Utility of C-reactive protein in the early diagnosis of anastomotic leakage in colorectal surgery

Utilidad de la proteína C reactiva en el diagnóstico oportuno de fuga de anastomosis en cirugía colorrectal

Guillermo R. Guevara-Morales^{1*}, Marco A. Regalado-Torres¹, Eduardo Cantarell-Castillo¹, Ricardo Castro-Salas², Rebeca Maldonado-Barrón³ and Juan C. Castellanos-Juárez³

¹Department of General Surgery; ²Surgical Oncology Department; ³Coloproctology Department, Hospital Regional de Veracruz, Instituto de Servicios y Seguridad Sociales de los Trabajadores del Estado, Veracruz, Veracruz, Mexico

Abstract

Introduction: The anastomotic leakage (AL) in colorectal surgery is a complication feared by the increase in morbidity and mortality. The rate of AF is reported from 1 to 25%. Making the diagnosis early is difficult. **Objective:** To determine the diagnostic performance of the C reactive protein (CRP) in a cohort of patients undergoing elective colorectal surgery with anastomosis. **Method:** A prospective, comparative study was conducted in 138 patients undergoing elective anastomosis with colorectal surgery, analyzing the serum values of CRP on postoperative days 1, 3, 5 and 7, as well as leukocytes and other abdominal sepsis data. **Results:** The AL rate was 6.5%, the CRP values were significantly higher in the group of patients with AF on the 3rd postoperative day; with a cut-off point of 18.5 mg/dl on the third postoperative day, it obtained sensitivity 81%, specificity 91%, positive predictive value 45%, negative predictive value 98%. **Conclusion:** Measurement of CRP on the third postoperative day in patients undergoing elective colorectal surgery with primary or secondary anastomosis allows the identification of septic complications including leakage of anastomosis.

KEY WORDS: Anastomotic leakage. Colorectal surgery. C reactive protein.

Resumen

Introducción: La fuga de anastomosis (FA) en cirugía colorrectal es una complicación temida por el incremento de la morbimortalidad. La tasa de FA se reporta desde el 1 hasta el 25%. Realizar el diagnóstico de forma temprana es difícil. **Objetivo:** Determinar el rendimiento diagnóstico de la proteína C reactiva (PCR) en una cohorte de pacientes sometidos a cirugía colorrectal electiva con anastomosis. **Método:** Se realizó un estudio prospectivo, comparativo, en 138 pacientes sometidos a cirugía colorrectal con anastomosis de forma electiva, analizando los valores séricos de la PCR los días 1, 3, 5 y 7 del posoperatorio, así como los de leucocitos y otros datos de sepsis abdominal. **Resultados:** La tasa de FA fue del 6.5%, y los valores de la PCR fueron significativamente más altos en el grupo de pacientes con FA en el tercer día del posoperatorio. Con un punto de corte de 18.5 mg/dl en el tercer día del posoperatorio se obtuvo una sensibilidad del 81%, una especificidad del 91%, un valor predictivo positivo del 45% y un valor predictivo negativo del 98%. **Conclusión:** La medición de la PCR en el tercer día del posoperatorio en pacientes sometidos a cirugía colorrectal electiva con anastomosis primaria o secundaria permite identificar las complicaciones sépticas, incluida la FA.

PALABRAS CLAVE: Fuga de anastomosis. Cirugía colorrectal. Proteína C reactiva.

Correspondence:

*Guillermo R. Guevara Morales
Av. Díaz Mirón esquina Sayula s/n
fraccionamiento moderno,
C.P. 91918, Veracruz, Veracruz, México
E-mail: grobertoguevara@gmail.com

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Introduction

Anastomotic leakage (AL) in colorectal surgery is a dreaded complication due to the increase in morbidity and mortality of patients in whom it occurs. In an attempt to avoid or decrease AL, multiple predisposing factors have been described, such as old age, use of corticosteroids, hypoalbuminemia, anemia, inflammatory bowel disease and distance from the anastomotic line to the anal margin, among others. Despite the identification of risk factors, the emergence of intestinal stapling and improvement of surgical techniques, the reported AL rate ranges from 1 to 25%¹. AL diagnostic time is variable and ranges between 3 and 45 days postoperatively; the goal is to diagnose it early in order to reduce the severity of the complication and mortality, which sometimes can be as high as 39%.

AL is defined as the escape of luminal content through the surgical junction of two hollow viscera, which can be established with contrasted imaging studies, computed tomography or by presence of perianastomotic leak or abscess observed in a laparotomy, which may or may not (subclinical AL) show data consistent with systemic inflammatory response²⁻⁴.

Establishing the AL diagnosis in colorectal surgery in a timely manner is difficult and involves a challenge for surgeons, even when there is close post-surgical monitoring. Abdominal, respiratory and neurological signs and symptoms generally occur after the fourth postoperative day. In addition, sensitivity and specificity of some imaging tests (ultrasound, computed tomography, contrasted enema) can sometimes underestimate the AL diagnosis due to their false-negative rates⁵⁻⁹.

