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Clinical Article

Comparison of Serum CRP and Procalcitonin in Patients after Spine Surgery

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Objective : Classical markers of infection cannot differentiate reliably between inflammation and infection after neurosurgery. This study investigated the dynamics of serum procalcitonin (PCT) in patients who had elective spine surgeries without complications.
Methods : Participants were 103 patients (47 women, 56 men) who underwent elective spinal surgery. Clinical variables relevant to the study included age, sex, medical history, body mass index (BMI), site and type of surgery, and surgery duration. Clinical and laboratory data were body temperature, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and PCT, all measured preoperatively and postoperatively on days 1, 3, and 5.
Results : PCT concentrations remained at <0.25 ng/mL during the postoperative course except in 2 patients. PCT concentrations did not correlate with age, sex, DM, hypertension, BMI, operation time, operation site, or use of instrumentation. In contrast, CRP concentrations were significantly higher with older age, male, DM, hypertension, longer operation time, cervical operation, and use of instrumentation.
Conclusion : PCT may be useful in the diagnosing neurosurgical patients with postoperative fever of unknown origin.

Key Words : White Blood Cell · Erythrocyte sediment rate · C-reactive protein · Procalcitonin.

INTRODUCTION

Despite advances in prophylaxis, the incidence of deep infection after instrumented spinal surgery remains between 0.4% and 4.3%[14,16,19] and may be higher in patients undergoing fusion after spinal trauma[26]. Although infection can be a disabling complication of any surgical procedure, spinal infection can be particularly devastating due to the close proximity of the neurological structures. Early detection of an infection may prevent substantial problem later.

It is often difficult to diagnose postoperative spinal infection before clinical symptoms become apparent. Magnetic resonance imaging can help to diagnose the soft-tissue change but is expensive to use as a screening tool and may not be available. Although inflammatory markers, such as C-reactive protein (CRP), white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and body temperature (BT), easily are measured, their specificities are not high.

In a recent meta-analysis, procalcitonin (PCT) was superior to CRP in differentiating bacterial from non-infectious causes of inflammation[25]. Several small studies of bacterial meningitis patients obtained similar results[6,23,29]. Since localized bacterial infections produce lower PCT levels, clinicians need to use assays with superior functional sensitivities. However, the course of PCT serum levels over time following spinal surgery is unknown.

In this study, we investigated the CRP and PCT responses of patients who did not develop infections after spine surgery for degenerative spine disease.

MATERIALS AND METHODS

This was retrospective study. All patients underwent elective spinal surgery between January 2008 and December 2008 in a single institution. Exclusion criteria were as follows : preceding the spine surgery in the previous 2 weeks, preexisting or postoperative infection, being less than 18 years of age, and being discharged less than 5 days after the spinal surgery. Clinical data relevant to the study included age, sex, body mass index (BMI), BT, site and type of surgery, and surgery duration.

All patients received a preoperative antibiotic prophylaxis with a first generation cephalosporin, cefazolin, and also postoperative antibiotics were injected through their fourth postoperative day. All patients were operated under general anesthesia and received daily clinical examinations until discharge.

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Laboratory parameters

We obtained blood samples of patients for laboratory analysis preoperatively and also postoperatively on days 1, 3, and 5. Relevant parameters included PCT, CRP, ESR, and WBC. Plasma PCT levels were measured by a time-resolved amplified cryptate emission technology assay, based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-katacalcin antibody, with a functional assay sensitivity of 0.05 ng/mL.

Statistical analysis

Statistical analysis was performed using PASW statistics (version 17.0, SPSS Inc., Chicago, IL). Data are presented as mean ± standard deviation, and statistical significance was defined as $p<0.05$ for all comparisons. We used a repeated measures ANOVA to compare means between the groups.

RESULTS

Of the patients who underwent elective spinal surgery during the study period, we initially enrolled 223 patients. We excluded 120 patients, 7 due to infection (6 previous infections and 1 postoperative) and remaining 113 patients because they either did not undergo PCT testing or were hospitalized less than 5 postoperative days. The final 103 patients were included in this study population.

