Clinical Neurology and Neurosurgery 183 (2019) 105396

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Intraoperative point-of-care assessment of an inflammatory biomarker in chronic subdural hematomas: Technical note

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ARTICLE INFO

Keywords:
Hemorrhage
Chronic subdural hematoma
Subdural effusion
Trepanation
Biomarkers

ABSTRACT

Objective: Inflammatory processes have been associated with the development and recurrence of chronic subdural hematomas (cSDH). Elevated levels of presepsin, a truncated N-terminal fragment of soluble CD14, occur in various inflammatory conditions of bacterial and non-bacterial origin. Here we report on our initial experiences with the intraoperative point-of-care (POC) assessment of presepsin in patients treated for cSDH.

Patients and methods: The POC analyser Pathfast® was used in 21 patients treated for cSDH at our institution. Prior to surgery, levels of C-reactive protein (CRP) and white blood cells (WBC) were assessed. After burr hole trephination and dura incision, samples of subdural fluid and whole blood were collected and immediately assessed with the POC analyser. Values of presepsin were compared between samples of the subdural compartment and whole blood.

Results: Presepsin levels were assessed within 13 min in all patients and no technical difficulties occurred. Compared to the reported normal range values of presepsin (55–184 pg/mL), mean levels of presepsin in samples of the subdural compartiment was increased more than 5-fold (821 ± 110.1 pg/mL). Furthermore, mean presepsin values in samples of the subdural compartiment were significantly higher than in samples of whole blood (154.8 ± 19.2 pg/mL; $p < 0.0001$).

Conclusion: POC assessment of the inflammatory biomarker presepsin is feasible within minutes during surgical treatment of cSDH. Corresponding to previous studies, presepsin levels were highly elevated in the subdural fluid, indicating processes of inflammation. Whether results of intraoperative POC assessment of inflammatory biomarkers is associated with outcome parameters in patients treated for cSDH has to be addressed in further studies. In our view, there is a role for this promising technique in improving future treatment strategies in respective patients.

1. Introduction

Chronic subdural hematoma (cSDH) is a frequent disease in the elderly population. Minor head trauma is the most common cause of cSDH and is present in 60%–80% of cases [1]. Coagulopathy, defective clot formation and membrane proliferation as well as inflammatory processes have been associated with the progression [2,3] and recurrence [4] of cSDH. Thus, evaluation of inflammatory biomarkers could provide valuable information during surgical treatment of patients with cSDH.

CD-14 is one of the main proteins of the inflammatory response. As a receptor of the lipopolysaccharide (LPS)/LPS-binding protein (LBP) complexes it acts as a co-receptor for the Toll Like Receptor 4 (TLR4) [5]. It transduces endotoxin signals (via TLR4), which activate the immune response. CD14 occurs in two forms – membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). sCD14 is produced through direct secretion or cleavage of mCD14 [6]. Cleaving the sCD14 by circulating plasma proteases, truncated N-terminal fragment named sCD14-subtype, or presepsin (PSEP) is generated [7]. PSEP is associated with inflammatory processes and recently, it has been recognised as a marker of sepsis [8]. Furthermore, elevated concentrations of PSEP in blood and cerebral fluid were detected in patients suffering from bacterial and non-bacterial infections of the central nervous system [9].

The point-of-care (POC) device Pathfast® (Mitsubishi Chemical Europe, Düsseldorf, Germany) has been recently introduced into clinical practice. Pathfast® Presepsin is a chemiluminescent enzyme immunoassay for the measurement of PSEP concentrations [10]. The potential value of Pathfast® Presepsin has been reported in various clinical

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https://doi.org/10.1016/j.clineuro.2019.105396
Received 11 May 2019; Received in revised form 11 June 2019; Accepted 23 June 2019
Available online 24 June 2019
0303-8467/

settings such as sepsis [11,12], after cardiac surgery [13] or in pediatric patients [9]. However, to the best of our knowledge, no data on the use of PSEP assessment in neurosurgical patients have been reported so far.

Inflammatory processes may increase the concentration of PSEP in the fluid of cSDH. Here we report our initial experiences on the intraoperative use of this POC device to assess this inflammatory biomarker marker in patients treated for cSDH at our institution.

