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ORIGINAL ARTICLE

Procalcitonin as an early predictor of postoperative infectious complications in patients with acute traumatic spinal cord injury

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Study design: Prospective, nonrandomized, observational cohort study.
Objectives: To analyze procalcitonin (PCT) level in acute traumatic spinal cord injury patients with and without postoperative infectious complications, and to determine whether PCT is a prognostic parameter of infectious complications in the early postoperative period compared with other inflammatory markers.
Setting: Spine center of Chongqing, China; Trauma center of Chinese People's Liberation Army, China.
Methods: A total of 339 consecutive patients with acute spinal cord injury undergone surgery were evaluated. All patients underwent measurement of leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum PCT preoperatively and 24–48 h postoperatively.
Results: In all, 26 (7.7%) of 339 participants experienced postoperative infectious complication. Patients with infection exhibited significantly higher PCT and CRP levels compared with noninfection (both $P<0.01$). Multivariate logistic regression analysis showed that PCT and CRP levels were independent predicators for postoperative infection. The area under the receiver operating characteristics curve of PCT and CRP were 0.82 (95% confidence intervals (CI) 0.74–0.91) and 0.68 (95%CI, 0.57–0.78), respectively. A PCT cutoff of 0.1 ng ml^{-1} had a reasonable sensitivity of 92% to exclude an infection and antibiotics can be initially withheld. However, in patients with PCT level above 0.5 ng ml^{-1}, a rapid initiation of antibiotics may be warranted.
Conclusions: Serum PCT is a more reliable biologic marker for the early prediction of postoperative infectious complications in patients with acute traumatic spinal cord injury compared with CRP. PCT can early identify postoperative infections for establishing effective antibiotic therapy.
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Keywords: spinal cord injury; procalcitonin; predictor; infectious complication

Introduction

Postoperative infectious complication is a significant problem in patients with acute traumatic spinal cord injury. Infection rates in the postoperative period reported in the literature range from 0.7 to 11%.[1,2] Once diagnosed, aggressive treatment should be taken carefully and seriously in most cases to eradicate the infection, prevent potential seeding of the spine and retain instrumentation and stability. However, distinguishing diagnosis is difficult in the early postoperative course because traditional indicators of infection such as fever, leukocytosis, pain, delirium and wound drainage are commonly present during this period in the absence of infection. So, timely and accurate diagnosis of postoperative infections is of major importance because it strongly influences further therapeutic decision making.[3]

Facing this clinical dilemma, there is major interest in a valid tool for predicting postoperative infectious complications in these patients. Commonly, laboratory tests, primarily leukocyte count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are detected when there is a suspicion of postoperative infection. These tests are markers of inflammation that rise in the presence of systemic inflammation. None of these parameters are specific for infection and may be elevated because of an infection unrelated to surgery or other noninfectious complications such as deep vein thrombosis or myocardial infarction.[4]

Procalcitonin (PCT) is a calcitonin precursor that was first defined as an inflammatory biomarker in the plasma of patients with infection and sepsis in the 1990s.[5] Measurement of PCT in particular has gained interest because it is a quantitative test that exhibits predictable value and is more

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responsive to postoperative events compared with CRP and ESR.[6–8] Nevertheless, in current clinical practice, PCT are not widely used as routine screening tests in the early postoperative period, with most surgeons relying on the leukocyte count, CRP and ESR despite evidence that these are poor diagnostic tests.[9] PCT was already used in several other studies to predict postoperative infections after several different operations,[5–8,10,11] however, the predictive value of serum PCT in detecting postoperative infectious complications in spinal cord injury patients has not been studied.

The aims of the current study were to analyze the PCT level in acute traumatic spinal cord injury patients with and without postoperative infectious complications, and to determine PCT as a prognostic parameters of infectious complications in the early postoperative period compared with other inflammatory markers.

Patients and methods

Patient population

Data were collected prospectively from consecutive patients with acute traumatic spinal cord injury who met inclusion criteria and underwent spinal surgery by one of the six well-trainned spine surgeons between January 2007 and September 2010. Inclusion criteria were of at least 18 years of age, single level or greater decompression or fusion, and length of stay of at least 4 days after surgery. Exclusion criteria were acquired or inherited immunodeficiency, history of inflammatory disorder, hepatitis or liver disease, and tumor or cancer. The study was approved by the local hospital ethics committee. Oral consent was obtained from each patient before study enrollment.

