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ORIGINAL ARTICLE

C-reactive protein and its progression over time for the detection of anastomotic leaks

Proteína C reactiva y su progresión en el tiempo para la detección de las fugas anastomóticas

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Abstract

Introduction. Anastomotic leaks are a common and critical complication in gastrointestinal surgery. Their identification and early treatment are necessary to avoid adverse results, and conventional use with a cutoff value of C-reactive protein has shown limited utility. The objective of this study was to determine the usefulness of serial measurement of C-reactive protein in the detection of anastomotic leaks.

Methods. Prospective review of a retrospective database of patients undergoing major abdominal surgery with at least one intestinal anastomosis. C-reactive protein was measured on the third and fifth postoperative days. Complications were classified according to the Clavien-Dindo classification. Diagnostic accuracy was evaluated by the area under the curve.

Results. 157 patients were included. The average age was 63.7 years, 47% were male. The largest number of surgeries corresponded to gastrectomies (36.3%), anterior resection of the rectum (15.3%) and right hemicolectomies (13.4%). 25.5% had some postoperative complication and 32.5% (n=13) had anastomosis leaks. The increase in C-reactive protein had an area under the curve of 0.918 with an increase cut-off point of 1.3 mg/L, sensitivity of 92.3% (CI 78-100) and specificity of 92.4%. (CI 88-96).

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Conclusions. The 1.3 mg/L increase in C-reactive protein between the day of surgery and the fifth day was an accurate predictor of anastomotic leaks in patients with major abdominal surgery.

Keywords: C-reactive protein; surgical anastomosis; digestive system surgical procedures; gastrectomy; postoperative complications; anastomotic leak; clinical evolution.

Resumen

Introducción. Las fugas anastomóticas son una complicación común y crítica en cirugía gastrointestinal, por lo que su identificación y tratamiento temprano son necesarios para evitar resultados adversos. El uso convencional con un valor límite de la proteína C reactiva ha demostrado una utilidad limitada. El objetivo de este estudio fue determinar la utilidad de la medición seriada de la proteína C reactiva en la detección de fugas anastomóticas.

Métodos. Revisión prospectiva de base de datos retrospectiva de pacientes sometidos a cirugía abdominal mayor con al menos una anastomosis intestinal. Se midió la proteína C reactiva al tercer y quinto día posoperatorio. Las complicaciones se categorizaron según la clasificación de Clavien-Dindo. La precisión diagnóstica fue evaluada por el área bajo la curva.

Resultados. Se incluyeron 157 pacientes, el 52 % mujeres. La edad promedio fue de 63,7 años. El mayor número de cirugías correspondió a gastrectomía (36,3 %), resección anterior de recto (15,3 %) y hemicolectomía derecha (13,4 %). El 25,5 % tuvieron alguna complicación postoperatoria y el 32,5 % (n=13) presentaron fuga en la anastomosis. El aumento de la proteína C reactiva tuvo un área bajo la curva de 0,918 con un punto de corte de aumento en 1,3 mg/L, sensibilidad de 92,3 % ($IC_{95\%}$ 78- 100) y una especificidad de 92,4 % ($IC_{95\%}$ 88 – 96).

Conclusiones. El aumento de 1,3 mg/L en la proteína C reactiva entre el día de la cirugía y el quinto día fue un predictor preciso de fugas anastomóticas en pacientes con cirugía abdominal mayor.

Palabras clave: proteína C-reactiva; anastomosis quirúrgica; procedimientos quirúrgicos del sistema digestivo; gastrectomía; complicaciones posoperatorias; fuga anastomótica; evolución clínica.

Introduction

Anastomotic leaks (AL) are a common and severe complication in surgery of the digestive tract. Reinterventions and the additional support required for their treatment cause a prolonged hospital stay and high morbidity and mortality, especially in cancer patients [1-5]. The need to leave ostomies also affects quality of life [6].

