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The Use of Postoperative CRP Levels in Patients with Crohn's Disease

Short title: Postoperative CRP in Crohn's Disease

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List of abbreviations: CRP- C-reactive protein, CD - Crohn's disease, AL - anastomotic leak, EL- exploratory laparoscopy, CT- computed tomography, GI - gastrointestinal, BMI - body mass index, WBC - white blood cell count, PLT - platelet count, IV - intravenous, PO - per oral, ROC - Receiver operating characteristic, AUC - area under the curve, PPV - positive predictive value, NPV - negative predictive value, POD - postoperative day, CRC - colorectal cancer.

Abstract

Background: In colorectal cancer, CRP levels on postoperative days 3-4 have a strong negative predictive value for an anastomotic leak, with threshold values of ~15 on POD 3 and ~13 on POD 4. In Crohn's disease, CRP levels are perceived as unreliable in the postoperative period because of the underlying inflammatory process. The aim of this study was to investigate the use of postoperative CRP levels in patients with Crohn's Disease and set threshold values for this population.

Methods: This is a retrospective study of the medical records of adult patients with Crohn's Disease who underwent bowel anastomoses, at a single, high volume center. The operations were performed by a single colorectal consultant who is an inflammatory bowel disease specialist, between 1/2012 and 12/2017.

Results: 92 operations were performed. Mean CRP levels and CRP threshold values were higher in the study's population compared with studies on colorectal cancer patients. A CRP level of 19.56 mg/dL on postoperative day 3 had an area under the curve of 0.865 (sensitivity 88%, specificity 73%) and a NPV of 98% for an anastomotic leak. Patients with an anastomotic leak showed a trend towards decreased postoperative albumin levels ($p=0.06$).

Conclusions: Postoperative CRP values are higher in Crohn's Disease compared with colorectal cancer. Postoperative CRP levels may rule out anastomotic leaks in patients with Crohn's Disease with threshold values of 20.3 mg/dL in POD 3, 19.5 mg/dL in POD 4 and 16.7 mg/dL in POD 5.

Keywords: postoperative, CRP, anastomotic leak, Crohn's disease, NPV

Introduction

Anastomotic leak (AL) is one of the most feared complications of gastrointestinal (GI) surgery. With rates ranging between 2-15%, AL is associated with high morbidity and mortality [1-7]. There is no specific method to prevent or to predict an AL. In addition, its diagnosis is not always trivial [8-11]. Abnormal clinical findings or objective physiological parameters may be absent in the early days after surgery [12,13], a normal CT scan does not eliminate the possibility of intra-abdominal complications with false negative rates of ~ 20% [14] and output from pelvic drains may be unreliable.

In recent years C-reactive protein (CRP) has been widely studied as an early predictor for septic complications, including AL, after elective colorectal cancer (CRC) surgery [8-11]. CRP is an acute phase reactant protein, synthesized in the liver. It is a main component in the inflammatory cascade, with a half-life of 19 hours, which makes it a very sensitive marker for inflammation [15]. It is commonly used as one of the factors influencing the decision of whether or not a patient is suitable for early discharge after surgery, mainly because of its high negative predictive value (NPV) for ALs [16].

The 10-year risk of surgery in patients with CD is as high as 50% [17]. CRP levels are routinely used as a marker for disease activity in these patients [18,19]. However, patients with CD are usually excluded from studies on postoperative CRP levels, because of their altered inflammatory response and common use of anti-inflammatory medications [20].

The objective of this study was to investigate postoperative CRP levels in patients with CD who underwent surgery with bowel anastomoses, and to assess its use in the early diagnosis of ALs.

Materials and Methods

This is a retrospective study of patients with CD who underwent elective, semi-elective and urgent abdominal surgery with bowel anastomosis at Meir Medical Center, between 1/2012 and 12/2017. The operations were performed by a single colorectal consultant who is an inflammatory bowel disease (IBD) specialist. Laparoscopic and open bowel resections and "ostomy" reversal surgeries were included in the study. Patients under the age of 18, surgeries with bowel resections without anastomosis and diversion surgeries were excluded.

Patients' demographics (age, sex and BMI), CD characteristics (anatomic location of the inflamed bowel, past and current medical treatments, past surgeries and extra-intestinal manifestations), operative details (indication, laparoscopic, open or converted, site of anastomosis), complications (return to theatre, re-admission) and length of stay were recorded. All patients received a single dose of prophylactic broad-spectrum antibiotics and pre-/postoperative low molecular weight heparin.

