Value of Serum Procalcitonin in Evaluating the Prognosis of Sepsis in Elderly Patients with Colorectal Cancer Undergoing Emergency Colorectal Surgery

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Received: 20 December 2011 / Accepted: 12 June 2012 / Published online: 28 June 2012
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Abstract Serum procalcitonin (PCT) levels may have predictive value in the prognosis of postoperative sepsis in elderly patients who have undergone colorectal surgery for colorectal cancer in intensive care units (ICUs). A prospective study involving 90 critically ill patients who underwent colorectal surgery for colorectal cancer in ICUs was performed. Twenty-eight patients were diagnosed with sepsis, in accordance with the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria, and these patients were included in the sepsis group. Sixty-two patients, who were without evidence of sepsis, were enrolled in the control group. We measured the serum PCT concentrations preoperatively (immediately before induction of anesthesia), upon arrival in the ICU (ICU day 0), on the morning of the first postoperative day (postoperative day 1), and on the morning of the third postoperative day (postoperative day 3). The C-reactive protein (CRP) index, acute physiology and chronic health evaluation II (APACHE II) score, mechanical duration of ventilation, mortality rate, incidence of multiple organ failure, and usage of continuous renal replacement therapy were evaluated. The area under the

curve for the receiver operating characteristic curve (AUC-ROCC) was measured to explore the association between the serum PCT and the prognosis. In the sepsis group, 12/28 patients died (mortality rate 43 %). In the control group, 6/62 patients died (mortality rate 9.7 %). On the first postoperative day, the serum PCT level was dramatically higher in the sepsis group than in the control group (2.71 ± 1.13 vs. 1.37 ± 0.57 , $P \leq 0.05$). The PCT level on the first postoperative day was distinctly higher than that measured upon arrival in the ICU (2.71 ± 1.13 vs. 1.31 ± 0.58 , $P \leq 0.05$). In the two groups, the CRP concentrations were both markedly higher on the first postoperative day than upon arrival in the ICU (138.89 ± 45.12 vs. 70.43 ± 23.54 in the sepsis group, and 133.13 ± 44.91 vs. 69.65 ± 24.98 in the control group, $P \leq 0.05$). Linear regression analysis was performed. The results suggest that the PCT and APACHE-II scores were not significantly associated. On the first and third postoperative days, the PCT levels were associated with increased odds of sepsis (AUC-ROCC, 95 % confidence interval 0.817–0.973, $P = 0.000$, and 0.755–0.944, $P = 0.000$, respectively). The outcomes of patients in the sepsis group were worse than those in the control group. PCT levels appear to be early markers of postoperative sepsis in elderly patients undergoing colorectal surgery for colorectal cancer during the ICU course. These findings could allow for early identification of postoperative septic complications and be used for prognostic evaluation of these patients.

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Keywords Elderly patients · Sepsis · Emergency colorectal surgery · Procalcitonin · Prognosis

Introduction

Sepsis is a major cause of mortality and morbidity in critically ill patients, especially in elderly patients following

emergency colorectal surgery [1]. The negative impact of emergency surgery for colon cancer is confined to the immediate postoperative period [2]. These patients are prone to bacterial infection because they have a greater frequency of obstructing and perforated colonic lesions, as well as for other reasons. Therefore, it is very important to identify a reliable biomarker for sepsis, which can be used to evaluate the therapeutic response in septic patients. Procalcitonin (PCT) is a promising sepsis marker [3] that is capable of complementing clinical signs and routine lab parameters, which are suggestive of sepsis [4, 5]. Patients' PCT levels may guide the antibiotic treatment and be used to evaluate the prognosis [6]. However, the diagnostic and prognostic utility of PCT is contradictory [7]. Indeed, the accuracy of using PCT levels for diagnosing sepsis has been challenged in critically ill patients [8]. In general, the diagnostic value of PCT was higher in surgical than in medical patients [9]. Despite many promising observations in adults, the predictive value of measuring serum PCT levels immediately after surgery has not yet been fully assessed in adult patients who underwent emergency colorectal surgery. The aim of this study was to measure the amount and the time course of PCT and C-reactive protein (CRP) induction in elderly patients who underwent emergency colorectal surgery. Furthermore, we tested the value of PCT for evaluating the prognosis of sepsis in elderly patients with colorectal cancer who underwent emergency colorectal surgery in the intensive care unit (ICU).