There were no major complications during surgery in any of patients. Table 1 shows patient demographics and surgical characteristics. The mean age was 52.36 ± 16.13 years (range, 19-82 years), and mean surgery duration was 192.89 ± 91.78 minutes (range, 55-570 minutes).

Table 2 shows the time course of mean BT, WBC, ESR, CRP, and PCT on days 0, 1, 3, and 5. The mean BT and WBC peaked on day 1, and then declined. The mean ESR had not declined by day 5. Preoperative CRP levels were below 0.35 mg/dL in all patients but 14 patients. On the first postoperative day, CRP increased above 0.35 mg/dL in 77 patients. On the third postoperative day, 85 patients' CRP rose above 0.35 mg/dL. However, CRP decreased below 0.35mg/dL in five of the 77 patients whose CRP had increased above 0.35 mg/dL on the first day. On the fifth postoperative day, 25 patients' CRP levels were within the normal range. PCT levels before surgery were below 0.05 ng/mL in all patients. After surgery, PCT increased in 27 patients, reaching a mean value of 0.17±0.17 ng/mL, but it was still below 0.05 ng/mL in remaining patients on the first postoperative day. On the third postoperative day, PCT decreased slightly, reaching a mean value of 0.16±0.22 ng/mL in 20 patients. In eight of the 27 patients who had experienced a first-day increase, PCT normalized below 0.05 ng/mL. However, in one patient who had a PCT level below 0.05 ng/mL on the first postoperative day, the PCT level increased up to 0.25 ng/mL. On the fifth postoperative day, 6 patients had a mean PCT value of 0.15±0.15 ng/mL, while the remaining 14 patients had normalized PCT levels.

Table 1. Demographics and surgical characteristics of patients

Variables		No of patients (%)
Age	Age<40 yrs	24 (23.5)
	40 yrs≤age<60 yrs	40 (39.2)
	Age≥60 yrs	38 (37.3)
Sex	Male	56 (54.9)
	Female	46 (45.1)
Medical History	Diabetes	13 (12.7)
	Hypertension	22 (21.6)
BMI(kg/m^2)	BMI<20	3 (2.9)
	20≤BMI<25	59 (57.8)
	BMI≥25	40 (39.2)
Duration of surgery	<2 hrs	18 (17.6)
	2-4 hrs	59 (57.8)
	>4 hrs	25 (24.5)
Type of surgery		
Cervical	ACDF	14 (13.7)
	Arthroplasty	4 (3.9)
	ACDF+Arthroplasty	1 (1.0)
	Corpectomy+fusion	2 (2.0)
Lumbar	Laminectomy±discectomy	76 (74.5)
	PLIF and fixation	5 (4)

ACDF : anterior cervical discectomy and fusion, BMI : Body mass index, PLIF : posterior lumbar interbody fusion

Table 2. WBC, BT, ESR, CRP, and PCT values over time

	Time			
	Day 0	Day 1	Day 3	Day 5
WBC (×103 cells/mm^3)	7.04±1.94	10.44±2.71	8.07±2.34	7.27±2.21
BT (℃)	36.62±0.27	36.91±0.33	36.80±0.31	36.75±0.26
ESR (mm/hr)	5.64±4.53	5.89±5.50	14.09±11.82	14.32±0.61
CRP (mg/dL)	0.84±0.43	1.72±1.48	2.67±2.54	1.66±1.31
PCT (ng/mL)	*	0.17±0.17	0.16±0.22	0.15±0.15

Results are presented as the means±standard deviation. *All data were below 0.05ng/mL. We could not quantify PCT if its value was below 0.05 ng/mL due to detection limit

Time course of CRP and PCT according to factors

Fig. 1 shows CRP changes during the preoperative and postoperative days. CRP concentrations were significantly higher in association with older age, male, DM, hypertension, longer operation time, cervical operation, and use of instrumentation. There was no significant difference in CRP concentration

according to BMI.

