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SHORT COMMUNICATION

Procalcitonin and C-reactive protein as early markers of postoperative intra-abdominal infection in patients operated on colorectal cancer

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Abstract
Purpose The aim of this study was to evaluate the accuracy of serum procalcitonin (PCT) and C-reactive protein (CRP) for early diagnosis of postoperative intra-abdominal infections (PIAI) after elective surgery for colorectal cancer.
Methods Prospective observational study including patients operated on for colorectal cancer between January and December of 2015 was performed. Serum PCT and CRP levels were measured before surgery and daily until postoperative day 3.
Results One hundred twenty patients were included. Seven patients (5.8%) had PIAI. PCT levels were significantly higher in patients with PIAI on postoperative days 1 and 3, whereas CRP levels only were significantly more elevated on postoperative day 3. The ratio between CRP levels on postoperative day 3 and CRP levels on postoperative days 2 (CRP D3/CRP D2) and 1 (CRP D3/CRP D1) was significantly higher in patients with PIAI. PCT on postoperative day 3, for a cutoff of 0.45 ng/mL, had the best sensitivity (100%) with a specificity of 73.8%. The ratio CRP D3/CRP D1 yielded the higher specificity and positive predictive value (90.9 and 27.3%, respectively, for a cutoff of 1.8). The higher negative predictive value was obtained for PCT on postoperative days 1 and 3 (100%, with cutoff of 0.76 and 0.45 ng/mL, respectively) and for CRP on postoperative day 3 (100% with cutoff of 10 mg/dL).
Conclusion PCT and CRP serum levels are associated with the appearance of PIAI after colorectal cancer surgery, although the positive predictive values were low for both PCT and CRP. However, the negative predictive values were high.

Keywords C-reactive protein · Postoperative intra-abdominal infections · Procalcitonin

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Introduction

After colorectal surgery, intra-abdominal sepsis is a major complication with an important impact on both final surgical outcome and cost. As it has been emphasized by the Surviving Sepsis Program, early recognition and initiation of adequate therapy are essential steps to minimize sepsis-related mortality. Postoperative intra-abdominal infections (PIAI) are usually suspected on the basis of clinical signs including fever, tachycardia, oliguria, and elevated leukocyte count. The diagnosis of such infections usually occurs late, between the sixth and ninth postoperative days [1] even though most of their causes, as anastomotic leaks, may take place long before. Therefore, a suitable serum marker could have a great interest for earlier diagnosis of PIAI, provided it is sensitive and specific enough. The aim of this study was to evaluate the kinetics of procalcitonin (PCT) and CRP in the three first days after elective colorectal surgery and to demonstrate if these molecules are reliable biomarkers to early diagnoses of postoperative intra-abdominal infections.

Methods

An observational prospective study was performed involving consecutive patients who underwent elective surgery for colorectal cancer between January and December of 2015 at

Pontevedra University Hospital. All procedures were laparotomic. All patients underwent preoperative bowel preparation with Bohm solution and systemic antimicrobial prophylaxis (1500 mg of metronidazole and 1000 mg of ceftriaxone). All patients provided written informed consent and the study was approved by the Regional Ethical Committee. Exclusion criteria were age younger than 18 years, emergency or palliative surgery, active infection before surgery, and preoperative PCT values higher than 0.5 ng/mL. All patients were examined 1 month after surgery in the outpatient clinic.

Procalcitonin and CRP serum levels, as well as leukocyte count (LC), were measured on the day prior to surgery and on the first, second, and third postoperative days (D0, D1, D2, and D3). Procalcitonin was determined by enzyme-linked fluorescent immunoassay (VIDAS^{R}) (Brahms; Diagnostica, Berlin, Germany). For CRP and PCT, the ratios between a value and the value corresponding to the prior day were calculated (D3/D2, D3/D1, and D2/D1).