Materials and Methods

Subjects

This study was conducted prospectively over a period of 3 years in our hospital. From January 2008 to January 2011, 90 consecutive patients undergoing emergency colorectal surgery were studied. The criteria for inclusion were colorectal tumor resection and an age of more than 70 years. The preoperative exclusion factors were elective surgery, preoperative anti-inflammatory drugs, preoperative infection treatment with corticosteroids or morphine, and immunosuppressive illness other than neoplasm. All patients who stayed in the ICU for more than 72 h were consecutively enrolled in the study. All patients presented with obstructive ileus or perforation and peritonitis. Standard preoperative preparation, supportive care, surgical procedures, and broad-spectrum antibiotics were provided to each patient. The study was approved by the institutional ethics committees at the Affiliated People's Hospital of Jiangsu University. Written informed consent was obtained from all patients or their relatives before enrollment.

Experimental Assignment

The signs of systemic inflammatory response syndrome (SIRS) were identified if the patient had a body temperature $<35.6^{\circ}\text{C}$ or $>38.3^{\circ}\text{C}$, tachycardia >90 beats per min (bpm), ventilatory frequency >20 bpm or $\text{PaCO}_2 <4.27$ kPa (unless the patient was mechanically ventilated), a white cell count $\geq 12 \times 10^9/\text{l}$ or $\leq 4 \times 10^9/\text{l}$, or $>10\%$ immature neutrophils (bands), as previously described [10]. Sepsis was defined when the patients had SIRS associated with infection according to Bones' criteria [11]. Infection was identified if microbiological cultures obtained from the patients at possible sites of infection were positive (proven infection) or if clinical signs of infection were evident. Patients were assigned into two groups: the sepsis group (patients with sepsis, severe sepsis [10], and septic shock [10]) and the control group (patients with SIRS or no evidence of sepsis).

Determination of Serum PCT and CRP Levels

Serum PCT and CRP samples were collected immediately before the induction of anesthesia, upon arrival in the ICU, on the morning of the first postoperative day and on the morning of the third postoperative day. Blood samples were centrifuged at $1,500\text{ g}$ for 5 min (Rotina 35; Cheftich Zentrifugen, Hennigsdorf, Berlin, Germany), and the serum was collected in sterile tubes for PCT and CRP determination. The PCT levels were measured using the luminometric assay (B.R.A.H.M.S. AG, Berlin-Hennigsdorf, Germany), and the CRP levels were measured using the nephelometric assay (Boehringer, Mannheim, Germany). The functional assay sensitivity was the PCT is 0.3 ng/ml . The treating clinicians were blinded to the PCT results, and those performing the PCT assays were blinded to the clinical status of the patient. The PCT results were not available during the study period.

Data Analysis

The following parameters were assessed: patient's age, sex, acute physiology and chronic health evaluation II (APACHE II) score, mechanical duration of ventilation, incidence of multiple organ failure (MOF), usage of continuous renal replacement therapy (CRRT), and 28-day mortality. Statistical evaluation was carried out using the SPSS 13.0 program (SPSS Inc, Chicago, IL) for Windows. The clinical characteristics of the patients were compared using the χ^2 -test or the Mann–Whitney U test according to the variable type and the data distribution. Data for the clinical characteristics of patients were expressed as the median (25th–75th percentile). $P < 0.05$ was considered to be statistically significant. The accuracy of PCT levels, APACHE II scores, and CRP concentration in determining the prognosis

Fig. 1 Enrollment of the study patients

of sepsis in elderly patients with colorectal cancer who underwent emergency colorectal surgery in the ICU was assessed by comparing area under the receiver operating characteristics curves (AUC-ROCCs). Survival analysis in the two groups was performed using Kaplan–Meier estimates. A linear regression model was used to test the changes between the PCT levels and the APACHE II scores on the morning of the first postoperative day in the sepsis group.