Fig. 2 shows PCT change during the preoperative and postoperative days. PCT concentrations did not correlate with age, sex, DM, hypertension, BMI, operation time, operation site, or use of instrumentation.

DISCUSSION

Surgical site infection often causes a devastating complication in spine surgeries that prolongs the duration of the patient's hospital stay, increases medical expenditures, and worsens the patient quality of life[10,24,31]. One recent study reported a 1.25% surgical site infection rate after laminectomy and a 2.1% rate following spinal arthrodesis[12]. Rates of surgical site infection reported from individual institutions have ranged from 0% to 15%, depending on the reason for the operation, the site, the approach, and the use of instrumentation[1,9,17,30,32] The use of prophylactic antibiotics has been documented to reduce the

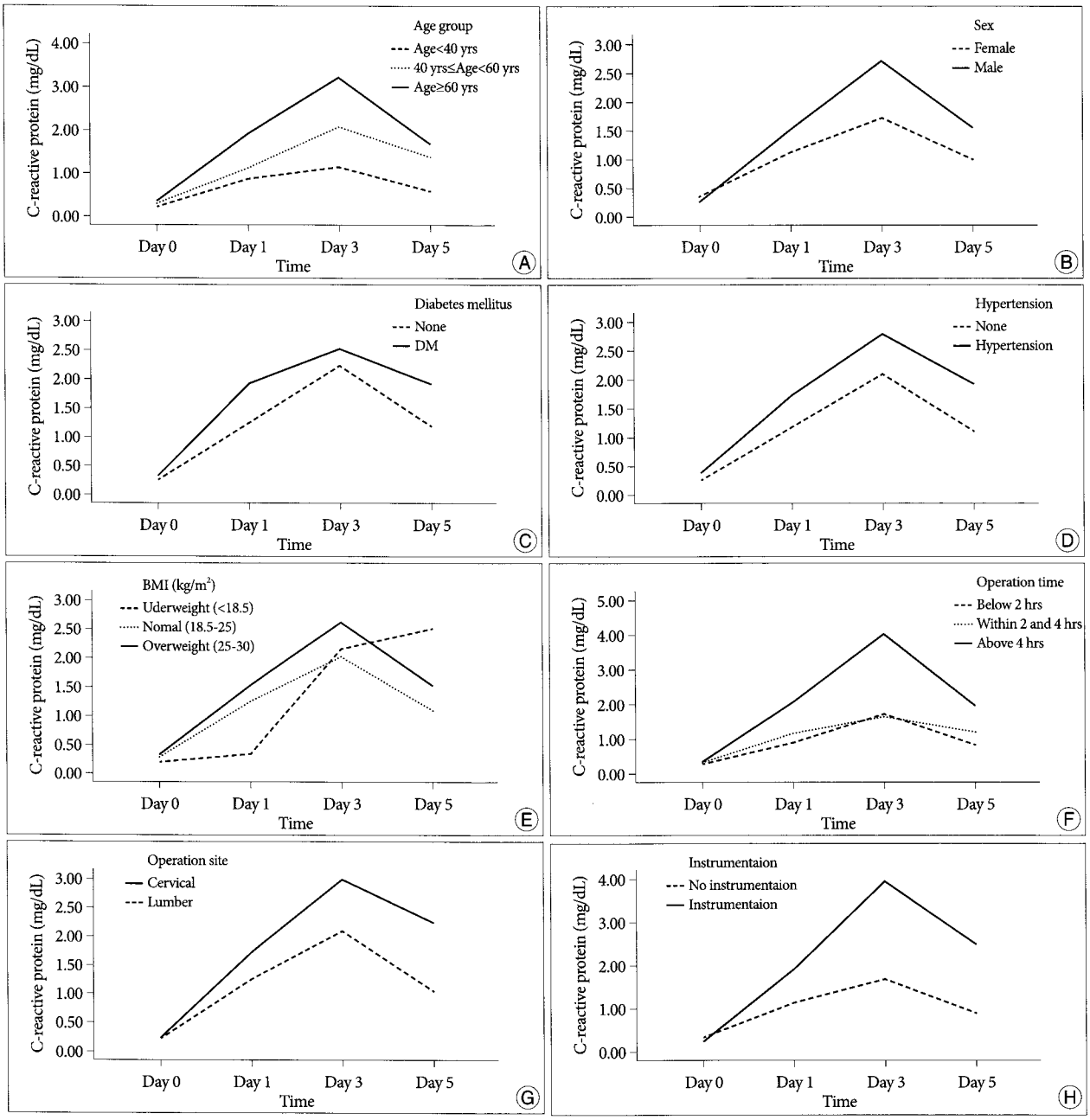

Fig. 1. Serial mean CRP concentrations. Repeated measures ANOVA demonstrated statistical significance for each factor. If a patient's CRP was below 0.35 ng/mL, we utilized the median value (0.17 mg/dL) for this analysis. A : CRP change in age groups (Age by time interaction, p=0.011). B : CRP change in sex groups (sex by time interaction, p=0.042). C : CRP change in DM groups (DM by time interaction, p=0.03). D : CRP change in Hypertension groups (hypertension by time interaction, p=0047). E : CRP change in BMI groups (BMI by time interaction, p=0.135). F : CRP change in operation time groups (operation time by time interaction, p=0.001). G : CRP change in operation site groups (operation site by time interaction, p<0.001). H : CRP change in instrumentation groups (instrumentation by time interaction, p<0.001).

surgical site infection rate. For example, the rate of surgical site infection in lumbar spine surgery has been reported as 1% to 4% with prophylactic antibiotics and 6% to 13% without them[3,20]. However, the proper duration of such antibiotic usage has long been a matter of debate.

A postoperative fever above 38°C is common in the first few days after major surgery[8]. Most early postoperative fever is caused by the inflammatory stimulus of surgery and resolves spontaneously[18]. However, postoperative fevers can also be the manifestation of a serious complication. Fever may arise due to surgical site infection, drug fever, or deep vein thrombosis. In evaluating a postoperative patient with fever, the clinician needs to consider a broad scope of possible causes and refrain from assuming the fever is due to infection.

Laboratory parameters are used for evaluating postoperative fevers. Among the laboratory parameters, ESR and CRP level

