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Preoperative inflammation increases the risk of infection after elective colorectal surgery: results from a prospective cohort

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Key words: colorectal surgery, C-reactive protein, albumin, procalcitonin, anastomotic leak, postoperative complications, intra-abdominal infection, surgical site infection.

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Abstract

Background

Septic complications after colorectal surgery are frequent and sometimes life-threatening. It is well-known that inflammation impairs the healing process. It has been suggested that preoperative ongoing inflammation could increase the risk of postoperative infections. This study aimed to elucidate the role of preoperative inflammation on postoperative infectious complications and to understand if, through biological markers, it is possible to identify preoperatively patients at higher risk of infection.

Methods

A prospective, observational study was conducted in three centers from November 2011 to April 2014. Consecutive patients undergoing elective colorectal surgery with anastomosis were included.Any ongoing infection was an exclusion criterion. C-reactive protein, albumin, prealbumin and procalcitoninplasma levels were measured preoperatively. Postoperative infections were recorded according to the definitions of the Centers for Diseases Control. The areas under the receiver operating characteristic curve were analyzed and compared to assess the accuracy of each preoperative marker.

Results

Four-hundred and seventy two patients were analyzed. Infectious complications occurred in 118 patients (25%) and mortality in 6 patients (1.3%). In the univariate analysis, preoperative C-reactive protein andalbuminemiawere found significantly associated withpostoperative infectious complications (P = 0.008 and P = 0.0002, respectively). Areas under the ROC curve for preoperative C-reactive protein and albuminemia were 0.57and 0.62, respectively.

Conclusions

This study confirms the association between preoperative inflammatory activity, hypoalbuminemia and the onset of infections after surgery. Trials aiming to decrease the inflammatory activity before surgery in order to prevent postoperative complications are warranted.

Introduction

Septic complications are responsible for most morbidity, mortality and failure to rescue after colorectal surgery. Despite the steady progress of surgical techniques, preoperative assessment and perioperative management,the risk of overall infection after colorectal surgery is between 16 and 51%[1-4]. In addition to their short-term clinical impact leading sometimes to life-threatening situations, postoperative infections increase the length of hospital stay, costsand decrease cancer survival.Hence, the identification of patients at risk of developing postoperative infectious complications (PIC) is essential. It has been shown by several authors that high blood levels of C-reactive protein (CRP) and procalcitonin (PCT) between postoperative days 2 and 5 predict postoperative infections[5]. Inflammatory markers monitoring is thus becoming a standard of care in gastrointestinal surgery.

Recently, some authors suggested that *preoperative* inflammatory activity is related to a higher risk of PIC[6-9]. It is well known that local inflammation impairs the healing process and systemic inflammation impairs the immune response[10]. Preoperative hypoalbuminemia and a low nutritional index are also well-known risk factors of PIC that warrant a specific nutritional support[11-13]. Whether the effect of hypoalbuminemia is more related to an impaired healing process or to an impaired immune response is not clear. Hypoalbuminemia may also be due to an increased catabolism induced by ongoing inflammation and not only to malnutrition.It has been stated that preoperative immunonutrition decreases the risk of postoperative infections, even in well-nourished patients. Immunonutrition has both, immuno-modulating and anti-inflammatory properties, as well as it reduces the insulin-resistance which has been related to the risk of PIC[14-16]. These data suggest that modulating preoperative inflammation could decrease the risk of PIC.

The aim of this study was to analyze the link between preoperative inflammation, hypoalbuminemia and PIC.

Materials and methods

Design

From November 2011 to April 2014, patients who underwent elective colorectal surgery with anastomosis in the Departments of Digestive Surgery of the University Hospitals of Dijon and Besançon and the "Georges-François Leclerc Anticancer Center" in Dijon were included in a prospective database (IMACORS: Inflammatory MArkersafter COloRectal Surgery)[2].