Laboratory analyses included the determination of the white blood cell count, CRP, ESR and PCT. Blood specimens were collected before surgery and 24–48 h after surgery. Samples were centrifuged at 2000 g for 15 min to separate serum from cellular blood contents and the serum were stored at −20 °C until analysis. PCT was quantified by an immunoluminometric assay, which has a functional assay sensitivity of 0.06 ng ml^{-1}. CRP was measured by an automated nephelometry. ESR was a manual test in which the level of blood collected in a Westergren sedimentation rate tube was read by a technologist after a specific time period.

Patient data collected included age and gender. Clinical characteristitcs was obtained from the preoperative history and physical examination. Surgery data included injury region (cervical, thoracic or lumbar), cause of injury (Traffic incident, fall, violence and other), the American Spinal Injury Association Impairment Scale, surgical type (fusion or decompression), number of levels, approach (anterior, posterior or combined), operative time from skin incision to closure, estimated blood loss and length of stay postoperatively. All patients received prophylactic antibiotics intravenously within 1 h of incision consisting of cefotiam 1 g every 12 h or in the presence of a penicillin allergy, vancomycin 1 g every 12 h and continued 24 h after surgery or until postoperative drains were discontinued, usually on the second postoperative day. If the surgery exceeded 8–12 h, the antibiotics were readministered as above. During the patient's hospitalization, daily progress notes, discharge summaries, diagnostic tests, microbiology tests and laboratory tests were reviewed for evidence or suspicion of a postoperative infectious complication.

Infectious complications

The common infectious complications consisted of urinary tract infection, deep wound infection and pneumonia, others included cellulitis, bacteremia, gastroenteritis. Diagnostic criteria of infectious complications were established on the basis of Centers for Disease Control and Prevention definitions.[12–16] In brief, the presence of urinary tract infection was defined as (1) substantial leukocyturia (>10 white blood cell per visual field on microscopy of sediment per high-power field) or (2) substantial bacteriuria ($>10^5$ microorganisms per cm^3 of urine); pneumonia was defined as the presence of (1) at lease one respiratory symptom (cough, purulent sputum, dyspnea or pleuritic pain) and at least one finding during auscultation (rales or crepitation), or (2) one sign of infection (a core body temperature of >38.0 °C, shivering or a white blood cell count of $>10\times10^9$ per l or $<4\times10^9$ per l) and a new or progressive infiltrate on a chest radiographic examination; deep wound infection was defined as (1) purulent draining or a deep incision spontaneously dehisces, or (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the surgical incision, or (3) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination and bloodstream infection (bacteremia) was defined as growth of relevant bacteria in blood cultures.

Statistical analysis

All statistical analysis was performed using the SPSS 16.0 statistical software package (SPSS Corp, Chicago, IL, USA). The quantitative variables are expressed as the median and interquartile range, or mean and standard deviation. Qualitative variables are expressed as frequencies and percentages. The Student's *t*-test or Mann–Whitney *U* test was used to investigate differences between groups (patients with suspected or unsuspected infection) depending on the distribution of data. Uni- and multivariate binary logistic regression analysis was used to determine the significant variable in predicting the presence and absence of postoperative infectious complications in patients with acute spinal cord injury. To investigate the prognostic impact of the factors considered, receiver-operating characteristic (ROC) curves were plotted and areas under the curves were assessed. The Optimal Cutoff Point on the ROC curve was determined by the maximum of the Youden index. Differences were considered significant when the *P*-value was less than 0.05.

Results

Clinical profile of patients

A total of 339 acute spinal cord injured individuals met inclusion criteria and were included in the study. According