2. Patients and methods

2.1. Sample collection and biomarker measurements

This retrospective analysis was approved by the local ethics committee. Levels of C-reactive protein (CRP), white blood cells (WBC) and PSEP were analysed in whole blood and in cSDH-fluid of 21 patients undergoing surgical treatment of cSDH via burr hole trephination. Whole blood samples of all patients admitted to surgical treatment were preoperatively drawn and collected in ethylenediaminetetraacetic acid (EDTA) monovettes® (Sarstedt Ag & Co.; Nürnberg, Germany) and subjected to immediate examination (CRP, WBC) in the central laboratory of our institution. A total of 100 µl of whole blood was collected into separate EDTA tubes and immediately evaluated with the Pathfast® Presepsin analyser (bPSEP). Intraoperatively, after burr hole trephination and incision of the dura mater, 1 ml of the evacuated subdural fluid was collected into an EDTA tube and subjected to measurement of PSEP (sPSEP) using Pathfast® Presepsin. Two patients suffered from bilateral cSDH, thus 23 samples of subdural fluid were assessed.

2.2. Statistical analysis

The Kolmogorov-Smirnov-test was used to test normal distribution of data on values of PSEP from blood and the subdural compartment. Two paired non-normally distributed datasets were tested using the Wilcoxon test. Two independent samples were tested using the Mann-Whitney-U test. Values are presented as mean and standard error. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA).

3. Results

A total 21 patients were included in the present analysis and details are described in Table 1. Two patients suffered from bilateral cSDH, thus 23 operations via burr hole trephination under general anesthesia were performed. Intraoperatively, 23 samples of subdural fluid were collected and immediate assessment of PSEP was carried out. We did not encounter any technical difficulties in assessing PSEP and all measurements were completed within 13 min.

Mean values of CRP and WBC were 27.2 ± 6.7 mg/L and 8.8 ± 0.6/L, respectively. The Kolmogorov-Smirnov-test revealed non-normal distribution of sPSEP and bPSEP ($p = 0.04$ and 0.02 respectively). Mean values of sPSEP were significantly higher than bPSEP values (821 ± 110.1 pg/ml vs. 154.8 ± 19.2 pg/ml; $p < 0.0001$; $Z = -4.167$) (Fig. 1). No signs of sepsis or severe infection were observed in patients. Three patients were postoperatively treated with oral antibiotics because of mild urinary tract infection ($n = 2$) and bronchopneumonia ($n = 1$) and were discharged from hospital within 7 days after the operation.

In 12 cases of cSDH, patients had been treated with antithrombotic treatment prior to surgery. We did not observe any significant differences in mean sPSEP values of patients with antithrombotic treatment and without antithrombotic treatment (926.5 ± 173.9 pg/ml vs. 705.9 ± 130.2 pg/ml; $p = 0.218$; $Z = -1.231$). In two patients without antithrombotic treatment, subdural re-hemorrhage requiring craniotomy and hematoma evacuation occurred. Due to limited patient numbers, no statistical analysis was performed. However, the mean values of sPSEP values of patients without re-hemorrhage and with re-hemorrhage requiring surgical revision were comparable (807.9 ± 119.8 pg/ml vs. 958.0 ± 182 pg/ml).

4. Discussion

The results of our study demonstrate that intraoperative POC assessment of PSEP is feasible in patients undergoing neurosurgical procedures. Levels of PSEP in patients treated for cSDH were highly elevated in the subdural fluid and were significantly higher than in samples of whole blood. These findings support previous reports that inflammation plays a key role in the pathophysiology of cSDH.

Data of previous studies indicate an important role of PSEP as an early marker of sepsis [14]. PSEP were correlated higher with clinical outcome parameters compared to other established markers such as CRP, procalcitonin or IL-6 [11,12,15]. De Guadiana Romualdo et al [16] assessed PSEP in a group of 37 patients with bacteremic systemic inflammatory response syndrome (SIRS) and in 189 patients with non-bacteremic SIRS. PSEP levels were significantly higher in the septic group of patients (mean value: 1219 pg/ml) compared with the non-bacterial SIRS-group of patients (mean value: 606 pg/ml, $p < 0.001$). Levels of PSEP were elevated in both groups compared to PSEP levels in 128 healthy subjects (mean value: 190 pg/ml) [17]. Similarly to these reports, other groups also reported [18,19] significantly higher levels of PSEP in SIRS/sepsis patients compared to the results of healthy controls and higher levels of PSEP in bacterial SIRS patients compared to non-bacterial SIRS patients. Giavarina and Carta [20] evaluated PSEP in 200 patients without infection in order to determine reference limits. The normal range of PSEP in healthy individuals was 55–184 pg/mL (90% confidence intervals, CI, were 45–58 pg/ml and 161–214 pg/ml, respectively).