Inclusion and exclusion criteria

Patients were eligible for the study if they met all the following criteria: age 18 years or older, a scheduled colorectal resection with anastomosis, preoperative values of CRP, PCT, albuminemia and prealbuminemia available. Patients with a previous ongoing infection, operated on in an emergency or with suspected peritoneal carcinomatosis were excluded. Before inclusion, written informed consent was obtained from all patients.The study was approved by the regional ethics committee CPP Est 1.

Clinical and laboratory assessment and follow-up

Potential patient-specific and preoperative risk factors were recorded prospectively for each patient. The preoperative factors included age, gender, obesity, surgical indication (cancer, polyps, chronic inflammatory bowel disease, chronic diverticular disease, other diseases), laboratory data on the day before surgery (CRP, PCT, prealbuminemia, albuminemia and white blood cell count), American Society of Anesthesia score, comorbidities (cardiovascular, respiratory or hepatic diseases, presence of diabetes mellitus and immunosuppression status) and bowel preparation (decision made by operating surgeon). The surgical data recorded included the procedure and approach (laparoscopy or laparotomy), level of anastomosis and technique (mechanical or handsewn), operative time, perioperative accidents, presence of drainage, diverting stoma and perioperative blood transfusion.

During the postoperative period, patients were examined by the attending surgeon daily. The presence of fever (central temperature >38°C), abdominal signs, bowel movements, and the volume and aspect of drainage (if present) were recorded daily. The attending surgeon made the decision to

carry out imaging examinations according to his/her own criteria. The rate of septic complications was calculated, including intra-abdominal infection, wound infection, central line infection, pneumonia and urinary tract infection, independently of their severity. Patients were seen in the outpatient clinic within 6 weeks after operationand all complications occurring before POD 30 were recorded.

CRP levels were determined by immunonephelometry (Dimension Vista system, Siemens Healthcare France) in all participating centers. PCT levels were measured by using the Brahms PCT Kryptor® or Vidas®assays (Thermo Fisher Scientific, Hennigsdorf, Germany). The first assay is a homogeneous one-step sandwich immunoassay using time-resolved amplified cryptate emission technology on a Kryptor® system (Thermo-scientific, Asnière, France). The second assay is a one-step immunoassay sandwich method associated with a final fluorescent detection step on a Vidas® system(Biomérieux, Marcy, France). Close concordance between the two assays has been previously established elsewhere.[17] Plasma levels of albumin (g/l) and prealbumin (g/l) were assayed using commercially available colorimetric (albumin-bromocresol purple complex) and immunoturbidimetric assay kits (Dimension Vista System Flex reagent cartridge, Saint-Denis, France), respectively, in all participating centers.

Assessment and definition of complications

Intra-abdominal infection was defined according to the Centres for Disease Control and Prevention. This definition includesany one of the following criteria: the presence of pus or enteric contents within the drains, the presence of abdominal or pelvic collections in the area of the anastomosis on postoperative imaging (abdominal CT scanner), leakage of contrast through the anastomosis during enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis. All intra-abdominal infection were considered independently of their clinical significance. Wound infection, urinary-tract infection, catheter-related infection, and pneumonia were also defined according to the Centres for Disease Control and Prevention[18].

Statistical analysis

Statistical analysis was performed using of SAS software, version 9.4 (SAS Institute Inc; Cary NC, USA) and Stata software version 12 (StataCorpInc, College Station, TX USA). Continuous outcomes were presented as means and standard deviations for normally distributed variables, and with median and interquartile range (IQR) otherwise, and compared with Student tests or non-parametric tests as appropriate. Categorical data were expressed with percentage frequencies and compared with Chi-2 tests.Logistic regressions were used in order to estimate associations between CRP, PCT, albuminemia and PIC, while adjusting for confounding factors. Variables associated with PIC with a p-value below 0.20 in bivariate analyses were included in the model. A backward selection strategy was then applied. The log-linearity of the relation between each continuous variable and PIC was assessed using the fractional polynomial approach[19]. Interactions with cancer were systematically tested.