According to the world literature, the incidence of AL varies from 0.6-17.4%; in Colombia it is estimated to be 10.8%, being generally diagnosed on the seventh postoperative day [7-11]. AL is defined as the presence of clinical signs of peritonitis, evidence of free intestinal content within the abdomen or exiting it through a drain, due to loss of continuity of the suture line of an intestinal anastomosis, which may occur from a few days after the surgical procedure to several weeks later [1,4,12].

For its early diagnosis, multiple clinical, imaging, endoscopic methods and the use of biomarkers have been proposed, with limited utility. Since C-reactive protein (CRP) can reflect the presence and severity of an inflammatory process, it has been used in the evaluation of postoperative complications with variable cut-off values [13-17]. The objective of this study was to determine the usefulness of serial measurement of C-reactive protein in the early detection of anastomotic leaks.

Methods

Prospective review of a retrospective database of patients who underwent major abdominal surgery with at least one intestinal anastomosis, operated between November 2018 and August 2022 at Liga contra el Cáncer Seccional Risaralda, Pereira, Colombia. CRP was evaluated on

the third and fifth postoperative day in patients who, in the opinion of the treating surgeon, did not present an adequate evolution. The inclusion criteria were patients older than 18 years, undergoing major abdominal surgery with at least one intestinal anastomosis, and PCR taking on 3 and 5 days postoperatively. Patients with incomplete clinical history and without intestinal anastomoses were excluded.

The clinical and sociodemographic variables of age, sex, diagnosis, surgical procedure, presence of complications and their management were analyzed. Serum PCR was measured on days 3 and 5 after surgery. Delta (Δ) was defined as the difference between the PCR concentration on the fifth and third day. Complications were categorized according to the Clavien-Dindo classification. The diagnostic accuracy of the PCR delta was evaluated by the area under the curve.

Statistical analysis was performed using SPSS version 19 (Copyright© SPSS Inc., 2000). The data was collected in an Excel spreadsheet. Quantitative data were presented as mean and standard deviation (SD). Proportions were compared using the c2 test or Fisher's exact test where appropriate. Student's t test was used to compare normal distribution variables. A level of 5% was established as a criterion of statistical significance. Diagnostic accuracy was evaluated with the area under the ROC (receiver operating characteristic) curve.

Results

One-hundred-fifty-seven patients undergoing major abdominal surgery with at least one intestinal anastomosis were included. The average age was 63.7 years, with a range between 30 and 89 years; 47% were men and 52% women. The most frequent diagnoses were gastric cancer (39.6%) and colon cancer (30.7%) (Table 1). The most frequent surgical procedures were total gastrectomy (18.5%), subtotal gastrectomy (15.9%), anterior resection of the rectum (15.3%), and right hemicolectomy (13.4%) (Table 2).

Out of those, 25.5% of the patients (n=40) had some type of postoperative complication, the most frequent being grade I (32.5%) according

Table 1. Diagnoses in the patients included in the study (n=157).

Diagnosis	Frequency (%)
Stomach cancer	62 (39.6)
Colon cancer	48 (30.7)
Rectal cancer	26 (16.6)
Diverticular disease	9 (5.7)
Gastroesophageal junction cancer	4 (2.5)
Esophagus cancer	3 (1.9)
Jejunal cancer	1 (0.6)
Familial adenomatous polyposis	1 (0.6)
Bladder cancer	1 (0.6)
Cervical cancer	1 (0.6)
Open abdomen sequelae	1 (0.6)

Table 2. Procedures performed on the patients included in the study (n=157).

Surgical procedures performed	Frequency (%)
Ostomy closure	12 (7.6)
Total colectomy	1 (0.6)
Degastro-gastrectomy	5 (3.2)
Abdominal demolition	2 (1.3)
Internal bypass	8 (5.1)
Esophagectomy	2 (1.3)
Esophago-gastrectomy	2 (1.3)
Pelvic exenteration	2 (1.3)
Subtotal gastrectomy	25 (15.9)
Total gastrectomy	29 (18.5)
Total gastrectomy distal esophagectomy	3 (1.9)
Right hemicolectomy	21 (13.4)
Left hemicolectomy	5 (3.2)
Anterior resection of the rectum	24 (15.3)
Multi-visceral resection	4 (2.5)
Sigmoidectomy	10 (6.4)
Sigmoidectomy and colo-vesical fistula correction	2 (1.3)

Table 3. Complications presented according to the Clavien-Dindo classification.

