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ORIGINAL RESEARCH

Early monitoring of ventriculostomy-related infections with procalcitonin in patients with ventricular drains

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Abstract Several factors are implicated in the increased vulnerability of multiple trauma victims to infection, especially in intensive care units. The incidence of EVD related infections ranges from 5 to 20 %. To assess the accuracy of serum procalcitonin (PCT) in predicting central nervous system (CNS) infection in patients with EVDs. Thirty-six adult patients with severe head trauma were enrolled in this prospective study, after exclusion of other causes of fever; patients were subjected to sampling of C-reactive protein (CRP), PCT, and cerebrospinal fluid (CSF) cultures every other day. Five patients developed ventriculostomy-related infections, and all had an elevated serum PCT concentration. Patients with negative CSF cultures had mean serum PCT <2.0 ng/ml, while patients with positive culture had early elevation of serum PCT with mean of 4.18 ng/ml, CRP did not show similar early changes. Patients who acquire CNS infection had prolonged length of stay in hospital and length of ventilation. In absence of other nosocomial infections, early high serum PCT concentrations appear to be a reliable indicator of bacterial CNS infection in patients with EVD.

Keywords Procacitonin · External ventricular drain · Meningitis

Abbreviations

APACHE II	Acute physiology and chronic health evaluation score II
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
CSF	Cerebrospinal fluid
CRP	C-reactive protein
DC	Decompressive craniectomy
ECL	Electrochemiluminescence
EVD	External ventricular drain
GCS	Glasgow coma scale
ICP	Intracranial pressure
ICU	Intensive care unit
ICULOS	Length of stay in ICU
ICULOV	Length of ventilation in ICU
MRSA	Methicillin-resistant staphylococcus aureus
PCT	Procalcitonin
T_{max}	Maximum temperature
WBC	White blood cell count

1 Introduction

Procalcitonin (PCT) has been widely studied as a marker for bacterial infection and the utility of PCT as an indicator

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of severe sepsis is now widely acknowledged. Limper et al., described PCT as a biomarker differentiating infections from non-infectious fever [1].

The clinical features of sepsis and non-infectious systemic inflammatory response syndrome (SIRS) are similar. Physiologic limitations, such as the criteria for SIRS, are neither specific nor sensitive for sepsis. Microbiologic cultures are time-consuming and sometimes inconclusive; a minimum of 24–48 h is needed for final quantitative results, and infection cannot be excluded on the basis of negative cultures. Clinical value would therefore be gained from the availability of a rapidly obtainable marker that was effective at distinguishing infectious from non-infectious sources, and ideally would also be highly specific, highly sensitive, conveniently measurable, inexpensive, and capable of providing information about severity and prognosis [2]. PCT plasma level tends to increase with severe bacterial or fungal infections, with levels as high as 1,000 ng/ml reported in cases of sepsis and septic shock [3].

External ventricular drain (EVD) is considered an important interventional procedure in emergency neurosurgery; it consists of a catheter inserted into the ventricular system connected to a tubing system that ends in a collection bag. The reason for placement of such a device is to drain cerebrospinal fluid (CSF), which is a secondary consequence of multiple intracranial disorders (e.g., traumatic brain injury, hydrocephalus, intracranial hypertension, intracranial hemorrhage, ventriculitis, and other intracranial neoplasms or vascular malformations) [4].

Ventriculostomy-related infection (VRI) is a relevant cause of morbidity and mortality, especially in traumatic head injury, and these patients are at high risk of nosocomial infections. Weisbrod et al. [5] reported an association between VRI and meningitis (24.8 %), systemic infection (27.0 %), and mortality (5.8 %) during hospital stay. Beer et al. [6] noted a high rate of VRI, with reported incidences between 5 and 20 %, where the predisposing factors are related to the non-adherence to strict insertion and maintenance protocols, leakage of CSF, frequency of EVD manipulation and catheter irrigation.

An increased risk of infection has been observed in cases of prolonged catheterization and with repeated insertions. Moreover, use of local or systemic antibiotics does not appear to reduce the infectious complications of EVD. Routine surveillance cultures of CSF were not more likely to detect infection than cultures obtained when clinically indicated [7]. Multiple interventions have been described for early prevention and treatment of VRI. Leverstein-van Hall et al. [8] observed that a significant reduction in the incidence of VRI was associated with a strategic approach composed of increased awareness, focused standard operating procedures, a diagnostic and therapeutic algorithm, timely administration of prophylaxis, improvement of the drainage system, hair removal, performing the procedure in the operating room, wearing protective precautions, disinfection of the lock system before handling, only sampling CSF when indicated, and suturing the skin when CSF leakage occurs after drain removal. Thus, early monitoring of VRI would appear to be an ideal goal.

