RESEARCH NOTE

Dynamics of serum procalcitonin in patients after major neurosurgery

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ABSTRACT

Classical markers of infection cannot differentiate reliably between inflammation and infection after neurosurgery. This study investigated the dynamics of serum procalcitonin (PCT) in patients following major neurosurgery. PCT concentrations remained <0.2 ng/mL during the post-operative course. In contrast, leukocyte and neutrophil counts, as well as C-reactive protein (CRP) levels, increased significantly post-operatively (leukocytes, range $7.1–23.7 \times 10^9$/L, $p < 0.001$; neutrophils, range 70.8–94.5%, $p < 0.001$; CRP, median 14 mg/L, range 3–95 mg/L, $p < 0.001$). Analysis of PCT levels using assays with improved sensitivity may be useful in the diagnosis of neurosurgical patients with post-operative fever of unknown origin.

Keywords Diagnosis, fever of unknown origin, meningitis, neurosurgery, post-operative, procalcitonin levels

Original Submission: 28 November 2004; **Revised Submission:** 17 February 2005; **Accepted:** 6 March 2005

Clin Microbiol Infect; 2005; 11: 679–681
10.1111/j.1469-0691.2005.01205.x

Clinical signs of meningitis and post-operative fever are frequent in neurosurgical patients [1], and antibiotics are often administered without proof of infection. The clinical characteristics of patients with aseptic and bacterial meningitis overlap markedly [2]. Standard tests with cerebrospinal fluid fail to discriminate between these two syndromes [3,4], with the exception of lactate concentrations ≥ 4 mmol/L [5]. Fever after neurosurgery is frequently caused by impaired thermoregulation, and a reliable marker for infection following neurosurgery is still required.

In a recent meta-analysis, procalcitonin (PCT) was superior to C-reactive protein (CRP) in differentiating bacterial from non-infectious causes of inflammation [6]. Similar results were obtained in several small studies of patients with bacterial meningitis [7–10]. However, the normal course of PCT serum levels following neurosurgery is unknown. Since localised bacterial infections produce lower levels of PCT [11], it is important to use assays with improved functional sensitivities. The aim of the present study was to investigate the dynamics of PCT levels in patients following uncomplicated major neurosurgery.

Between January and May 2002, the study prospectively enrolled all patients aged ≥ 18 years who were undergoing major neurosurgery at the University Hospital Basel, Switzerland, a 780-bed academic primary- and tertiary-care hospital. Major neurosurgery was defined as surgery that involved opening of the dura. Exclusion criteria were neurosurgery in the previous 2 weeks, a life-expectancy of <7 days, and infection. Blood samples for laboratory analyses (white blood cell count, neutrophil count, CRP and PCT levels) were obtained pre-operatively (day 0) and post-operatively on days 1, 2, 3, 5 and 7. All patients had a daily clinical examination until discharge. Diagnosis of post-operative infection was made in accordance with the CDC definitions of nosocomial infection [12]. Plasma PCT levels were measured by a time-resolved amplified cryptate emission technology assay (Kryptor; Brahms Hennigsdorf, Berlin, Germany), based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-katacalcin antibody [13], with a functional assay sensitivity of 0.06 ng/mL [14]. Categorical variables were compared using the chi-square-test, whereas continuous variables were compared using the Wilcoxon rank sum test or *t*-test, as appropriate. Proportions were compared using the proportions test. All statisti-

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cal analyses were performed using S-Plus Professional v. 6.1 (MathSoft, Cambridge, MA, USA). The study was conducted according to local ethics committee standards, with informed consent from each patient.

Fifty patients undergoing major neurosurgery were enrolled. Two patients were excluded because of post-operative central nervous system infection with *Propionibacterium acnes*. Baseline characteristics and final diagnoses for the remaining 48 patients are shown in Table 1. PCT levels were not elevated during the post-operative course, compared to pre-operative levels, and remained < 0.2 ng/mL (Fig. 1). In contrast, leukocyte and neutrophil counts, as well as CRP levels, were raised significantly post-operatively, with a maximum on day 1 (leukocytes, range 7.1–23.7 $\times 10^9$/L, $p < 0.001$; neutrophils, range 70.8–94.5%, $p < 0.001$; CRP, median 14.0 mg/L, range 3–95 mg/L, $p < 0.001$). Three days after surgery, 42.6% (25.0%) had elevated CRP levels of > 10 mg/L, 60.9% (55.8%) had an elevated leukocyte count, and 69.6% (31.0%) had elevated neutrophil counts. Core temperatures were raised post-operatively, with a maximum at day 1 compared to baseline levels ($p < 0.0001$), but did not exceed 38.5°C.