Table 1 Patient and surgery characteristics

	Infected (n = *26*)	*Noninfected* (n = *313*)	P-*value*
Age, years	44.5 ± 9.9	41.3 ± 14.5	0.266
Male, *n* (%)	19 (73)	245 (78)	0.540
Cause of injury, n			0.990
Motor vehicle accidents	11	134	
Fall	9	115	
Violence	2	21	
Other	4	43	
Injury region, n			0.673
Cervical	8	118	
Thoracic	13	129	
Lumbar	5	66	
AIS, n			0.302
A	12	109	
B	3	85	
C	6	76	
D	5	43	
Approach, n			0.367
Anterior	5	34	
Posterior	20	272	
Combined	1	7	
Surgical type, n			0.519
Decompression	4	35	
Fusion	22	278	
Number of levels, *n*	4.0 ± 1.1	4.2 ± 1.4	0.472
Operative time, min	202 ± 79	223 ± 68	0.136
Estimated blood loss, ml	908 ± 324	820 ± 415	0.289
Length of stay postoperatively, days	11.8 ± 2.5	9.8 ± 2.0	0.003
Preoperative WBC count, 10^9 per l	6.3 ± 2.5	6.9 ± 2.3	0.195
Preoperative PCT, ng ml^{-1}	0.09 (0.06–0.11)	0.08 (0.07–0.10)	0.399
Preoperative CRP, mg l^{-1}	9 (2–30)	9.9(3–53)	0.752
Preoperative ESR, mm h^{-1}	5 (2–10)	6 (2–9)	0.240
Postoperative WBC count, 10^9 per l	9.0 ± 3.8*	8.5 ± 3.3	0.495
Postoperative PCT, ng ml^{-1}	0.81 (0.53–1.97)*	0.33 (0.16–0.50)*	<0.001
Postoperative CRP, mg l^{-1}	68 (40–81)*	42 (9–63)*	0.003
Postoperative ESR, mm h^{-1}	8 (6–10)*	7 (4–10)	0.196

Abbreviations: AIS, ASIA Impairment Scale; ASIA, American Spinal Injury Association; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; PCT, procalcitonin. *$P<0.05$ versus preoperative makers.

to whether a postoperative infectious complication eventually developed, the patients were separated into two groups: one group of patients who eventually developed infection (infected group, $n=26$; 7.7%) and another group of patients who did not (noninfected group, $n=313$; 92.3%). Patient characteristics, surgery information and hospitalization information are presented in Table 1. Postoperative infectious complications developed on median postoperative day 5 (2–10), including four deep wound infections necessitating surgical incision and drainage. Table 2 showed suspected infectious complications after surgery in patients with acute traumatic spinal cord injury. Among 26 patients with infectious complications, 19 bacteriologic samples were positive. Pathogens included seven gram-positive cocci (four *Staphylococcus* sp., 20%; two *Enterococcus* sp., 10%; one *Streptococcus* sp., 5%); 12 gram-negative rods (eight *Enterobacteriaceae*, 40%; three *Pseudomonas* sp., 15%; one *Miscellaneous*, 5%); and one anaerobe (*Bacteroides fragilis*, 5%). One sample had two microorganism growing.

Table 2 postoperative infectious complications

Complication	n
Urinary tract infection	9
Pneumonia	8
Deep wound infection	4
Cellulitis	2
Bacteremia	2
Gastroenteritis	1

Prognostic clinical parameters

Using univariate and multivariate binary logistic regression models, PCT and CRP within 48 h after surgery could be identified as the significant independent predictors of postoperative infectious complications of all the parameters analyzed (Table 3). The adjusted odds ratios for possible risk factors related to postoperative infections were 1.347 (*95%* Confidence Interval (CI) 1.116–1.626, $P=0.002$) for PCT and 1.007 (95% CI 1.001–1.013, $P=0.030$) for CRP.

Table 3 Association of clinical parameters, PCT and CRP with suspected infection

Variable	*P-value*	
	Univariate	*Multivariate*
Age	0.265	0.326
Gender	0.540	0.665
Injury region	0.739	0.272
AIS	0.943	0.405
Approach	0.360	0.576
Surgical type	0.521	0.478
Operative time	0.137	0.143
Postoperative PCT	0.001	0.002
Postoperative CRP	0.019	0.030
Postoperative ESR	0.558	0.811

Abbreviations: AIS, ASIA Impairment Scale; ASIA, American Spinal Injury Association; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.

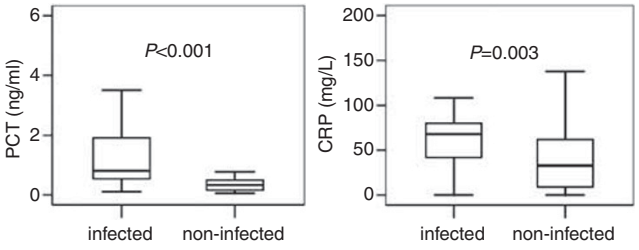

Figure 1 Serum PCT and CRP concentrations early after surgery in infected and noninfected patients. Significantly higher PCT ($P<0.001$) and CRP ($P<0.01$) levels were detected in patients with postoperative infectious complications. CRP, C-reactive protein; PCT, procalcitonin.