Medical records of all patients were reviewed to obtain the following parameters for the postoperative period: white blood cell count (WBC), platelet count (PLT), albumin level and CRP level.

Definitions

AL was defined as a defect seen in the anastomosis at re-operation, presence of feculent fluid in a pelvic drain at the bedside or evidence of free air, fluid or extra-luminal contrast around the anastomosis on CT. Other septic complications included the following: pneumonia, urinary tract infection, superficial wound sepsis and line sepsis. Non-infectious complications included myocardial infarction, deep vein thrombosis or pulmonary embolism.

Urgent surgeries were defined as those who took place less than 24 hours after non elective admissions. The indications for these operations were free perforation and intra-abdominal abscess (IAA) not amenable for percutaneous drainage.

Semi-elective surgeries were defined as operations indicated by CD exacerbations that did not require urgent surgical intervention; small (<5 cm) IAAs, IAAs amenable for percutaneous drainage and ongoing inflammation, leading to prolonged use of steroids or bowel obstructions. Patients with IAAs were treated preoperatively with intravenous (IV) or oral (PO) antibiotics for a period of at least two weeks prior to surgery and percutaneous drainage when necessary. Patients with inflammation induced bowel obstructions were treated with antibiotics and/or systemic steroids for a similar period of time. These patients were ideally operated on two weeks after completing the tapering down of systemic steroid treatment.

Elective surgeries were operations indicated by a stenotic bowel obstruction, a planned "ostomy" reversal in a patient in disease remission or bowel resection due to suspected or proven malignancy. These patients were not under systemic steroid treatment at the Time of the operation.

All semi-elective and elective patients received pre-operative nutritional preparation, either orally or parenterally, for 2-3 weeks.

Statistical analysis

The statistical software package SPSS 20 (IBM) was used to perform statistical analysis. Normality of data was tested by Shapiro-Wilks. The median was used as a measure of the central tendency for continuous variables. Continuous data was assessed using Student's *t* test, and the Mann Whitney *U* test was used for non-parametric data. Pearson's chi-square test was employed for comparison of categorical variables. A *p* value of <0.05 (two-tailed) was deemed statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of CRP at detecting AL on successive postoperative days. This method involves plotting a curve of sensitivity (true positives) against 1-specificity (true negatives). The accuracy of the test is calculated by measuring the AUC, and the curve itself can be used to identify an optimum cut-off value, which will provide the highest sensitivity and specificity combination to best diagnose the outcome measure. Positive predictive value (PPV) and negative predictive values (NPV) were calculated at the optimum threshold CRP for each day after surgery.

Compliance with Ethical Standards

This study was approved by the ethics committee of Meir Medical Center.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The informed consent was waived by the institutional research committee.

Results

Patients

The Patients' demographic data and pre-operative inflammatory markers are shown in table 1.

There was no difference between the group of patients who suffered an AL and those who did not in terms of age, gender, BMI, preoperative inflammatory markers and metabolic state.

Operative and preoperative treatment

52 procedures were laparoscopic and 40 were open or laparoscopic converted to open.

Table 2 describes the different types of operations that were performed.

There was no difference in leak rates between the laparoscopic and open groups (4 vs. 7, $p=0.15$).

There were 11 (11.9%) ALs of which eight were small bowel to large bowel anastomosis and three were small bowel to small bowel anastomosis ($p=0.79$). Antibiotic treatment sufficed as the only intervention in three cases, percutaneous drainage was added in three more cases and five cases required re-operation.

Of the five cases that required re-operation, two had a pin-point leak which was treated with an insertion of a T-drain, one underwent resection of the anastomosis and immediate re-anastomosis and two required take down of the anastomosis and formation of an ileostomy. Mean post-operative day for the diagnosis of an anastomotic leak was 5.3 ± 3.2 .

Six operations were urgent (~6%), 43 operations (47%) were semi-elective and 43 (47%) operations were elective. Only one AL occurred in the urgent operation group, five in the semi-elective group and five in the elective operation group ($p=0.9$).

At the time of the operation 29 patients were treated with systemic steroids, 23 patients were treated with biologic agents (infliximab, adalimumab or vedolizumab) and five patients were treated with a combination of systemic steroids and biologic agents. Other medical treatments included Azathioprine, Mercaptopurine and 5-ASA derivatives. None of the patients treated with systemic steroids at the time of the operation suffered an AL.