Clavien–Dindo classification	Frequency (%)
I	13 (32.5)
II	1 (2.5)
IIIA	2 (5)
IIIB	11(27.5)
IVA	7 (17.5)
IVB	6 (15)
Type of complication	
Anastomotic stricture	1 (2.5)
Evisceration	3 (7.5)
Anastomotic leak	13 (32.5)
Bruising / bleeding	4 (10)
Ileus	4 (10)
Nutrition intolerance	3 (7.5)
Organ / space SSI	2 (5)
Superficial SSI	6 (15)
Intestinal obstruction	4 (10)

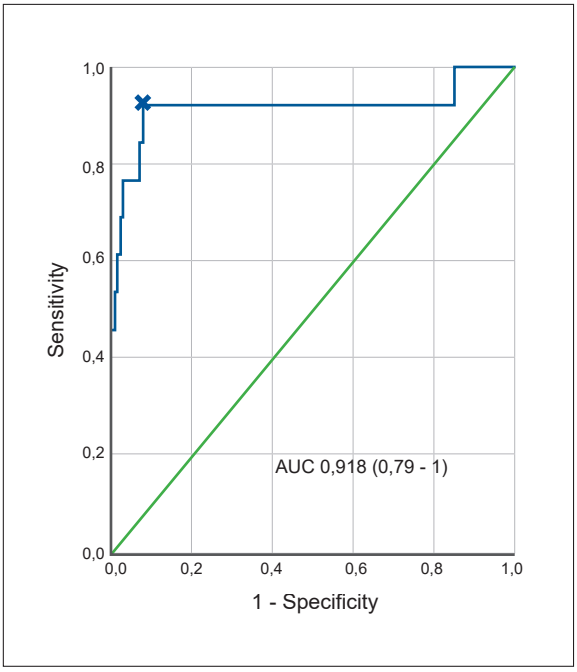

Figure 1. Receiver operating characteristic (ROC) curve for diagnostic accuracy of C-reactive protein concentration in predicting postoperative anastomotic leak. AUC: area under the curve.

to the Clavien-Dindo classification, followed by IIIB (27.5%). %). Of the patients who presented complications, 32.5% (n=13) corresponded to an anastomotic leak (Table 3).

Of these 40 patients who presented complications, 21 of them (52.5%) required surgical reintervention, three (7.5%) endoscopic management, 15 (37.5%) medical management, and one (2.5%) underwent interventional radiology management.

The increase in CRP between postoperative day 3 and day 5 had an area under the curve of 0.918 with a cut-off point for the increase of 1.3 mg/L, with a sensitivity of 92.3% (95% CI 78 -100), a specificity of 92.4% (95% CI 88-96), a positive likelihood ratio of 12.1 and a negative likelihood ratio of 0.08. The diagnostic accuracy of PCR expressed in a ROC curve is shown in Figure 1.

Discussion

Anastomotic leak represents one of the most serious complications in gastrointestinal tract surgery, which can lead to peritonitis, sepsis, multi-organ failure, and death. The symptoms and its clinical manifestations are confusing, so its diagnosis is frequently made late, with a mortality rate of up to 66% [18].

Early suspicion and detection of an anastomotic leak reduces the number of flare-ups, hospital stay, and the risk of requiring an ostomy, leading to better oncological outcomes, better quality of life, and lower risk of death. This study found that the increase in CRP between days 3 and 5 after surgery has a specificity of 92.4% and a sensitivity of 92.3% as an accurate diagnosis of anastomotic leak.