PCT possesses a high specificity for bacterial infections and is not found in fungal or viral infections; unlike C-reactive protein (CRP), PCT increases rapidly after infection with an initial peak at around 36 h [9]. PCT is a 116 amino acid protein with a molecular weight of 13 kDa and is a precursor of calcitonin hormone. A high PCT level is found in bacterial sepsis, and this may provide greater diagnostic reliability than CRP, and may also correlate with prognosis prediction [10]. We hypothesize that early diagnosis with this potent marker could direct an early treatment approach that would likely enhance patient safety.

2 Aim of the work

To assess the accuracy of serum PCT in early prediction of central nervous system (CNS) infection in patients with EVDs.

3 Patients and methods

The observational prospective study was conducted over a period of 2 years from February 2008 to January 2010 after approval by the ethical committee. Patients subjected to EVD treatment were included in the study. We excluded patients who had received prolonged antibiotic therapy, and patients with evidence of extracranial infection. Patients were tested every other day for serum (CRP and PCT), and CSF cultures, and daily for white blood cell count (WBC). All patients in the neurosurgical intensive care unit (ICU) were to receive EVD treatment during the period of study for treatment of: post-traumatic brain edema (31 patients); hydrocephalus caused by intracranial hemorrhage (three patients); and CSF pathway occlusion because of posterior fossa or ventricular tumors (two patients). Patients were either in critical condition because of their original disease or after surgical procedure for tumors. Patients received antibiotic prophylaxis in the form of ampicillin and sulbactam before EVD insertion. After scalp shaving, the skin was prepared with chlorhexidine ethanol solution, and a silicone catheter was then introduced through a precoronal burr hole into the ventricle, tunneled subcutaneously for a distance of 4–6 cm from the

insertion point. This was connected to an 8 cm pressure-resistant tube and then to a manifold consisting of two three-way stopcocks.

3.1 Catheter care and CSF sampling

Both the extracranial components of the drainage system and the intracranial pressure (ICP) transducer were exchanged every 48 h. The vacant tap was used for flushing the catheter, procuring CSF samples, and ICP transducer zeroing, while the CSF sampling was carried out according to strict protocol by experienced ICU staff. Chlorhexidine-ethanol was utilized for connecting-point disinfection, and system manipulation took place under complete aseptic precautions.

3.2 Laboratory parameters

A ventricular drain was used to obtain 2–3 mL of CSF every alternate day, which was examined for cell count, total protein concentration, and glucose concentration. Microbiological CSF cultures were taken every other day. Pleocytoisis was deemed when the CSF white cell count was above 50/mm^3 [11]. Peripheral white cell counts were taken daily and leucocytosis was defined when higher than 11,000 cells/mm^3. Patients' maximum temperature was recorded daily (T_{max}); temperatures in excess of 38 °C were considered fever. When the ventricular catheter was removed, the tip was cultured and patients with associated infections from other sources were excluded from the study. Patients were divided into two groups: Group I, who did not exhibit evidence of CSF infection; and Group II, from whom CSF organisms were cultured. Blood culture was also taken if T_{max} exceed 38 °C, and patients with associated infections from other sources were again excluded from the study.

3.3 Clinical and functional investigations

The Glasgow coma scale (GCS) was assessed on admission and acute physiology and chronic health evaluation (APACHE) II score was used to determine the initial severity of illness [12].

3.4 Blood sampling and biochemical assays

An electrochemiluminescence (ECL) technology cobas e411 analyzer for PCT was used, which was then measured by an immunoluminometric 'LUMItest®PCT'-kit (BRAHMS–Diagnostica GmbH, Berlin, Germany), and CRP quantified by the Turbi-Quanti method (Behring, Marburg, Germany) [13]. The test required 2 ± 3 h and 20 ml of serum or plasma. The PCT and CRP upper normal limits are 0.5 ng/ml and 0.5 mg/dl respectively. Drain-related infection was considered if the drain had been in place for at least 24 h or had been removed within 5 days prior to the diagnosis. The meningitis or ventriculitis criteria of Centers for Disease Control and Prevention (CDC) were used, consideration of infection to be drain-related if at the diagnosis time if the drain had been in place for at least 24 h or removed within 5 days before making the diagnosis [14]. Hospital-acquired infection was also defined according to CDC criteria, which included organisms cultured form CSF, or one of the signs and symptoms that might suggest infection without identified cause (fever > 38 °C, headache, stiff neck, meningeal signs, cranial nerve signs, or irritability) and at least one of the following: increased WBCs count; elevated protein and/or decreased glucose in CSF; organism apparent in CSF Gram stain of CSF; blood culture of organism; or diagnostic single antibody titer [15, 16].