PCT and CRP levels early after surgery were illustrated in Figure 1. Patients with infection exhibited significantly higher PCT and CRP levels compared with noninfection (both $P<0.01$). However, there were no statistically significant difference between infected and noninfected group for white blood cell count ($(9.0\pm3.8)\times10^9$ per l vs $(8.5\pm3.5)\times10^9$ per l, $P=0.445$) and ESR (8 (6–10) mm h^{-1} vs 7 (4–10) mm h^{-1}, $P=0.196$), respectively.

ROC

The area under the receiver operating characteristic curves of PCT (0.82, 95% CI 0.74–0.91, $P<0.001$) was greater than that of CRP (0.68, 95% CI 0.57–0.78, $P=0.003$), as shown in Figure 2. The Optimal Cutoff Points on the ROC curve were 0.5 ng ml^{-1} for PCT and 40 mg l^{-1} for CRP. The characteristics of the PCT and CRP measurements for predicting postoperative infection are summarized in Table 4.

Discussion

It has been largely confirmed that PCT is the only one among a large array of biochemical parameters, which closely correlates with the inflammatory host response to microbial infections.[6,17] Many studies found that PCT was an

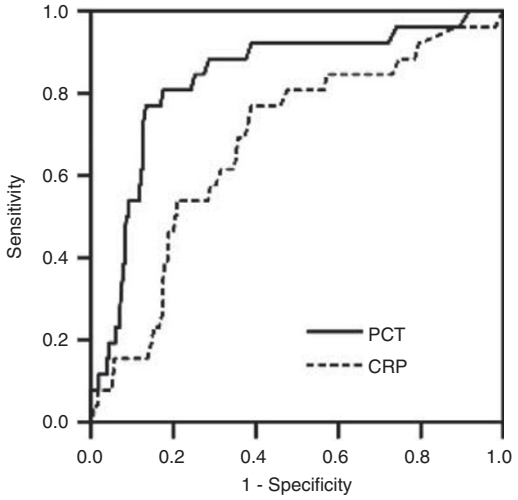

Figure 2 Receiver operating characteristic curves for the prediction of postoperative infection from PCT (straight line, AUC = 0.82) and CRP (dotted line, AUC = 0.68). CRP, C-reactive protein; PCT, procalcitonin.

excellent early predictor or diagnostic parameter superior to CRP.[6,7] Early diagnosis of a postoperative infectious complication is essential for timely and adequate treatment of this condition. However, some subsequent studies have shown opposite results,[10,18] and the prognostic and/or diagnostic value of this parameter still remains controversial. In the absence of relative study, we addressed this issue by conducting a prospective observational cohort study to determine the role of PCT in predicting postoperative infectious complication in spinal cord injury patients.

In this study, we found that a total of 26 (7.7%) of 339 patients with acute traumatic spinal cord injury were infected after surgery, which was similar to those reported in the literature.[1,2,19] Elevated leukocyte and ESR levels were more prominent in infected patients, although this did not reach statistical significance. Serum PCT and CRP concentrations early postoperatively were significantly higher in infected patients. Infections in the postoperative period of patients with spinal cord injury can lead to prolonged stay, increased morbidity and mortality, and high costs. Timely administration of adequate and effective antibiotic therapy is an important factor to solve those problems, and a thorough clinical examination and diagnostic workup is mandatory. Some reports showed that the administration of antibiotics alone had no effect on elevated PCT concentration[20] and simply administering antibiotics in the absence of an infection has no effect on CRP values,[21] suggesting that preoperative antibiotics might not direct influence on the PCT and CRP levels, however, it could have indirect effect on the PCT and CRP levels with presence or absence of infection or other relative condition. On the other hand, many previous studies demonstrated that PCT could be used to guide antibiotic therapy in patients with infection.[22–24] In patients with a new onset of infection after a procedure, various laboratory parameters such as CRP and ESR level may be misleading as they are increased in all patients in the postoperative period and are not specific for underlying

Table 4 Cutoff values of PCT and CRP for prediction of postoperative infectious complications