In some clinical studies, the usefulness of some serum inflammatory response markers, such as C-reactive protein (CRP), which has a half-life of 19 hours, to early establish the AL diagnosis has been demonstrated¹⁰⁻¹².

The purpose of this study was to determine the diagnostic performance of CRP in a cohort of patients undergoing elective colorectal surgery with anastomosis.

Method

A prospective, descriptive, comparative study was carried out in patients undergoing elective colorectal surgery with resection and anastomosis (primary and secondary), between July 2014 and November 2017.

CRP serum values were recorded at first, third, fifth and seventh postoperative day, as well as white blood cell determination, vital signs and some other data related to abdominal sepsis. All were recorded over the first 7 days in a database. The patients had a followed-up visit at 30 days. The rest of the studied variables were age, gender, surgery indication, type of anastomosis, resection location and hospital length of stay.

Patients with suspicion or evidence of pre-surgical infection, patients with inflammatory bowel disease, patients with protective stoma and those with incomplete clinical records were excluded.

Within the postoperative management, the patients started the oral route 3-5 days after the surgical event. For pain control, a non-steroidal anti-inflammatory drug (NSAID) plus an opioid were used. AL was corroborated by clinical and laboratory data, plus simple and contrasted abdominal and pelvic computed tomography (Fig. 1); in some cases, laparotomy was performed.

The AL treatment was carried out according to findings on imaging studies, patient clinical status and surgeon's criteria (laparotomy, percutaneous drainage or conservative management).

Statistical analysis

Descriptive statistics were used, with percentages and means being calculated. The chi-square test and Mann-Whitney test were used according to the type of variables. A receiver-operator characteristic (ROC) curve was plotted in order to determine the area under the curve on postoperative days 1, 3 and 5, as well as the positive predictive value, the negative predictive value and the likelihood ratios. The analysis was carried out with the SPSS 20 program (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

This work was carried out with previous authorization of the local ethics and research committee.

Results

During the study period, 138 patients were analyzed, out of which 52 were men (37.6%) and 86 women (62.3%), with an average age of 56.9 ± 13.4 years. The indication for surgery was cancer (clinical stages I, IIA, IIB, IIC, IIIA of the TNM classification, 7th ed.)¹³ in 30 cases (21%), diverticular disease in 65 (47%) and other indication in 43 (31%). As

Figure 1. Abdominal tomography axial section showing data consistent with perianastomotic abscess (fluid and gas) in a patient with ileo-transverse anastomosis leakage.

for comorbidities, 14% of the patients had type 2 diabetes mellitus and 11.4% had hypertension.

The resection site was the right colon in 36 patients (26%), left colon in 79 (57.24%) and the rectum in 23 (16.6%). In 94.92% of cases, the resection was performed by laparotomy, and in 5%, laparoscopic surgery was carried out. In 85% of patients, pneumatic testing was performed to confirm anastomosis integrity, and in 100%, permeability and absence of leaks were verified. The type of anastomosis performed was mechanical in 75 patients (54%) and manual in 63 (45.65%). Hospital length of stay was 7.7 ± 12 days (Table 1).

The AL rate was 6.5% in patients who underwent to colorectal surgery. According to the AL diagnosis, the patients were divided in two groups: group A, 129 patients without AL, and group B, nine patients with AL. The diagnosis was made between days 3 and 5 postoperatively; only in one patient was it established after 20 postoperative days. Among the studied characteristics, there was only significant difference in the days of hospital stay (7.3 days vs. 24.5 days; $p = 0.0014$). White blood cell values and the signs and symptoms of AL showed no differences before postoperative day 5.

When the CRP values were analyzed according to the presence of AL (Table 2), no statistical significance was found at first postoperative day ($p = 0.22$); on days 3, 5 and 7, CRP values were significantly higher in group B (third day, $p < 0.001$, and fifth day, $p = 0.001$) (Fig. 2).

The ROC analysis included the CRP values, and the area under the curve was 0.45 at first postoperative day, 0.98 at third postoperative day and 0.96 on the fifth day; since early diagnosis was a goal, the seventh day values were not included. The best

Table 1. Characteristics of patients undergoing colorectal surgery with anastomosis

	n	%
Age 56.9 ± 13.4 years		
Gender		
Males	52	38
Females	86	62
Indication		
Cancer	30	21
Diverticular disease	65	47
Other	43	32
Comorbidity		
Type 2 diabetes mellitus	19	14
Hypertension	15	11
Type of resection		
Right colon	36	26
Left colon	79	57
Rectum	23	16
Type of anastomosis		
Manual	63	45
Mechanical	75	54
Hospital length of stay 7.7 ± 12 days		

Table 2. C-reactive protein values (mg/dL) at postoperative days according to the study group

Postoperative day	Group A	Group B	p
Day 1	11.1	11.6	0.22
Day 3	9.8	30.7	< 0.001
Day 5	8.1	21.3	0.001
Day 7	7.4	11.6	0.005

diagnostic performance over the measured days was that of third day, since with a cutoff point of 18.5 mg/dL, a sensitivity of 81%, specificity of 91%, a positive predictive value of 45% and a negative predictive value of 98% were obtained, with likelihood ratios of +9 and -0.02 (Fig. 3).