There was no procedure related death in the study group.

Analysis of post-operative CRP levels

Post-operative CRP levels were higher in the AL group on POD 1 (17.9 ± 11 vs. 9.5 ± 5.4 , $p=0.09$) and POD 2 (22.2 ± 10.2 vs. 15.7 ± 9.7 , $p=0.11$), however this difference became significant only on POD 3 to 5 (see table 3).

Figure 1 demonstrates the difference in CRP levels and trends between the two groups from POD 1 to 5.

ROC curves were produced for POD 3 to 5 and analyzed to calculate the area under the curve and optimum CRP threshold (see figure 2). ROC curve analysis revealed POD 3 to be the most predictive for AL with an AUC of 0.863 for a CRP threshold value of 19.56 mg/dL (sensitivity 88%, specificity 73%). On POD 4 the AUC was 0.805 for a CRP threshold value of 20 mg/dL (sensitivity 66%, specificity 90%).

The threshold value of 19.56 on POD 3 was strongly exclusive of an AL with a NPV of 98%, and the threshold value of 12.5 on POD 5 had a NPV of 100%. The PPV trended upwards from day to day, reaching 100% at POD 5 for a threshold value of 12.5.

WBC and PLT levels on POD 3 did not show a statistically significant difference between the AL and no AL groups. Albumin level on POD 3 was lower in the AL group with borderline significance (see table 4).

Discussion

Whilst the measurement of postoperative CRP levels has become a standard practice in CRC surgery in many units, this is not the case for patients with CD undergoing surgery with bowel anastomoses. A main reason for this is the premise that these patients have an altered inflammatory response [21] which affects postoperative CRP levels and their interpretation. In addition, patients with CD have elevated baseline CRP levels [18,19]. Therefore, it is believed that postoperative CRP threshold values of CRC patients cannot be applied in CD.

Previous studies have shown that the clinical significance of postoperative CRP measurement is in its NPV for ALs, rather than its PPV [3,7-11,16]. Indeed this was the case in this study too. The NPV of a CRP level of 19.56 mg/dL on POD 3 was 98% but the PPV was only 35%. The PPV increases only later in the postoperative period.

Low albumin levels in the postoperative period have lately been shown to have a correlation with postoperative complications [22,23]. In this study patients in the AL group had a trend towards lower postoperative albumin levels (3.03 ± 0.5 vs 2.71 ± 0.4 , $p=0.06$)

A recent meta-analysis by Yeung et al. summarized the results of 23 studies that assessed the use of postoperative CRP levels as a tool to predict ALs in colorectal surgery [24]. In a day by day comparison of both the AL groups and the no-AL groups, CRP levels in Yeung's study were lower than in this one, A trend was consistent from POD 1 to 5 (see table 5). Also, threshold CRP values were lower than those reported here; 14.8 mg/dL vs. 19.56 mg/dL in POD 3, 12.3 vs. 20.0 in POD 4 and 11.5 vs 12.5 in POD 5. This finding of relatively elevated postoperative CRP levels in patients with CD correlates with previous reports by Carvello [20] and de Buck [21]. A summary of the differences in CRP values between patients with CD and other colorectal surgery patients are displayed in table 5.

This dedicated study of the CD population is one of the first to address the use of postoperative CRP levels as a tool to rule out ALs in these patients. Its clinical contribution is in showing that this practice can be implemented not only in the elective surgery setting, but in a heterogenous group of CD patients that includes emergent cases. This is significant since in CD, more often than not, patients reach surgical intervention during or soon after disease exacerbation.

The limitation of this study is its small cohort size and retrospective nature which subjects it to selection bias and record keeping issues.

In conclusion, mean postoperative CRP levels and threshold CRP values are higher in patients with CD undergoing bowel anastomoses, compared with patients undergoing operations for CRC. Nonetheless, the use of postoperative CRP levels to rule out ALs is applicable in patients with CD. We suggest a threshold of 20.3 mg/dL in POD 3, 19.5 mg/dL in POD 4 and 16.7 mg/dL in POD 5 to rule out an anastomotic leak in patients with CD. More dedicated studies on the CD population are required to validate these results.

Declarations*Funding*

Not applicable.

Conflict of interests

The authors declare no competing interests.