Results

Patient Characteristics

None of the 90 included patients were excluded from the data analysis (Fig. 1). The surgical procedures that patients received are summarized in Table 1. There were no significant differences in the preoperative clinical characteristics between the 28 patients who developed sepsis complications during the first postoperative day (sepsis group) and the 62 patients who did not (control group). The median ages of the sepsis and control groups were 76 ± 5 years and 78 ± 5 years, respectively. Twelve of the 28 patients died in the sepsis group and the mortality rate was 43 %, while 6 patients died in the control group and the mortality rate was 9.7 %. Further baseline characteristics for the patients are presented in Table 2.

Changes in Serum PCT and CRP Concentrations After Surgery

On the first postoperative day, the serum PCT levels were dramatically higher in the sepsis group than in the control group (2.71 ± 1.13 vs. 1.31 ± 0.57 , $P \leq 0.05$). However, the patients with high PCT levels after emergency colorectal

surgery in the sepsis group had similar PCT levels on the first and third postoperative days. Among these patients, the PCT levels on the first postoperative day were distinctly higher than upon arrival in the ICU (2.71 ± 1.13 vs. 1.31 ± 0.58 , $P < 0.05$). The PCT, but not CRP, concentrations on the third postoperative day were significantly decreased in the two groups (Fig. 2).

The CRP levels were similar in the two groups preoperatively and upon arrival in the ICU, and then were elevated on the first and third postoperative days. In both groups, the CRP concentrations were markedly increased on the first postoperative day in comparison to the concentration measured upon arrival in the ICU (138.89 ± 45.12 vs. 70.43 ± 23.54 in the sepsis group, and 133.13 ± 44.91 vs. 69.65 ± 24.98 in the control group, $P \leq 0.05$). The serum CRP concentrations were also elevated on the third postoperative day in comparison to the concentration measured upon arrival in the ICU. Compared with the CRP concentrations, the PCT levels more rapidly decreased to their preoperative levels on the third postoperative day (Fig. 3).

Table 1 Surgical procedures performed in two groups of patients

Procedure	Sepsis Group (n=28)	Control Group (n=62)
Left hemicolectomy	10 (35.7 %)	23 (37.1 %)
Right hemicolectomy	7 (25 %)	18 (29.0 %)
Hartmann's operation	5 (17.9 %)	12 (19.4 %)
Abdominoperineal resection of rectum	2 (7.1 %)	5 (8.1 %)
Anterior resection of rectum	2 (7.1 %)	2 (3.2 %)
Colonic bypass	2 (7.1 %)	2 (3.2 %)

Data are expressed as number of cases (percentage)

Table 2 Preoperative clinical characteristics of two groups of patients

Parameter	Sepsis Group (<i>n</i> =28)	Control Group (<i>n</i> =62)	Mann–Whitney <i>U</i> test <i>P</i> value
Age (mean±standard deviation)	76±5	78±5	>0.05
Gender (male/female)	13\15	30\32	>0.05
Initial procalcitonin (immediately before induction of anesthesia) (median, quartiles) (ng/ml)	0.69±0.31	0.70±0.32	>0.05
Initial C-reactive protein (immediately before induction of anesthesia) (median, quartiles) (mg/l)	60.21±23.35	61.67±22.98	>0.05

Linear Regression Analysis of APACHE II Scores and PCT Levels

There were no differences in the APACHE II scores between the two groups on the first postoperative day. Linear regression analysis suggested that the PCT levels and APACHE II scores were not significantly associated (Fig. 4).

Sensitivity, Specificity, Positive, and Negative Predictive Values, and Receiver Operating Characteristics (ROC) Curves

Figures 5 and 6 show the AUC-ROCCs for the prediction of sepsis by the PCT levels on the first and third postoperative days, respectively. The predictive performances of the PCT levels were very high at both time points. The AUC-ROCC for the PCT levels was greater than 0.80 for both the first and third postoperative days (AUC-ROCC, 95 % confidence interval 0.817–0.973, $P=0.000$, and 0.755–0.944, $p=0.000$, respectively).