A two-sided P value of less than 0.05 was considered to be significant. The areas under the ROC curves were calculated for the preoperative value of CRP, PCTand albumin.

Results

Patients and morbidity

Among the 510 patients included in the IMACORS cohort, 38 patients were excluded for this ancillary study due to missing preoperative data. Thus, 472 patients were retained for the analysis. The characteristics of the patients are presented in Table 1. In total, PIC occurred in 118 (25%) of the 472 patients: intra-abdominal infection occurred in 58 (49.2% of PIC, overall incidence of 12.3%), wound infection in 46 (9.7%), urinary-tract infections in 22 (4.7%), pneumonias in 5 (1%) and catheter-related infections in 9 (1.9%). Six patients (1.3%), all of whom having a PIC, died before POD 30. The median time between the operation and the diagnosis of PIC was 7 days (interquartile range: 5-11 days). The intra-abdominal infection diagnosis was established with imaging in 40 patients (69%), clinical features in 13 (22.4%), and at surgery in the remaining 5 patients (8.6%).

Preoperative risk factors

Albuminemia and CRP levels were significantly higher in patients going into develop PIC (P = 0.0002and P = 0.008, respectively); prealbuminemia did not reach significance (P = 0.0589)(Table 2). Preoperative PCT was not associated with an increased risk of developing infections (P> 0.9). When adjusting for confounding covariates (age and cancer) in a multivariate analysis, preoperative CRP and albuminemia were still associated with a later PIC occurrence (P = 0.036 and P< 0.001, respectively).No interaction with cancer was found (P = 0.420 for CRP, P = 0.183 for PCT and P = 0.902 for albuminemia).The area under the ROC curve for preoperative albumin, CRP and PCT was respectively of 0.62, 0.57 and 0.50 (figure 1). When a cut-off value of 5 mg/L was used, preoperative CRP yielded a sensitivity of 52%, a specificity of 58% and a negative predictive value of 78% for the prediction of PIC. Among surgical factors, only operating time > 4h predisposed patients to PIC (P = 0.046). CRP was not significantly associated with intra-abdominal infection.

When patients with preoperative CRP levels higher than 100 mg/L (9 patients) were excluded from the cohort (in these cases, extreme values could have reflected undetected ongoing infections or

inflammatory diseases), values of CRP remained significantly higher in those going into develop PIC(P = 0.016).

Patients operated on for cancer (330 patients) had higher preoperative values of CRP than those operated on for benign diseases (142 patients): 17.8 vs. 7.1 mg/L, p = 0.0002; but they did not have a significantly higher risk of PIC.

Discussion

Based on a prospective studydesigned toassess CRP and PCT as early predictors of postoperative infections following colorectal surgery, this analysis confirmed the relationship between preoperative systemic inflammation measured by CRP and the risk of PIC. Hypoalbuminemia was also associated with a higher risk of infections, as it has already been shown in several works[12,20,21]. Unsurprisingly, preoperative PCT was not related to the onset of PIC, as it is more a marker of ongoing bacterial infection than a marker of general inflammatory activity.

Intra-abdominal infections after colorectal surgery become clinically evident around postoperative days 6 and 7 or even later, except in case of technical default in which the onset of symptoms is earlier[2,22-24]. Even when routine CT scan is performed for the screening of intra-abdominal infection, its sensitivity is low before POD 4[25]. Overall, these data give an idea of anastomotic leakage as an event appearing at the end of the first postoperative week. However, levels of CRP and PCT rise significantly higher as early as postoperative day 1 in patients going into infection[5,9]. This fact raises the hypothesis of inflammatory response starting at the tissue level much earlier than the onset of the clinical picture. Inflammation may be not only a consequence but also a risk factor of surgical infection and its role might even begin preoperatively.