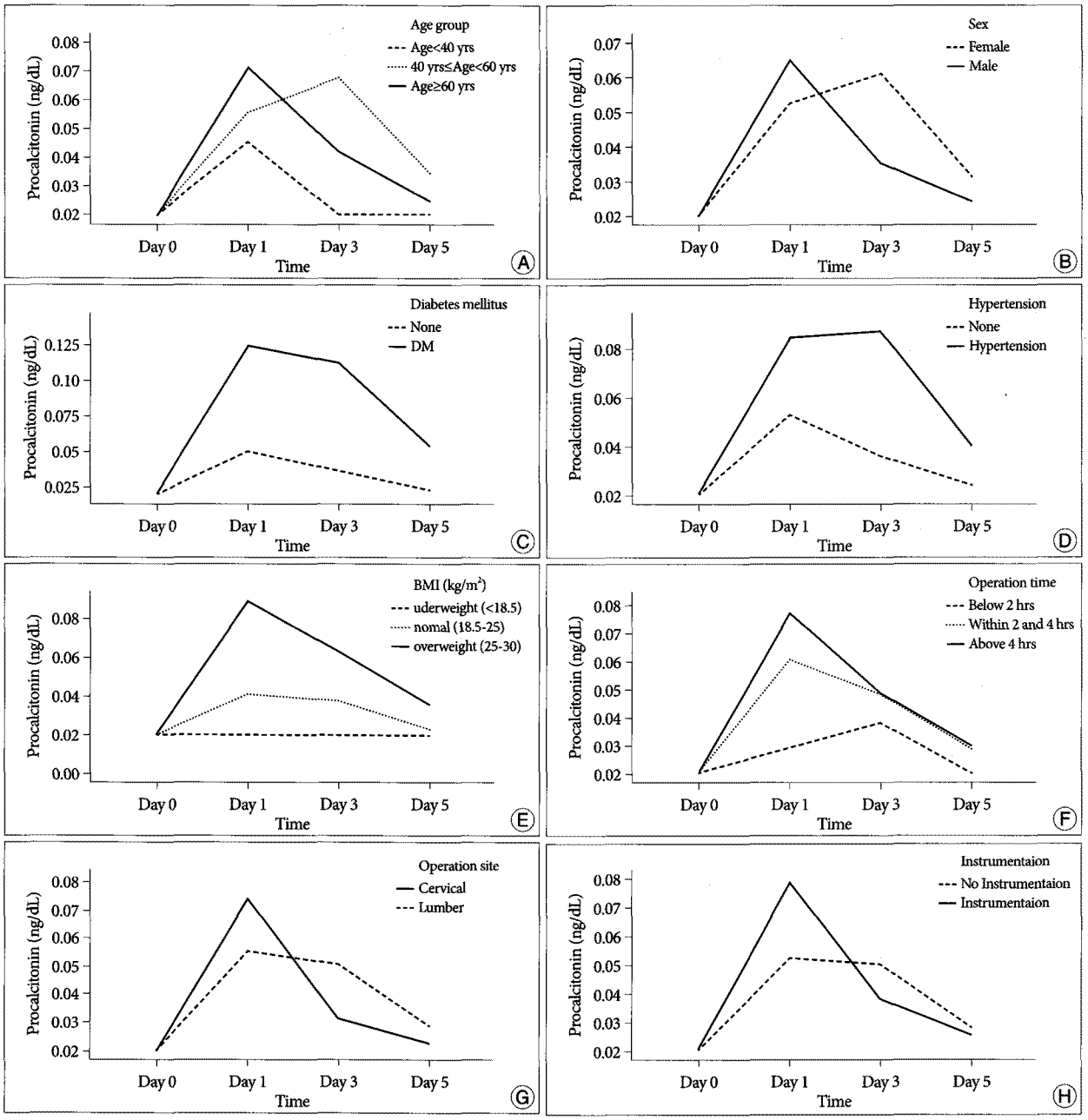

Fig. 2. Serial mean procalcitonin concentrations. Repeated measures ANOVA demonstrated statistical significance for each factor. If a patient's PCT was below 0.05 ng/mL, we utilized the median value (0.02 ng/mL) for this analysis. A : Procalcitonin change in age groups (age by time interaction, p=0.292). B : Procalcitonin change in sex groups (sex by time interaction, p=0.097). C : Procalcitonin change in DM groups (DM by time interaction, p=0.088). D : Procalcitonin change in Hypertension groups (hypertension by time interaction, p=0.156). E : Procalcitonin change in BMI groups (BMI by time interaction, p=0.298). F: Procalcitonin change in operation time groups (operation time by time interaction, p=0.461). G : Procalcitonin change in operation site groups (operation site by time interaction, p=0.340). H : Procalcitonin change in instrumentation groups (instrumentation by time interaction, p=0.247).

have been used and recently, PCT test has been tried as bacterial infection marker.

The ESR is the rate at which red blood cells precipitate in a period of 1 hour. It is a common hematology test which is a non-specific measure of inflammation. Any cause or focus of inflammation increases ESR. The ESR increases in pregnancy or rheumatoid arthritis, and decreases in polycythemia, sickle cell anemia, hereditary spherocytosis, and congestive heart failure[15,22,27]. The clinical usefulness of ESR is limited to monitoring. Its usefulness as a screening test is limited by its low sensitivity and specificity in postoperative patients. In this study, ESR did not decline until the postoperative day 5. Although we did not compare our cases with infection cases, we think ESR is not a good marker of bacterial infection.