Post-operative induction of PCT depends largely on the type of surgery and/or the degree of trauma. PCT levels > 0.5 ng/mL are observed in 21% of patients after minor aseptic orthopaedic or vascular surgery, in 48% after cardiothoracic surgery, and in 65% after major intra-abdominal surgery [14–16]. Peak levels are seen post-operatively on day 1, and decline thereafter according to the half-life of PCT, whereas CRP levels reach a maximum on day 2 [17]. Triggers and sites of PCT production remain unclear. In volunteers, PCT induction can be stimulated by intravenous injection of endotoxin, resulting in elevated PCT levels a few hours after an increase in interleukin-6 and tumour necrosis factor-α levels [18]. In meningitis, the pro-inflammatory effect of cytokines is controlled by anti-inflammatory cytokines, which may impair the host's inflammatory response [19] and suppress the production of PCT.

Table 1. Characteristics and final diagnoses of patients undergoing major neurosurgery (n = 48)

Gender, male, *n* (%)	23 (47.9)
Age (years), median (range)	52 (21–75)
Steroid therapy, *n* (%)	44 (91.7)
Duration of hospitalisation (days), median (range)	14 (9–30)
Duration of surgery (h), median (range)	3.9 (1.2–10.3)
Diagnosis	
Tumour resection, *n* (%)	34 (70.5)
Glioma, *n*	9
Meningeoma, *n*	8
Metastases, *n*	4
Adenoma, *n*	4
Haemangioma, *n*	3
Astrocytoma, *n*	3
Others, *n*	3
Aneurysm clipping, *n* (%)	6 (12.5)
Decompression, *n* (%)	3 (6.3)
Others, *n* (%)	5 (10.4)

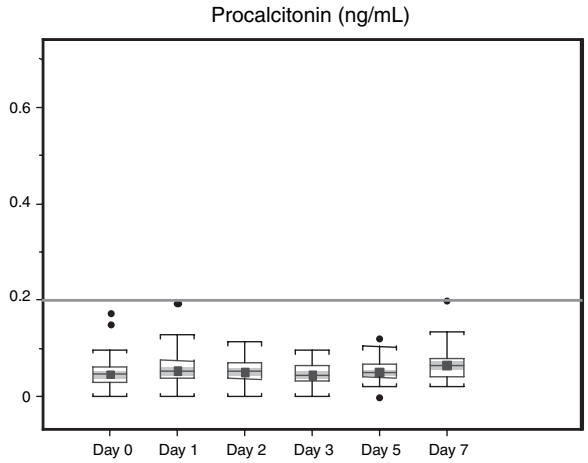

Fig. 1. Box-whisker plot of procalcitonin levels during the pre- and post-operative course in patients following uncomplicated neurosurgery (days 0–7). Data shown are the median (squares) with 95% confidence interval of the median (shaded areas), 25th–75th percentile (open boxes), upper and lower fence (whiskers) and outlying values (circles).

The present study demonstrated that PCT levels, in contrast to conventional markers of inflammation, did not increase during the post-operative course following major neurosurgery and remained < 0.2 ng/mL. Thus, elevated serum PCT levels of > 0.2 ng/mL could serve as a useful tool for the evaluation of fever of unknown origin following neurosurgery. Because of the substantial morbidity and mortality resulting from treatment delay, empirical antibiotic therapy is recommended for every case of suspected infection in patients following neurosurgery [4]. A test that could reliably identify patients with infections would have the potential to minimise unnecessary antibiotic therapy in non-infected patients. However, limited experience suggests that only 50% of patients with localised bacterial infections of the central nervous system (brain abscesses, post-operative abscesses and ventriculo-peritoneal shunt-related infections) have elevated serum

PCT levels of > 0.2 ng/mL (unpublished data). A small study showed a low sensitivity for PCT in the diagnosis of bacterial meningitis in adults, especially for nosocomial bacterial meningitis following neurosurgery [20]. Conflicting results exist in patients with bacterial ventriculitis related to temporal external ventricular drainage. Thus, Martinez *et al.* [21] reported low PCT levels in the presence of a positive bacterial culture, whereas Berger *et al.* [22] demonstrated elevated PCT levels, even for infections with bacteria of low virulence.

In order to determine the future diagnostic role of PCT, tests with improved low-level sensitivity must be used [23], with particular regard to a possible cut-off value of 0.2 ng/mL following neurosurgery. PCT levels in almost all clinical studies published previously have been measured by less sensitive assays, unable to measure levels < 0.3 ng/mL. The present study used a commercially available ultrasensitive assay with a functional sensitivity of 0.06 ng/mL. PCT levels did not appear to be elevated above 0.2 ng/mL in the post-operative course following major neurosurgery. Therefore, a similarly sensitive PCT assay should be used in future studies evaluating neurosurgical patients with post-operative fever of unknown origin.

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