3.5 Statistical analysis

Descriptive statistics (i.e., mean, SDs, and frequency distribution of the variables with percentages) were calculated according to the characteristics of the variables. Student's *t* tests were applied to determine significant mean differences between non-organism and organism categories for interval variables. Levene's test for equal variances was checked and the probability for non-equal variance is taken if the interval variable is not normally distributed. Chi square tests and Fisher's exact tests (wherever applicable) were applied to determine the significant associations between non-organism and organism with other categorical variables. SPSS 20.0 statistical package was used for the analysis. *P* value 0.05 (two tailed) was considered as the statistical significance level.

4 Results

For this study, 74 prospective participants were reviewed; of these, 36 adult patients due to receive an EVD were enrolled in the final analysis. The demographic and clinical variables are noted in Table 1; 30 male and 6 female subjects were enrolled in our study, with a mean age of 32.83 ± 10.8 years. The most common reason for placing an EVD was severe head trauma (86.1 %), followed by intracerebral hemorrhage (5.6 %), tumors (5.6 %), and subdural hemorrhage (2.8 %). Twenty-nine patients required placement of one EVD through their ICU course, six patients had placement of EVD twice, and one patient required replacement three times. Decompressive craniectomy (DC) was needed to control severe intracranial hypertension in 25 patients (69.4 %). Five patients (13.9 %) developed VRI. The mean time of drains in the

Table 1 Characteristics of demographic and clinical variables

Variable	N (%)
Gender	
Males	30 (83.3)
Females	6 (16.7)
Age (mean ± SD)	32.83 ± 10.8
Indication for placement	
Trauma	31 (86.1)
Interacerbral haemorrhage	2 (5.6)
Tumours	2 (5.6)
Subdural haemorrhage	1 (2.8)
Hypertension	3 (8.3)
Diabetes	4 (11.1)
Number of drain along the course	
1	29 (80.6)
2	6 (16.7)
3	1 (2.8)
Decompressive craniectomy	25 (69.4)
Meningitis	5 (13.9)
Drain days	1–16
(mean ± SD)	(7.11 ± 3.67)
Isolated organism	5 (13.9)
Escherichia coli	2
Pseudomonas aeruginosa	1
MRSA	1
Staphylococcus epidermidis	1

Figures in parenthesis are in percentages

Table 2 Clinical and laboratory variables

Value	Mean ± SD	Median	Range
Drain days 1–16	7.11 ± 3.67		
Initial PCT 48 h (ng/ml)	2.26 ± 1.97	2.0	6
Initial CRP 48 h (mg/l)	28.81 ± 13.88	22.0	42
PCT $4t^h$ day (ng/ml)	4.72 ± 8.53	1.00	6
CRP $4t^h$ day (mg/l)	34.31 ± 20.83	24	56
PCT $6t^h$ day (ng/ml)	5.69 ± 9.32	2.0	16.5
CRP $6t^h$ day (μg/l)	44.83 ± 43.28	3	67
APACHE II score	17.67 ± 5.37	4	27
Initial GCS	5.58 ± 2.26	3	11
ICU length of stay (days)	12.94 ± 8.69	5	36
Length of ventilator (days)	11.31 ± 8.98	2	32

related ventricle was 7.11 ± 3.67 days. The causative organism was Escherichia coli in two patients, *Pseudomonas aeruginosa*, *Methicillin-resistant staphylococcus aureus* (*MRSA),* and *Staphylococcus epidermidis* in one patient each. We relied on the CDC criteria for initial VRI diagnosis [14–16]. A positive Gram stain of the CSF was found in four out of the five patients that had developed fever and high WBCs count, supporting the validity of CSF diagnosis.

The clinical and laboratory variables assessed included mean drain days, and the initial CRP and PCT at 48 h after drain insertion, before microbiologic evidence of infection, and on the $4t^h$ and $6t^h$ days (Table 2). The mean APACHE II and GCS scores were noted on admission. The mean length of stay in ICU (ICULOS) and mean length of ventilation (LOV) were reported.

Both groups in our study were matched regarding sex, indication for insertion of an EVD, and association of diabetes or hypertension (Table 3), as well as initial APACHE II score and GCS (Table 4). In Table 3, the main differences between patients with culture-positive meningitis and those without evidence of CNS infection were highlighted. There was no statistical difference between the groups regarding gender, clinical cause of insertion of the EVD, association of diabetes or hypertension, number of drains inserted, and the association with DC. The catheter tip was positive in three patients in Group I, versus two patients in Group II.