Several studies have evaluated the indication of PCR to predict anastomotic leak. The study by Aaron et al., conducted in India [19], included 84 patients undergoing gastrointestinal surgery and determined that CRP measurement on the third postoperative day (cut-off value of 44.32 mg/dl) could predict anastomotic leak. with a sensitivity of 72.7%, specificity of 66.1%, positive predictive value of 30%, negative predictive value of 75.9%, and an accuracy of 59.5%. While the Ja-

panese study by Masuda et al. [20], who included 247 patients who underwent elective right hemicolectomy or ileocecal resection with ileocolic anastomosis, found that a serum CRP level greater than or equal to 11.8 mg/dl on the third postoperative day predicted leak detection. anastomotic on the seventh postoperative day. Although both studies coincide with ours in demonstrating the prediction of CRP for anastomotic leakage, we consider that there may be inaccuracies, interindividual and interinstitutional variability in the analysis of the test, for which reason an exact CRP value should not be defined. We consider that the increase of the initial value of the PCR is more significant than a single value for the detection of anastomotic leak [21].

In the same study by Aaron, other inflammatory markers were analyzed in addition to PCR, such as serial measurement of serum procalcitonin, which was not sensitive enough to detect AL early [19]. This study simplified the detection of anastomotic leaks using a single marker, demonstrating that the increase in CRP on the fifth day compared to the third is sufficient to predict the appearance of this complication, which is very useful, especially considering that the resources, supplies, or reagents necessary to test other costly inflammatory markers are not available at all institutions in the country.

In a study conducted by Si-Hak et al. [22], it was found that the reduction in CRP concentration between the second and third postoperative days and between the third and fifth days were the greatest predictors of adequate evolution in 613 patients who underwent gastrectomy for gastric cancer. The most important predictors were the rate of reduction of 11.1% in CRP concentration between days 2 and 3 (sensitivity 73%, specificity 76%) and 38.1% between days 3 and 5 (sensitivity, 76.4%, specificity, 76.1%), and when both data were combined, the specificity was 91.6%. These results are only applicable to gastric surgery, unlike our study that included surgeries of the entire gastrointestinal tract, evaluating any postoperative complications.

Conclusions

Despite limitations, such as sample size, this study found that anastomotic leaks in adult patients with major abdominal surgery can be accurately predicted with high sensitivity and specificity, by observing an increase in CRP between third and fifth postoperative day.

Compliance with ethical standards

Informed consent: This study was approved by the Bioethics Committee of the Liga contra el Cáncer Seccional Risaralda, Colombia, under the category of risk-free research and the principles of confidentiality established by the Declaration of Helsinki were followed.

Conflict of interest: none declared by the authors.

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Author's contributions

- Conception and design of the study: Bernardo Borráez-Segura, Felipe Anduquia-Garay, Juliana Gómez-Raigosa, Valentina Santa-Gil, Mario Erazo, Andrés Felipe Castaño-Montoya, Leonardo Ramírez.
- Acquisition of data: Bernardo Borráez-Segura, Felipe Anduquia-Garay, Juliana Gómez-Raigosa, Valentina Santa-Gil, Mario Erazo, Andrés Felipe Castaño-Montoya, Leonardo Ramírez.
- Data analysis and interpretation: Bernardo Borráez-Segura, Felipe Anduquia-Garay, Juliana Gómez-Raigosa, Valentina Santa-Gil, Mario Erazo, Andrés Felipe Castaño-Montoya, Leonardo Ramírez.
- Drafting the manuscript: Bernardo Borráez-Segura, Felipe Anduquia-Garay, Juliana Gómez-Raigosa, Valentina Santa-Gil, Mario Erazo, Andrés Felipe Castaño-Montoya, Leonardo Ramírez.
- Critical review: Bernardo Borráez-Segura, Felipe Anduquia-Garay, Juliana Gómez-Raigosa, Valentina Santa-Gil, Mario Erazo, Andrés Felipe Castaño-Montoya, Leonardo Ramírez.

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