In our study, PSEP levels were significantly higher in the subdural fluid compared to PSEP levels in samples of whole blood. Levels of bPSEP were within normal ranges and these findings correspond to the results of other laboratory examinations in patients (WBC (8.8 ± 0.6/L; CRP: 27.2 ± 6.7 mg/L). Highly elevated PSEP levels in the subdural fluid may indicate the presence of inflammatory processes within chronic subdural hematomas. Based on histopathological findings, chronic inflammatory processes within chronic subdural hematomas have been hypothesized by Virchow in 1857 [21]. Various markers of inflammation such as IL-6, IL-8 and TNFα were found to be higher in the subdural fluid than in blood of patients with cSDH [22,23]. Elevated levels of IL-6 has been associated with increased intravascular permeability [24] and IL-8 promotes adherence of leucocyte to endothelial cells and their migration to the site of inflammation [25]. TNFα promotes activation and proliferation of T-cells [26] as well as adherence to the endothelial cells and extravasal migration [27]. Other authors [3] demonstrated high activity of the kallikrein-kinin system in cSDH. Several reports have suggested a key role of inflammation not only in the development of cSDH but also in the recurrence after surgical treatment. Frati and colleagues analysed data of 100 patients who were surgically treated for cSDH. Inflammatory cytokines were elevated in the subdural fluid, and moreover, levels were significantly higher in patients who developed recurrence of cSDH [4]. A further study revealed significantly higher values of IL-6 in the subdural fluid of patients who developed recurrence of surgically treated cSDH compared to patients without recurrence [28].

The role of inflammation has also presented the pathophysiological rationale for the use of anti-inflammatory drugs in patients with cSDH. A recent meta-analysed included 5 studies on the use of dexamethasone in patients treated for cSDH [29]. No benefit was observed when dexamethasone was solely used as an alternative to surgical treatment. However, the risk of recurrence of cSDH following surgery was significantly reduced when dexamethasone therapy was initiated. Two large multicentre trials are currently carried out in order to define the

Table 1

Characteristics of patients as well as mean values of Presepsin, CRP and WBC. Volume of the hematoma was calculated according to formula ABC/2. *Midline shift was evaluated only in patients with one sided hematomas.

Nr.	Age (years)	Sex	Side	Volume (ml)	Midline shift (mm)	sPSEP (pg/ml)	bPSEP (pg/ml)	CRP (mg/L)	WBC (/L)	Antithrombotics	Re-hemorrhage
1	81	male	left	95.4	0*	944	132	NA	NA	Aspirin	none
1	81	male	right	206.6	0*	510	132	NA	NA	Aspirin	none
2	63	male	left	94.8	0*	909	138	2.4	11.16	None	none
2	63	male	right	67.4	0*	620	138	2.4	11.16	None	none
3	81	female	left	121.5	9	588	110	2	6.79	None	none
4	87	male	right	135.0	0	693	316	2.9	6.02	Phenprocoumon	none
5	93	male	left	54.7	0	487	135	41.8	4.27	Aspirin	none
6	75	male	left	188.8	6	535	121	4	8.91	None	none
7	77	male	right	42.4	0	957	379	83.6	12,04	None	none
8	83	female	right	98.1	6	1140	320	2	5.42	Clopidogrel	yes
9	82	male	left	225.9	13	840	224	63.4	9.92	Rivaroxaban	none
10	78	male	left	96.5	4	776	227	9.6	9.31	Aspirin	yes
11	68	male	right	71.3	8	410	78.5	NA	8.03	None	none
12	85	female	left	124.0	11	917	146	8.4	12.81	Edoxaban	none
13	85	male	left	58.0	6	393	53.2	1	13.77	Aspirin	none
14	81	male	right	107.7	2	1821	256	72	7.53	None	none
15	64	female	left	144.1	5	596	171	57.5	7.3	None	none
16	77	male	right	114.3	7	117	133	41.9	7.92	None	none
17	78	female	left	86.0	6	2694	9.1	14.4	8.25	Aspirin	none
18	86	male	left	82.2	4	577	94.6	55	9.08	None	none
19	84	male	right	166.7	15	635	105	NA	NA	None	none
20	82	female	right	86.7	12	1057	73.7	NA	NA	Rivaroxaban	none
21	82	male	left	79.3	6	667	68.2	25.04	7.04	Aspirin	none
All (n = 23)	79 ± 8 (mean, SD)	17/6 (male/female)	10/13 (right/left)	110.8 ± 10.1 (mean, SEM)	5 ± 1 (mean, SEM)	821 ± 110 (mean, SEM)	154,8 ± 19.2 (mean, SEM)	27.2 ± 6.7 (mean, SEM)	8.8. ± 0.6 (mean, SEM)	12/11 (yes/no)	2/21 (yes/no)