Availability of data and material

The data analyzed in this study is available upon request.

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Authors contributions:

M.S - literature search, study design, data analysis, data interpretation, figures, writing of drafts and final version;

A.G - literature search, data collection, data analysis; B.R - data collection, data analysis, data interpretation; Y.R - data analysis, data interpretation, figures; S.A - data interpretation, writing of drafts and final version; I.W - study design, data interpretation, writing of drafts and final version.

Figure legends

Figure 1. CRP levels in the AL and the no AL groups

Figure 2. AUC by POD

Tables

Table 1. Demographics and pre-operative inflammatory markers

	All patients (n=92)	No leak (n=81)	Leak (n=11)	p value
Age (years)	40.6 ± 15.7	40.3 ± 15.7	43.3 ± 16.1	0.55
Gender (Male/Female)	46/46	39/42	7/4	0.52
BMI	22.3 ± 5.5	22.4 ± 5.5	21.9 ± 5.4	0.75
Preoperative WBC (10 ³ cells /μL)	9.0 ± 4	9.0 ± 4.1	8.8 ± 3.7	0.84
Preoperative PLT (10 ³ platelets/ μL)	353.4 ± 119.7	351.9 ± 121.8	364.4 ± 107.5	0.74
Preoperative albumin (g/dL)	3.51±0.58	3.51 ± 0.56	3.51 ± 0.82	0.99
Preoperative CRP (mg/dL)	4.68 ± 7.04	4.75 ± 7.32	4.28 ± 5.28	0.84

(BMI; body mass index)

Table 2. Types of operations

Operation	n (%)
Right colectomy	33 (35.8%)
Ileocectomy	27 (29.3%)
Stoma reversal	15 (16.3%)
Small bowel resection	14 (15.2%)
Left colectomy	2 (2.2%)
Subtotal colectomy	1 (1%)

Table 3. Post-operative CRP

	POD 3	POD 4	POD 5
Mean CRP leak	25.9 ± 5.4	24.8 ± 9.6	25.5 ± 10.9
Mean CRP no leak	14.4 ± 8.0	12.3 ± 8.3	13.0 ± 11.1
p	0.000	0.001	0.004
AUC	0.863	0.805	0.789

	POD 3	POD 4	POD 5
CRP cutoff	19.56	20.0	12.5
Sensitivity	0.88	0.66	1.0
Specificity	0.73	0.90	0.62
PPV (%)	35%	60%	100%
NPV (%)	98%	88%	100%

Table 4. Other inflammatory markers on POD 3

	No leak (<i>n</i> =81)	Leak (<i>n</i> =11)	<i>p</i> value
WBC (10^3 cells / μ L)	9.0 $\pm$ 3.6	11.0 $\pm$ 6.7	0.46
PLT (10^3 platelets/ μ L)	319.7 $\pm$ 113.1	306.3 $\pm$ 116.4	0.59
Albumin (g/dL)	3.03 $\pm$ 0.5	2.71 $\pm$ 0.4	0.06

Table 5. Mean CRP levels and CRP threshold values

	Yeung et al. (colorectal surgery)	This study (CD)	Carvello et al. (CD)
	leak\ no leak	leak\ no leak	-
Mean CRP POD 1	11.4 $\pm$ 3.25 \ 9.58 $\pm$ 2.9	17.9 $\pm$ 11 \ 9.5 $\pm$ 5.4	-
Mean CRP POD 2	20.1 $\pm$ 2.9 \ 14.5 $\pm$ 3.1	22.2 $\pm$ 10.2 \ 15.7 $\pm$ 9.7	-
Mean CRP POD 3	22.4 $\pm$ 5.1 \ 12.3 $\pm$ 3.2	25.9 $\pm$ 5.4 \ 14.4 $\pm$ 8.0	-
Mean CRP POD 4	20.38 $\pm$ 3.8 \ 10.5 $\pm$ 1.7	24.8 $\pm$ 9.6 \ 12.3 $\pm$ 8.3	-
Mean CRP POD 5	18.7 $\pm$ 3.5 \ 6.5 $\pm$ 2.37	25.5 $\pm$ 10.9 \ 13.0 $\pm$ 11.1	-
CRP threshold POD 3	14.8	19.56	21.0
CRP threshold POD 4	12.3	20.0	19.0
CRP threshold POD 5	11.5	12.5	21.0