Fig. 2 Histogram of PCT levels before anaesthesia and on ICU day 0, postoperative day 1, and postoperative day 3 in the sepsis group ($n=28$) and the control group ($n=62$). * $P<0.05$ compared with control group, # $P<0.05$ compared with ICU day 0 or postoperative day 3

Patients' Outcomes

The outcomes of the sepsis and control groups differed from each other at the end of 28-day treatment course. The sepsis patients had more fatal outcomes than the controls. Overall, the outcomes of patients in the sepsis group were worse than in the control group (Table 3 and Fig. 7).

Discussion

In this study, we analyzed the plasma concentrations of various biochemical markers with respect to their potential use in predicting the prognosis of patients suffering from sepsis following emergency colorectal surgery in the ICU. Emergency colon surgery itself had a higher mortality rate than non-emergency colon surgery [2, 12–14]. The present study is of potential interest because sepsis is a very common problem in elderly patients who undergo emergency colorectal surgery. Sepsis can lead to a high mortality rate, and it is extremely difficult to treat. The negative impact of emergency surgery for colon carcinoma is confined to the immediate postoperative period [2]. Most colorectal cancers occur in elderly people, and due to perforation, obstruction, and other reasons, these patients need emergency surgical

Fig. 3 Histogram of CRP levels before anaesthesia and on ICU day 0, postoperative day 1, and postoperative day 3 in the sepsis group ($n=28$) and the control group ($n=62$). * $P<0.05$ compared with ICU day 0, # $P<0.05$ compared with ICU day 0

Fig. 4 Linear regression analysis of APACHE II scores and PCT on the first postoperative day in the sepsis group

treatment. In elderly patients with low immunity and inadequate bowel preparation, surgery can lead to complications like sepsis, and result in death. The most common cause of mortality in general surgical ICUs is sepsis, which may lead to MOF [15]. Earlier diagnosis and treatment to prevent sepsis in patients who undergo emergency operations for colorectal disease will improve surgical results [16]. Therefore, identifying a biomarker that can detect or rule out sepsis in the early postoperative period can help elderly patients, who may benefit from specific therapies. Additionally, this type of

biomarker could be used to assess the patient's response to sepsis therapy.

PCT was found to be an accurate diagnostic parameter for differentiating SIRS and sepsis [5]. Previously, PCT was reported to be a better discriminator than CRP in characterizing the degree of inflammation related to infection [17], especially infection complicated by sepsis or organ failure [18]. With this background, PCT has been proposed as a better prognostic marker than CRP [19, 20]. Intestinal surgery and major operations often increase PCT [21]. The induction and action of PCT is a multifactorial process,

Fig. 5 ROC curve and performance characteristics for serum PCT measured on the first postoperative day in the sepsis group. The area under the ROC curve for the PCT test is 89.5 %, demonstrating a good performance for the diagnosis of sepsis

Fig. 6 ROC curve and performance characteristics for serum PCT measured on the third postoperative day in the sepsis group. The area under the ROC curve for the PCT test is 85 %, demonstrating a good performance for the diagnosis of sepsis

Table 3 Duration of ICU treatment and outcomes of two groups of patients

Parameters	Sepsis Group (n=28)	Control Group (n=62)	Mann–Whitney <i>U</i> test or χ^2 -Test <i>P</i> value
Ventilator duration (days)	9.75±6.25	5.26±4.32	0.001
MOF (%)	64.2 %	18.8 %	0.000
CRRT (%)	53.6 %	22.6 %	0.004
28-day mortality rate (%)	42.9 %	9.7 %	0.000

which involves different cell–cell interactions, a time-dependent pattern of cellular activation, and different cellular behaviors when cells are native or pre-exposed to pro-inflammatory stimuli [22]. A major source of PCT during sepsis is parenchymatous cells [23], such as intestinal cells in patients who underwent emergency colorectal surgery. These patients often suffer from microbial infections that easily lead to sepsis. Under septic circumstances, the entire body could be viewed as an endocrine gland [24]. Sepsis may contribute to the induction of PCT and may also promote the development of organ dysfunction and poor outcomes in these patients.