The initial PCT level was significantly higher in patients who developed VRI than in patients without VRI. Three patients also developed early microbiological evidence of meningitis and the CRP was also higher in these patients, but this did not reach statistical significance; the PCT would be expected to show a statistically significant difference between patients with meningitis and those without. APACHE II score and GCS scores did not show a significant difference between both groups on admission. Group II showed longer ICU length of stay and longer length of ventilation. The mean T_{max} was higher in patients with infection but did not reach statistical significance (Table 4).

Decompressive craniectomy patients had significantly higher initial CRP ($P = 0.04$) than patients without DC, but no significant differences in the rest of the mediators over the course.

5 Discussion

The identification of an indicator that reports progress of infection in ICU patients is a desirable goal. In our study, we found significantly higher PCT levels in subjects with VRI (Table 4), which was not the case with CRP. Martinez et al. [17] emphasized the value of early detection of VRI in relation to outcome. Dismal outcome could be associated with high levels of acute-phase proteins including

Table 3 Associations in organism and non organism in categorical variables

Variable	Non-organism (N = 31)	Organism (N = 5)	*P* Value
Gender—male	26 (83.9)	4 (80)	1.00
Indication			
Trauma	26 (83.9)	5 (100)	0.82
Intracerebral haemorrhage	2 (6.5)	0 (0)	
Tumours	2 (6.5)	0 (0)	
Subdural haemorrhage	1 (3.2)	0 (0)	
Hypertension	2 (6.5)	1 (20)	0.88
Diabetes	2 (6.5)	2 (40)	0.55
Isolated organism from catheter tip	3 (11.5)	2 (40)	0.45
No of drains			
1	27 (87.1)	2 (40.0)	0.11
2	4 (12.9)	2 (40.0)	
3	0 (0.0)	1 (20.0)	
Decompressive craniectomy	22 (71.0)	3 (60.0)	1.00

Figures in parenthesis are in percentages

Table 4 Demographic and clinical variables and their comparison according to organism vs non-organism

Variable	No-organism	organism	*P* value
Age	31 ± 9.23	41 ± 16.6	0.07
Initial PCT 48 h (ng/ml)	1.88 ± 1.33	4.18 ± 4.41	0.05
T_{max} (°C)	37.45 ± 0.65	38.84 ± 0.37	0.3
Initial CRP 48 h (mg/l)	27.97 ± 14.29	34.00 ± 10.77	0.38
PCT4 (ng/ml)	1.91 ± 1.57	22.14 ± 13.37	0.03
CRP4 (mg/l)	29.42 ± 15.23	64.60 ± 26.97	0.001
PCT6 (ng/ml)	2.46 ± 3.01	25.80 ± 10.26	0.007
CRP6 (mg/l)	29.26 ± 16.21	141.40 ± 29.64	0.001
APACHE II score	17.42 ± 5.31	19.20 ± 6.10	0.50
Initial GCS	5.81 ± 2.29	4.20 ± 1.64	0.14
ICU days	10.97 ± 6.94	25.20 ± 9.04	0.001
Ventilator days	9.26 ± 7.22	24.0 ± 9.03	0.001

CRP and PCT at the onset of sepsis [18]. Tschaikowsky et al. [19] found that PCT and interleukin (IL) 6 levels significantly decreased from days 1–14, whereas CRP did not. However, no single cut-off value of PCT, IL-6, or CRP allowed survival prediction. EVD has recently emerged as a monitoring and treating device that allows external CSF drainage. However, bacterial meningitis is a principal complication of this approach, the consequences of which are higher morbidity, mortality, and health care costs [8]. We observed a relatively high rate (13.9 %) of nosocomial meningitis in our study (Table 1). Hoefnagel et al. [20] reported a VRI incidence range of 23.2 % when EVDs were placed.

Multiple factors may cause drain contamination and related bacterial meningitis, including insertion-associated contamination, colonization of the drain during unprompted disconnection, and site specific-infection which contaminates the drain directly with CSF from infected soft tissue; the latter may be associated with Staphylococcus aureus, where CSF leakage is a strong association [21]. Early diagnosis of VRI remains an optimum target, where prompt intervention could save the patient's life as removal of the catheter is usually advocated [22], and some authors advise prophylactic antibiotics and the usage of an antibiotic-coated EVD [23]. In our study, the catheter was removed when we found evidence of infection in the CSF.

Establishing the diagnostic accuracy of serum PCT in CNS infection in patients with EVDs was the primary objective of our study. We followed the multidisciplinary bundle suggested by Leverstein-van Hall to reduce infections [8]. Despite these measures, we found an infection level of 13.9 % in our patients; while this is within international standards, it mandates that early measures should be taken to prevent and treat these potential infection.