When the CRP values at third postoperative day were assessed, it was 8.98 mg/dL (95% confidence interval [CI]: 8.72-9.26) for patients without complications, whereas in subjects with AL it was 30.7 mg/dL (95% CI: 23.54-37.9), and in patients with some other complication (AL was ruled out), it was 14.18 mg/dL (95% CI: 12.6-20.6) (Table 3 and Fig. 4).

The rate of septic complications (including AL) was 14%. According to Clavien-Dindo classification, in 2 patients (1.4%) it was grade I, in 5 (3.6%) it was grade II, in 4 (2.8%) it was grade IIIa, in 2 (1.4%) it was grade IIIb, in 3 (2.1%) it was grade IV, in 2 (1.4%) it was grade IVb and only in 1 (0.7%) it was grade V.

Figure 2. Box-and-whisker plot showing C-reactive protein values (mg/dL) on postoperative days 1, 3 and 5 according to the study group.

Figure 3. C-reactive protein values ROC curve analysis on postoperative days 1, 3 and 5. Area under the curve at first day, 0.45; third day, 0.98; and fifth day, 0.96.

Figure 4. Box-and-whisker plot showing C-reactive protein values (mg/dL) at postoperative day 3 according to the type of complication.

Discussion

Establishing AL early diagnosis is difficult. Sensitivity and specificity of AL diagnosis by surgeons are

Table 3. C-reactive protein values (mg/dL) at postoperative day 3 according to the type of complication

	CRP values	95% CI
Without complication	8.98	8.72-9.26
Anastomosis leak	30.7	23.54-37.9
Other septic complication	14.18	17.6-20.6

CI: confidence interval; CRP: C-reactive protein.

estimated to be 41% and 59%, respectively¹⁴. This can be explained by the appearance of data consistent with inflammatory response after postoperative day 5-6⁵⁻⁹.

Numerous strategies have been described to identify the risk of AL, such as assessing anastomotic perfusion or using indocyanine green, which has been shown to lower the AL rate by up to 5%¹⁵.

Some markers have been assessed as AL predictors, such as peritoneal fluid cytokines, CRP, procalcitonin, calprotectin and fatty acid binding proteins (I-FABP), among others, and have been associated with good diagnostic accuracy^{3,16,17}.

CRP is a marker with broad availability and non-elevated or lower cost than the above-mentioned ones. Its usefulness as an AL predictor in colorectal surgery has been assessed in multiple studies. In this work, it was shown to possess high sensitivity and specificity; however, the cutoff point obtained was higher than in some published studies, such as the meta-analysis conducted by Warschkow et al.¹⁸ with six studies ($n = 1,832$), where, with a cutoff point > 13.5 mg/dL on the fourth postoperative day, a sensitivity of 68% and specificity of 83% were obtained (95% CI: 77-90%), with a negative predictive value of 89%.

Perhaps our results resemble more those published by Singh et al.¹¹, in whose meta-analysis, which included seven studies ($n = 2,483$), the AL rate was 9.6% with a cutoff point of 17.2 mg/dL, an area under the curve of 0.81 and a negative predictive value of 97%.

CRP has been documented not differ from procalcitonin for establishing AL diagnostic performance on postoperative day 3. Moreover, its sensitivity and specificity increase when combined with the use of other biomarkers, as it was concluded in the study conducted by Reisinger et al.³, where CRP showed a sensitivity of 100% and specificity of 64%, with an area under the ROC curve of 0.82 for a value > 9.9 mg/dL on postoperative day 4; furthermore, with the addition of calprotectin, specificity increases to 89%, with an area under the curve of 0.93¹⁰.

By itself, a CRP value > 14 mg/dL at third postoperative day is indicative of septic complication, which

should be investigated with a diagnostic algorithm (blood count, electrolytes, chest X-ray, urine and wound cultures, and even contrasted computed tomography) in order to rule out or confirm AL¹².

Another point to consider are AL-predicting scores or scales. A scoring with the diagnostic protocol proposed by Den Dulk et al.¹ (which includes the use of CRP), tested in 1,066 patients, showed a reduction in AL diagnosis time ranging from 1.5 to 4 days.

In general, the limitation of this type of studies when assessing AL is the lack of a true reference method³, and in this study in particular the main limitation was the lack of CRP measurements at patient admission or daily measurements, the lack of a control group and not having imaging studies in all patients. It should be mentioned that the hospital where the present study was conducted is public and has resident doctors on training, which may have contributed to these results.

Conclusion

CRP measurement at third day after surgery in patients undergoing elective colorectal surgery with primary or secondary anastomosis allows identifying septic complications, including AL, which should be confirmed by contrasted imaging studies or laparotomy, or both, depending on patient clinical status and surgeon's criteria.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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