In patients with multiple traumas, PCT values provide more information than CRP levels [22]. Moreover, a higher concentration of PCT correlates with more severe trauma and a higher incidence of various complications, including sepsis [22]. In the postoperative period following elective colorectal or aortal surgery, PCT seems to be a valuable early predictive marker of infective complications when high postoperative levels are found [25]. Although the association between PCT and elective colorectal surgery has been widely investigated [25, 26], the predictive role of PCT levels on the prognosis of sepsis in the elderly following emergency colorectal surgery has not yet been investigated. Moreover, the predictive value of this parameter is controversial. In this study, we showed that the outcomes of

patients in the sepsis group were much worse than in the control group. In addition, the postoperative PCT levels in septic patients increased, suggesting that sepsis induced an immediate increase in postoperative PCT levels. On the first postoperative day, the patients in the sepsis group had PCT levels that were significantly higher than the patients in the control group. The cut-off ROC curve value of PCT levels to predict postoperative sepsis was excellent. In general, an ROC curve value of 0.80–0.89 is a good indicator. The area under the ROC curve for the PCT test was 89.5 % on the first postoperative day, and the result was 85 % on the third postoperative day. The AUC value of PCT that we obtained is a little lower than that reported previously (96.9 %), which might be due to differences between the elderly and other patients with sepsis [5]. It is interesting to note that no correlation was found between elevated PCT concentrations and APACHE II scores, which is consistent with a previous report [5]. There are at least two possible explanations for this phenomenon. First, APACHE II scores are the result of a comprehensive analysis of various parameters, and PCT may not be severe enough to predictably lead to severe systemic inflammatory response and change the APACHE II scores. Second, the PCT levels decreased rapidly on the third postoperative day, so they may have had a smaller impact on the APACHE II scores.

Fig. 7 Kaplan–Meier estimated patient survival in the sepsis group versus the control group over 28 days

However, the CRP level on the day of sepsis diagnosis was not a good marker of prognosis in septic patients [27]. A previous report indicated that the serum concentrations of CRT were not statistically different between the SIRS, sepsis, and septic shock groups [5]. Consistent with these observations, our study suggests that the diagnostic use of CRP postoperatively is limited since a significant induction of CRP occurred in almost all patients, and the kinetics were slow. There were no significant differences in the CRP levels in the two groups on the first and third postoperative days. These factors may explain why CRP was unable to predict the disease outcome or severity. Therefore, our data suggested that increased PCT levels could be used to predict the prognoses of postoperative septic elderly patients who underwent emergency colorectal surgery. Additionally, PCT levels could be a valuable serum marker for sepsis to improve patient management. Compared to CRP levels, evaluation of PCT levels may be valuable for estimating postoperative inflammatory responses.

Despite yielding clinically relevant results, the limitations of this study must be acknowledged. This is a single-center study, and the results need to be further confirmed or refuted in other centers. Our study design did not allow us to explain the exact relationship between the prognosis of patients and the PCT values. Age, septic shock at presentation, large estimated intraoperative blood loss, delayed operation, and development of complications were all associated with in-hospital mortality [14]. The relationship between the dynamic changes in PCT and the above complications was extremely complex. To date, there is no biomarker that can clearly differentiate septic syndrome from an inflammatory response due to other causes [12]. Moreover, as there is no “gold standard” for the diagnosis of sepsis, the effectiveness of a biomarker needs to be compared with current methods used to diagnose and monitor sepsis in everyday clinical practice (i.e., the combination of clinical signs and available laboratory variables) [28]. Therefore, the final relationship between PCT levels and the prognosis of patients should be assessed in further studies.

Acknowledgments This study was supported by grants from the Affiliated People's Hospital of Jiangsu University Fund.

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