The clinical findings are often confusing in patients with severe head trauma, where fever may be due to multiple etiologies. Moreover, deeply sedated or comatose patients cannot exhibit the early clinical warning signals of

meningitis, and the use of antipyretics may suppress fever symptoms. Criteria for SIRS are neither specific nor sensitive for sepsis, and non-specific inflammatory markers tend to increase with tissue injury. Moreover, microbiological data are time-consuming and may be non-diagnostic. Therefore, a rapidly obtainable marker that is capable of discriminating sepsis from non-infectious SIRS would be clinically valuable [2]. Rath et al. [24] recently concluded that a combined approach utilizing a multiplex PCR assay on CSF samples in combination with intrathecal biomarkers could diagnose EVD related infections.

To detect infection in patients with drains, CRP and WBC counts are typically used, which are unable to differentiate infection and inflammation; the appropriate diagnosis is usually based on microbiological cultures [25]. Given the need for rapid prediction of infection in such a scenario, we decided to test the hypothesis that PCT may possess this function. In our study, we find that PCT was significantly elevated in patients who have microbiological evidence of CNS infection 48 h before the report could be withdrawn. Whereas, CRP was slightly elevated in the infected group without statistical significance (Table 4). Setting a PCT level for predicting bacterial meningitis was not among our objectives, however, we found that patients with a PCT level of less than 2 ng/ml were unlikely to have bacterial meningitis. This was in agreement with Alkholi et al. [26] who mentioned that a serum PCT level higher than a 2 ng/ml cut-off is associated with high sensitivity (100 %) and high negative predictive value (100 %) in diagnosing bacterial infection within CSF. However, Viallon et al. [27] set a far lower limit for diagnosis for the latter infection in 254 patients, and mentioned a cut-off of 0.2 ng/ml for diagnosis with sensitivity, specificity, and positive predictive value of 95, 100 and 97 % respectively. Berger reported that ventriculitis related to intromission of EVD was associated with PCT levels greater than 1 ng/ml [25]. Whereas, Martinez et al., studied 15 patients with VRI and found that the PCT level remains normal and is assumed to be due to a localized type of infection where early detection is possible through CSF analysis [17].

In our study, we found that PCT was significantly different between patients with VRI and those without, on days 4 and 6 respectively (Table 4). A limited number of studies have investigated the latter problem in an adult population. In a relatively small study conducted with just 12 patients, Hoffmann et al., found that PCT had low sensitivity in neurosurgical bacterial meningitis diagnosis, although they found a higher diagnostic sensitivity in typical meningitis [28]. We did not observe that the number of drains inserted through the ICU course, or the association with DC, were associated with a higher infection rate; the smaller sample volume in terms of number of drains changed (only seven patients had their drains changed) and the strict protocol may explain the insignificant changes in terms of infection (Table 3). Takeuchi et al., studied the association of meningitis with DC, and found a similarly low rate (only 3 patients out of 21) [29]. The observed high initial CRP in patients could be explained by the initial inflammatory stage following the procedure, the propensity of early utilization of PCT, and the exclusion of inflammation as a reason for marker elevation.

The catheter tip was positive in three patients in Group I versus two patients in Group II; we did not use catheter tip for diagnosing VRI, rather for possible confirmation. However, catheter tip culture has been reported not to have diagnostic value in the ventriculitis settings [30]. The causative organisms in our study were highly virulent in 80 % of the diagnoses: *E. coli* was found in two patients and *P. aeruginosa*, *methicillin-resistant S. aureus* (*MRSA),* and *S. epidermidis* in one patient each. Tomio et al. [31] mentioned that the majority of intracranial-device-related infections are caused by *S. epidermidis,* although the author did not find a relation between PCT and catheter-related infection in his case report. In our study the isolated organisms were more virulent, and this may explain the early rise in PCT.

5.1 Study limitation

The relatively small number of patients, the extended study period (conducted over 2 years), and excluding patients with other sources of infection, limited the number of patients included. The diagnosis was made by targeting early diagnosis. Moreover, recent diagnostic procedures, such as multiplex PCR assay on CSF samples in combination with intrathecal biomarkers, could not be used here due to their unavailability in our laboratory [24].

6 Conclusion

In absence of other nosocomial infections, early high serum PCT concentrations appear to be a reliable indicator of bacterial CNS infection in patients with EVD.

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manuscript now, however Hamad medical corporation is going to fund for article processing charges. I did not hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. I did not hold or are you currently applying for any patents relating to the content of the manuscript. I did not receive reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript. I do not have any other financial competing interests. No other any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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