Abbreviations: NE - not evaluated, NA - not available, SEM - standard error of mean, SD - standard deviation, n - number.

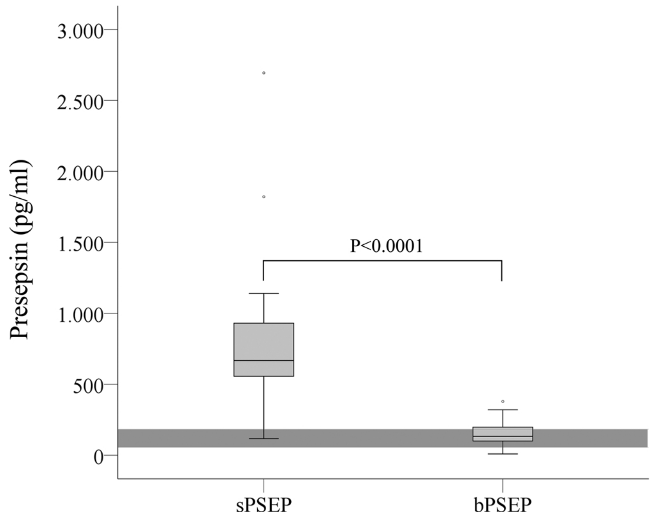

Fig. 1. Levels of presepsin are significantly higher in samples of subdural fluid (sPSEP) compared to levels of presepsin in samples of whole blood (bPSEP). The grey bar depicts normal range values of presepsin in healthy patients.

role of dexamethasone therapy in the treatment of cSDH [30,31].

Intraoperative assessment of inflammatory processes through the use of a POC device may provide valuable information during surgery and may have an impact on the further treatment. Theoretically, information regarding inflammatory processes within the subdural compartiment may aid in deciding on insertion of subdural drains or initiating treatment with inflammatory drugs. Furthermore, findings could help in the differentiation between non-inflammatory hygromas and cSDH. The development of neomembranes within the subdural compartiment has been associated with high capillary surface areas promoting extravasation of plasma components into the subdural space and subsequent development of space-occupying cSDH [32]. The ideal surgical approach in patients with cSDH and underlying neomembranes remains a debate: While burr-hole trephinations are most commonly performed [33], some authors advocate craniotomy for hematoma evacuation and membranectomy in these patients [34]. Further studies on the role of inflammation and the risk of hematoma recurrence may shed light on this controversial issue. Once the impact of the inflammatory biomarker presepsin on the rate of hematoma recurrence and clinical outcome has been defined in further studies, it may provide useful information during surgical treatment.

Our findings have to be considered preliminary and further studies with large patient numbers are clearly needed. However, POC devices are increasingly used in various fields of medicine such as intensive care medicine or cardiac surgery. Major advantages include the rapid assessment of parameters which can be instantly implemented into clinical decision-making. POC devices are increasingly used for the assessment of hemostasis in neurosurgical patients suffering from trauma or requiring urgent surgical intervention while on treatment with antithrombotic drugs [35].

5. Conclusion

Our initial experiences demonstrate that POC assessment of inflammatory biomarkers is feasible within minutes during surgery in patients treated for cSDH. Values of PSEP were highly elevated in the subdural fluid of patients and approximately 5-fold higher than respective values in samples of whole blood. These findings support previous reports of elevated inflammatory markers in the subdural fluid of patients with cSDH. Further studies are necessary to evaluate the potential and limitations of intraoperative POC assessment of inflammatory biomarkers in these patients.

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