CRP is an acute phase protein, and hepatocytes synthesize in at an increased rate in the acute phase of many human afflictions. Its normal concentration in healthy human serum is usually lower than 1 mg/dL, increasing slightly with ageing. Higher levels are found in late pregnancy, mild inflammation, and viral infections (1-4 mg/dL); active inflammation and bacterial infection (4-20 mg/dL); severe bacterial infections and burns (> 20 mg/dL)[4]. CRP levels normally rise within 2 to 6 hours after surgery and then go down by the third day after surgery. Ellitsgaard et al. conducted a study (on 140 elderly patients with hip fractures) that measured CRP and ESR during the week after the operations[7]. The postoperative ESR in uncomplicated cases remained elevated 1 week after surgery, while the CRP peaked at day 2 and normalized by day 7. Mun et al.[11] reported that, if there is persistent elevation or second rise around a week after surgery, the wound infection should be considered. Takahashi et al. found that the post-operative CRP reached its peak on day 2 and remained abnormally elevated even after six weeks[28]. Aono et al. reported that age, gender, body temperature, operating time, and blood loss did not correlate with the CRP level[2]. Our data showed that CRP peaked around the third postoperative day and had not normalized by day 5. CRP concentrations were significantly higher in older age, male, DM, hypertension, longer operation time, cervical operation, and use of instrumentation. During the postoperative period, high CRP levels could confuse the physician's interpretation and lead to unnecessary antibiotic usage.

PCT is a 116-amino-acid peptide. Its sequence is identical to that of the pro-hormone of calcitoinin, but PCT itself has no known hormonal activity[21]. Under normal metabolic conditions, PCT is only present in the thyroid gland's C cells. PCT is cleaved into calcitonin, katacalcin and a protein residue. The PCT level in healthy individuals is below clinical assay's detection threshold (0.01 ng/mL), and its half life is 25 to 30 hours[13]. Previous studies have shown that it is closely associated with the human host response to bacterial infection. In bacterial infection and sepsis, intact PCT is found in the blood in response to endotoxins, and several pro-inflammatory mediators and its concentration appear to be roughly linear with the degree of insult[5]. In our data, PCT levels peaked on the first postoperative day and dropped below 0.5 ng/mL, except for 2 patients, during the postoperative period. In addition, PCT levels did not correlate with clinical and surgical factors.

There were 7 patients with infection during study period (4 tuberculosis spondylitis, 2 epidural abscess, and 1 suspicious postoperative infection). PCT was checked on only admission day and was not checked in suspicious cases of postoperative infection. In patients with tuberculosis spondylitis, ESR and CRP increased above normal level but PCT did not increase (below 0.10 ng/mL). In patients with epidural abscess (Streptococcus pneumoniae and Staphylococcus aureus were identified in abscess culture, respectively), ESR, CRP, and PCT increased. In patient with suspicious postoperative infection, CRP mildly increased, ESR did not increased and PCT was not checked. Intraoperative finding showed only postoperative change and no bacteria was identified in tissue culture.

The present study's limitations include that it was not a case-controlled study. Therefore, we do not know what the sensitivity and specificity of the tests are. A second limitation is the short follow-up parameter with a relatively small sample size. We could not show the parameter's exact time courses due to the short follow-ups and could have missed meaningful differences due to small sample size. One final limitation is the routine administration of antibiotics to these patients through postoperative day 4.

CONCLUSION

The present study demonstrates that PCT levels, in contrast to conventional markers of inflammation, did not increase during the postoperative course following elective spinal surgeries of infection-free patients. It remained at <0.5 ng/mL in all but 2 patients. Elevated serum PCT levels of >0.5 ng/mL may serve as a useful tool for the evaluating fevers of unknown origin following neurosurgery. Because of the substantial morbidity and mortality resulting from treatment delays, empirical antibiotic therapy is recommended for every case of suspected infection in post-operative patients. A test having high sensitivity and specificity could have the potential to minimize unnecessary antibiotics therapy in non-infected patients. We believe that the PCT test could be one candidate for such test.

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