentrations on day three or four are the most accurate⁷. A value over 12.5 mg/dl of serum

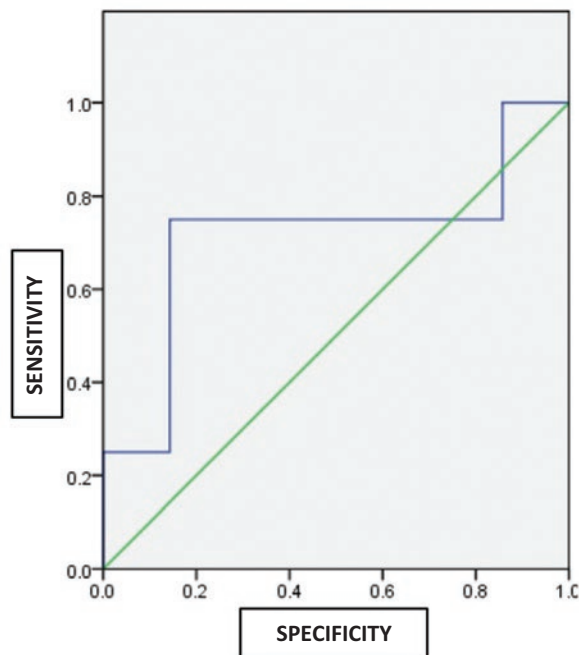


Figure 1. ROC curve showing the sensitivity and specificity of procalcitonin three days after surgery.

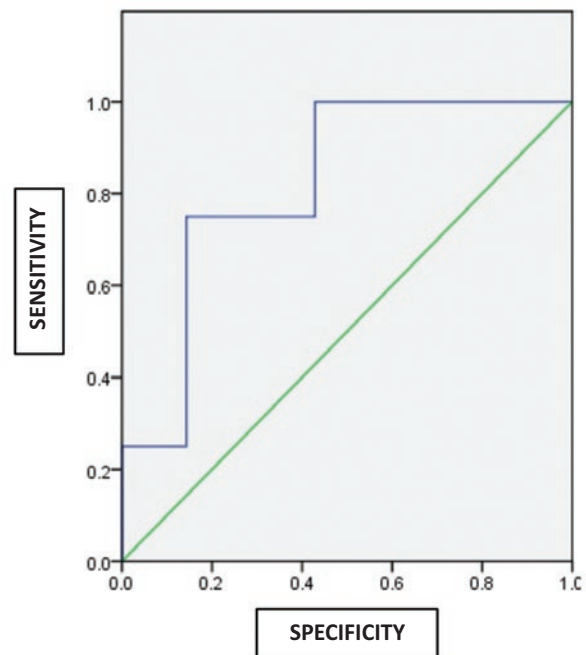


Figure 2. ROC curve showing the sensitivity and specificity of procalcitonin five days after surgery.

PCR is considered to be highly likely to present septic complications⁸. Welsch et al.⁹ concluded that serum PCR was sensitive, but not a specific biological marker for infectious complications. Pedersen et al.¹⁰ reported that serum PCR values over 200 mg/l three days after surgery suggested further evaluation, as they were not sufficient for diagnosis. Almeida et al.¹¹ showed that a serum PCR value above 140 mg/l three days after surgery could be predictive of anastomotic dehiscence when other infectious sources have been ruled out. Ortega-Deballon et al.⁷ concluded that, with serum PCR values below 125 mg/l four days after surgery, it is safe to discharge the patient.

It has been shown that PCT is a biological marker for bacterial sepsis, and it is useful for early infection detection during pancreatitis or after surgery, and it is a prognosis factor in patients with secondary peritonitis. Despite the fact that PCT is a reliable predictor for systemic inflammatory response syndrome during the first 24 hours after colorectal surgery, its usefulness as anastomotic dehiscence marker after colorectal surgery has not been studied¹². Chromik et al.¹³ conducted a randomized prospective study with 20 patients with PCT levels above 0.15 mg/dl after colorectal surgery, who were randomized in a group that received antibiotics or another group that did not receive them.

Patients who received antibiotics had less infectious complications, but they were not specific for anastomotic dehiscence. Lagoutte et al.¹⁴ determined PCT kinetics with anastomotic dehiscence compared to the reports for serum PCR. They determined that PCT measurement does not seem to be more sensitive or earlier than PCR when diagnosis anastomotic dehiscence, and furthermore, when cases of anastomotic dehiscence were individually analyzed, a higher PCT peak occurred in less than half of the patients, while the majority showed PCT values similar to those who did not have said complication. García-Granero et al.¹⁵ observed that serum PCT increased in all patients on day 1 after surgery, with a trend towards normalization on day 4 after surgery or in patients that did not show complications, in contrast with a statistically significant increase in PCT serum in patients with higher anastomotic dehiscence on days 3 and 5 after surgery, concluding that serum PCT was better than serum PCR for higher rates of early detection of anastomotic dehiscence, observing a similar trend in this study, as serum PCT on days three and five showed greater sensitivity and specificity for early anastomotic dehiscence compared to PCR. The percentage of anastomotic dehiscence observed in this study (36.4%) is higher than what has been reported in the literature (13%)¹⁵. However, this may be explained by the reduced sample of

patients and by the fact that the majority of them, seen in a third-level referral hospital, has multiple comorbidities or prior surgeries, which in some cases were associated with abdominal sepsis. The mortality in this study was 0%; however, one patient with high serum PCR on day five, and with no anastomotic dehiscence passed away on day 11 after surgery from a myocardial infarction. No connection has been proven between high serum PCR and coronary disease.

Conclusions

Intestinal anastomotic dehiscence in colorectal surgery is still one of the most frequent and feared complications, both for surgeons and patients, as it requires a multiple discipline approach and long hospital stays, with high costs and poor quality of life, and for this reason, timely, reliable, and accessible diagnostic methods are needed to detect and manage these complications. In this study, despite not finding a statistically significant difference, the serum PCR and PCT values on days three and five after surgery appear to remain elevated in patients who developed anastomotic dehiscence. Studies with larger samples are still required to confirm or rule out the use of PCR and PCT as predictors of anastomotic dehiscence.

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As this is a referral hospital for at least four states of the Republic, it has a large number of patients with these pathologies, and it also has the experience of healthcare professionals who perform these surgical procedures. Hospital de Especialidades has 24-hour laboratory services, which allows testing at any time, and it also has the necessary materials to test such biomarkers, including gloves, syringes, sample tubes, etc., as well as qualified nurses and physicians who can perform those tests.

Conflicts of interest

The researchers and authors of this work state that they do not have conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors state that the procedures followed the ethical guidelines of the responsible human experimentation committee and were performed according to the World Medical Association and the Declaration of Helsinki.

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

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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