Variable	*Cutoff value*	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*Positive likelihood ratio*	*Negative likelihood ratio*
PCT ($ng\,ml^{-1}$)	0.1	92 (74–98)	32 (28–38)	1.35	0.23
	0.5	88 (70–97)	74 (69–79)	3.42	0.16
	2.0	23 (9–44)	94 (91–97)	4.01	0.82
CRP ($mg\,l^{-1}$)	10	85 (65–96)	27 (22–32)	1.16	0.57
	40	77 (56–91)	61 (55–67)	1.97	0.38
	80	23 (9–44)	83 (79–87)	1.39	0.92

Abbreviation: 95 % CI, 95% confidence interval; CRP, C-reactive protein; PCT, procalcitonin; .

infection.[11] A trauma itself and the inflammatory reaction caused by the trauma surgery may stimulate the production of cytokine, leading to a nonspecific increase of these commonly used markers of inflammation. Thus, there is unmet need for specific markers of infection after surgical procedure. A number of studies showed that PCT was less influenced by the different types of surgery and therefore was superior to other inflammatory markers.[8,25] However, a few of literature showed that CRP was a predictor of early postoperative infectious complications after surgery,[26,27] but not compared with PCT. Our study conforms in a cohort of postoperative patients with acute traumatic spinal cord injury that PCT is a reliable and useful biomarker for predicting postoperative infection compared with other inflammatory parameters. Some previous studies have showed that PCT could early predict or diagnose localized infections like urinary tract infection,[28] surgical site infection[8] or pneumonia.[29]

In a multivariate logistic regression analysis, both PCT and CRP concentrations were identified as independent, early predictive indicators of postoperative infectious complications. In addition, we presented receiver-operating characteristic curves evaluating the sensitivities and specificities at any given PCT cutoff point to compare the accuracy of PCT to diagnose postoperative infectious complications, and the results demonstrated that the biochemical markers PCT correlated well with postoperative infectious complications. Using cutoff points of 0.1, 0.5, and $2.0\,ng\,ml^{-1}$ for PCT showed excellent sensitivity, specificity, positive and negative likelihood ratios, with a cutoff value of $0.5\,ng\,ml^{-1}$ producing the best performance (Table 4). In addition, PCT was superior to CRP as an indicator of postoperative infection, because the ROC curve for specificity and sensitivity and the area under the ROC curve were greater for PCT than for CRP. At a cutoff of $0.1\,ng\,ml^{-1}$, PCT had a reasonable sensitivity of 92% of to exclude an infection. Conversely, in patients with PCT concentration above the cutoff of $0.5\,ng\,ml^{-1}$, the likelihood for underlying bacterial infection became high, which should be considered to diagnose an infectious etiology. Our findings suggest that, in patients with PCT levels $<0.1\,ng\,ml^{-1}$, antibiotics can be initially withheld if no obvious clinical manifestation of infection is present and the patient is in good general health. However, these patients should be reassessed the next day with a thorough clinical examination and repeat blood analysis. In contrast, in patients with PCT values of $>0.5\,ng\,ml^{-1}$, a rapid initiation of antibiotics may be warranted.

Several limitations merit consideration in this study. First, the serum markers were measured at a single time point after surgery, so we cannot exclude variability in the levels of these markers with time. However, previous studies showed that peak PCT levels are reached within 24–48 h postoperatively.[30] Second, clinical evaluation of the patients was performed on the basis of a comprehensive diagnostic and/or microbiological workup and/or the assessment by an infectious diseases consultant as diagnostic standard, so not all infectious complications met the diagnostic gold standards. Third, the case number in this study was relatively small in the infected group. Hence, findings from this study require validation in a larger population. Fourth, the determination of PCT is expensive, which is not readily accessible in all hospital.

In conclusion, this study suggests that serum PCT level is a reliable, accurate biologic marker for early predicting or diagnosing postoperative infectious complications in patients with acute spinal cord injury and exhibits greater sensitivity and specificity than CRP. Based on the results of this study, PCT can early identify postoperative infections in order to establish effective antibiotic therapy, and avoid unnecessary antimicrobial treatment in patients without infection. Obviously, postoperative infections are far too heterogeneous and complex to be reliably diagnosed on the basis of a specific cutoff value for any single surrogate marker, particularly in patients who have recently undergone surgery. So, the results are considered preliminary and need to be verified by additional large-scale multicenter prospecitve randomized controlled trials.

Conflict of interest

The authors declare no conflict of interest.

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