PIAI and other types of surgical site infection were diagnosed according to the criteria of the Centers for Disease Control and Prevention [2]. The statistical analysis was performed using SPSS v.20.0 for Mac (Statistical Package for Social Sciences Inc., Chicago, IL, USA) and MedCal v.12.2.1 for Windows (MedCalc Software, Marlakerke, Belgium). To assess differences between the two main groups, the Kruskal-Wallis test and the Mann-Whitney *U* test were used. The diagnostic accuracy was evaluated with the area under the curve (AUC) using the ROC methodology. Positive and negative predictive values and positive and negative likelihood ratios were calculated for an optimal cutoff point. Significance was accepted for $p < 0.05$.

Results

A total of 120 patients were enrolled: 80 were male (66.66%) and 40 were female (33.33%). The mean age was 69.9 ± 11 years. Eighty-four patients (70%) had colic cancer and 36 (30%), rectum cancer. Most of the patients underwent a right colectomy (36). The other patients underwent a left colectomy (18), transverse colectomy (6), sigmoid resection (24), low anterior resection (26), and abdominoperineal resection (10). Another four patients were excluded from the study—two due to preoperative PCT > 0.5 ng/mL and two due to palliative surgery.

One patient (0.83%) died postoperatively. Sixteen patients (13.3%) developed infectious postoperative complications. Seven patients had PIAI (6 intra-abdominal abscesses and 1 diffused peritonitis). The median interval between surgery and diagnosis of the PIAI was 10 days (range 5–18 days). All PIAI were diagnosed through CT. Twelve patients had another infectious complications: eight, incisional surgical site infections; 2, urinary tract infections; 2, left-sided pneumonias; and 1, venous central catheter-associated infection. No infectious complications were detected after patient discharge.

Preoperative CRP, PCT, and LC were not different in both groups of patients with and without PIAI ($P = 0.157$, $P = 0.866$, and $P = 0.217$, respectively). CRP, PCT, and LC increased in all patients after surgery. In the studied time period, CRP peaked on day 2 in patients without PIAI, with median of 11.19 mg/dL, and on day 3 in patients with PIAI, with median of 18.03 mg/dL. The peak level of PCT occurred on day 1 in both groups of patients, with and without PIAI, with median of 0.35 and 1.43 ng/mL, respectively. The peak value of LC occurred on day 1 in the group of patients without PIAI and on day 2 in the group of patients with PIAI, with median of 9950/mm^3 and 9000/mm^3, respectively.

CRP levels were not significantly different between patients with and without PIAI on day 1 and day 2 ($P = 0.07$ and $P = 0.121$, respectively); however, on day 3, they were higher in patients with PIAI ($P < 0.01$). PCT levels were higher in patients with PIAI on day 1 and day 3 ($P = 0.01$ and $P < 0.01$, respectively), but not on day 2 ($P = 0.064$). LC values were not different in both groups of patients in any day ($P = 0.336$, $P = 0.892$, and $P = 0.658$, respectively). Neither the ratios for PCT nor ratios for LC were significantly different between both groups of patients. However, the CRP D3/CRP D2 and CRP D3/CRP D1 ratios were significantly more elevated in patients with PIAI ($P = 0.01$ and $P = 0.04$, respectively). The median value for CRP D3/CRP D2 was 1.07 for patients with PIAI and 0.754 for patients without PIAI. The

Table 1 Sensitivity, specificity, predictive values, and likelihood ratios for significant variables. Confidence interval 95%

Criteria	PCT D1 > 0.76	PCT D2 > 0.5	PCT D3 > 0.45	CRP D3 > 10	CRP D3/CRP D2 > 0.79	CRPD3/CRP D1 > 1.8
Sensitivity	100 (47.8–100)	80 (28.4–99.5)	100 (47.8–100)	100 (47.8–100)	100 (47.8–100)	60 (14.7–94)
Specificity	69.3 (58.6–78.7)	61.3 (50.4–71.6)	73.8 (63.4–82.7)	62.5 (51.5–72.6)	63.6 (52.7–73.6)	90.9 (82.9–96)
PPV	15.6 (5.3–32.8)	10.5 (2.9–24.8)	17.9 (6.1–36.9)	13.2 (4.4–28.1)	11.1 (3.1–26.1)	27.3 (6–61)
NPV	100 (94.1–100)	98.2 (90.3–100)	100 (94.5–100)	100 (93.5–100)	98.2 (90.6–100)	97.6 (91.5–99.7)
PLR	3.2 (2.4–4.5)	2.07 (1.2–3.5)	3.8 (2.7–5.4)	2.6 (2–3.5)	2.2 (1.3–3.7)	6.6 (2.5–17.5)
NLR	0	0.33 (0.06–1.9)	0	0	0.3 (0.05–1.8)	0.4 (0.2–1.3)