Several authors have suggested that preoperative ongoing inflammation and hypoalbuminemia are associated with an increased risk of both, PIC and intra-abdominal infection[6-9,22,26-28]. Our results confirm this relationship between preoperative CRP and the risk of PIC. Hypoalbuminemia may result of malnutrition, particularly in cancer patients, but is also due to the accelerated catabolism induced by systemic inflammation. The mechanism by which these factors increase the risk of complications seems to be a composite of impaired healing and impaired immune response. Consistent results have been found recently in patients operated on for Crohn's disease: higher preoperative values of CRP (with a cutoff of 14.50 mg/L) and rising values in the 2 weeks before surgery were associated with an increased risk of intra-abdominal septic complications[29]. Preoperative elevation of serum CRP has been significantly related to the reduction of lymphocyte

percentages in peripheral blood, and it can be an indicator of impaired immunity in patients with colorectal cancer[10]. The increased inflammatory activity in patients operated on for colorectal cancer has also been shown in previous studies[30]. It could be expected that this could lead to an increase in the risk of PIC or surgical-site infection in cancer patients, but this was not the case in the present series, as it was not the case in previous series analyzing the risk factors of infection after colorectal surgery[26,27].

Other data supporting the role of preoperative systemic inflammation on the onset of PIC come from studies having measured adipocytokines preoperatively in patients undergoing elective colorectal surgery. Leptin is a proinflammatoryadipocytokine related to systemic inflammation and, more specifically, to the inflammatory activity in the fatty tissue. This has been suggested as an explanation of the increased risk of surgical site infection in obese patients[22,31]. Leptin is also related to insulin resistance, which is involved in the risk of infection[32], and its values are also consistently elevated in patients going into develop PIC[16].

Further results supporting the role of inflammation in the onset of PIC come from clinical trials which showed a benefit of preoperative immunonutrition and perioperative anti-inflammatory drugs. Actually, immunonutrition modulates the immune and inflammatory responses after surgery and decreases significantly the risk of PIC in patients undergoing major gastrointestinal or colorectal surgery for cancer, even in well-nourished patients[33-35]. On the same way, a benefit in morbidity and length of hospital stay has been shown with the use of glucocorticoids and non-steroidal anti-inflammatory drugs in the preoperative and early postoperative period, respectively[36-37]. Some authors have even used preoperative glucocorticoids to decrease CRP values without increasing the infectious risk[38]. Another issue is the specific impact of gut microbiota in the preoperative inflammatory and the risk of anastomotic leak and PIC. All thesedata converge in showing that preoperative inflammatory activity is related to an increased risk of both, postoperative infection and intra-abdominal infection. This opens the door to clinical trials aiming at reducing preoperative inflammation combining nutritional and pharmacological approaches.

Could preoperative CRP select patients who deserve a more intensive surveillance policy or even additional antibiotic prophylaxis? We think that its ability to discriminate patient who will develop a PIC from patients who will not (AUC=0.57) does not allow its use to change either the antibiotic prophylaxis policy or the postoperative surveillance.

This study has some limits. We did not measure other inflammatory, stress and healingmarkers (e.g. interleukin-6, insulin, leptin, adiponectin, praline, etc), whose values could have been helpful for a more global overview of the relationship between preoperative inflammation, healing and PIC.Seemingly, we did not analyze the preoperative imaging results looking for an explanation to elevated CRP levels in patients with higher values. However, all patients with preoperative known ongoing complications were excluded from the IMACORS cohort. Furthermore, the exclusion of the extremely high values of CRP did not change the relationship between the marker and the incidence of PIC. This suggests that the inflammatory preoperative status has a role on the onset of PIC, even for lower values.Finally, an analysis of the visceral adipose tissue in the preoperative imaging (as it is a source of inflammation) would have been of interest.

In conclusion, preoperative ongoing inflammation and hypoalbuminemia are related to the onset of postoperative infection after elective colorectal surgery. The benefit of therapeutic approaches to reverse the inflammatory activity before surgery should be assessed in future trials in which patients could be selected according to these markers.

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