CRP C-reactive protein (mg/dL), *PCT* procalcitonin (ng/mL), *PPV* positive predictive value, *NPV* negative predictive value, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio

median value for CRP D3/CRP D1 was 2.005 for patients with PIAI and 0.931 for patients without PIAI. The higher values for the area under the ROC curve corresponded to PCT D3, CRP D3, CRP D3/CRP D2, and CRP D3/CRP D1 (0.865, 0.864, 0.843, and 0.768, respectively). Table 1 shows the optimal cutoff, sensitivity, specificity, and predictive values for CRP and PCT on day 3 and for the ratios CRP D3/CRP D2 and CRP D3/CRP D1.

Discussion

This study shows that surgery of colorectal cancer induces an increase in serum levels of CRP and PCT in all patients, as well as the peak levels being reached earlier for PCT than for CRP. In our study, both proteins demonstrated to be useful in discriminating between patients with and without PIAI already in the first three postoperative days, preceding in some days, the clinical and radiologic diagnosis of this complication that, on average, took place on postoperative day 12 [3]. PCT is an earlier marker of PIAI than CRP since, according to our results, it can discriminate between infected and non-infected patients as soon as postoperative day 1. Taking into consideration only isolated values, PCT is a more valuable biomarker of PIAI than CRP, although its usefulness in diagnosing this complication is limited because its PPV is not too high. If we consider the evolution of the values of both proteins in the first three postoperative days, the situation is different and we observe that CRP can be a more suitable marker of PIAI. In fact, the ratio between CRP on day 3 and CRP on day 1 has a fairly high PPV, greater than those of isolated values of both PCT and CRP. Measurement of PCT and CRP on postoperative days 2 and 3 could be used for early identification of patients in risk of developing intra-abdominal infections. These patients could be selected for CT or other appropriate explorations, and the diagnosis of PIAI could be anticipated in several days. In this regard, a recent retrospective study by Holl et al. [4], including 170 patients, suggests that an abdominopelvic CT should be performed if an elevated CRP is found on postoperative day 4 after colorectal surgery. Both our study as well as those published previously agreed that the PPV of PCT and CRP is low [5–10], and, therefore, by itself, is not sufficient for the diagnosis of PIAI. Particularly relevant is the finding that PCT on postoperative day 3 has a very high negative predictive value. This allows us to identify patients with very low probability of PIAI, already in the third postoperative day, facilitating early discharge after colorectal surgery, as other authors have already shown in most of previously published studies [7, 11, 12]. In our study, the ratio between the serum levels of CRP on postoperative day 3 and on postoperative day 2 is significantly associated with the appearance of PIAI and has a PPV of 27%—greater than those for isolated values of PCT or CRP—although it is still low. This finding was not previously published, as far as we know, in patients operated on colorectal cancer. Our study had some limitations. It was a single-center study and the number of patients with PIAI was small, which limited the statistical power of the analysis.

In conclusion, our study suggests that measurement of PCT in the postoperative day 3 could be used in the early prediction of PIAI after elective colorectal cancer surgery and, above all, to identify a group of patients with a very low probability of this complication, which can be useful to plan a secure early discharge. The ratio between the serum levels of CRP on day 3 and CRP on day 2 could be useful to select patients for additional explorations before there is a clinical suspicion of PIAI.

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Authors' contributions E.D-C participated in the design of the study and in the statistical analysis and wrote the manuscript.

V.L-G participated in the design of the study and made the biochemical analysis.

SM.E-F, R.D-F, and JB-M helped in the database and draft the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards All patients provided written informed consent and the study was approved by the Regional Ethical Committee.

Conflict of interest The authors declare that they have no conflict of interest.

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