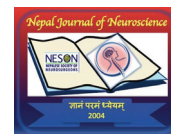


Predictive Value of Cerebrospinal Fluid Lactate Level for the Diagnosis of Bacterial Meningitis following Cranial Surgery



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Abstract

Introduction: To distinguish post-neurosurgical bacterial meningitis (PNBM) from aseptic meningitis is difficult. Inflammatory and biochemical cerebrospinal fluid (CSF) changes mimic those classically observed after CNS surgery. Cerebrospinal fluid lactate assay has therefore been proposed as a useful PNBM marker.

Methods and Materials: Between January 2016 and December 2016, a prospective clinical study was done at the Department of Neurosurgery, in which all patients with clinical suspicion of post-neurosurgical bacterial meningitis were enrolled. Patients with clinical suspicion of bacterial meningitis (BM) were categorized, according to preset criteria, into three groups: (1) proven BM; (2) presumed BM, and (3) non-bacterial meningeal syndrome (NBMS). Cerebrospinal fluid markers were plotted in a receiver operating curve (ROC) to evaluate their diagnostic accuracy.

Results: The study included seventy patients. Sixty five cerebrospinal fluid samples from patients with clinical suspicion of BM by cerebrospinal fluid analysis. Twenty corresponded to proven BM, 7 to presumed BM and 38 to excluded BM. Mean lactate in cerebrospinal fluid was: 8.4 ± 3.0 mmol/l for proven BM, 4.8 ± 0.99 mmol/l for presumed and 2.08 ± 0.822 mmol/l for non-bacterial meningeal syndrome ($P < .001$).

Conclusion: Cerebrospinal fluid lactate level has good predictive value to distinguish BM from (Non-bacterial meningeal syndrome) with sensitivity of 90% and specificity of 87% at cut-off value of 4.0 mmol/l.

Key words: Aseptic meningitis, Bacterial meningitis, CSF lactate.

Introduction

The occurrence of meningitis after neurosurgical procedures is uncommon, with an estimated incidence between 0.3% and 1.5% following different neurosurgical interventions.¹

However, it remains a significant problem associated with high morbidity, and reported mortality rates range between 20% and 50%.² Diagnosis is sometimes difficult, because the clinical manifestations are often mild and nonspecific during the immediate postoperative period. In addition, CSF protein and cell composition are modified by the surgical procedure itself, making it difficult to interpret laboratory results.

The concept of postoperative aseptic meningitis was first described by Cushing but the mechanisms remain unclear. Aseptic meningitis occurs more frequently in children and after surgery involving the posterior fossa, and it may occur as a result of a local inflammatory reaction to blood breakdown products or to tumor antigens.³

Aseptic meningitis comprises 60%–75% of all cases of postoperative meningitis. The clinical manifestations and CSF findings associated with aseptic meningitis are very similar to those associated with postoperative bacterial meningitis, and the distinction between the 2 entities is currently based solely on the results of CSF culture.⁴

The diagnosis of bacterial meningitis (BM) is difficult in patients after neurosurgery for several reasons. Meningeal syndrome with a stiff neck, fever, and headache occurs frequently in patients following craniotomy. Blood, surgical manipulation, surgical materials and bone dust appear to trigger inflammatory

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processes mimicking bacterial meningitis CSF changes. Neutrophil CSF pleocytosis can be present in various infectious and non-infectious forms of meningitis as a consequence of subarachnoid-space inflammation.⁵⁻⁷ Up to 50% of patients with clinical signs of meningitis have already been treated with steroids or antibiotics, at the time of lumbar puncture.^{4,8} Standard CSF studies (i.e., gram staining and determinations of leukocyte count and glucose and protein concentration) are unreliable for the diagnosis of BM after neurosurgery.⁴ Therefore, additional CSF parameters that allow differentiation of BM from nonbacterial meningeal syndrome (NBMS) are needed. The ideal biochemical PNBM marker should be highly sensitive and present for early measurement in the course of infection. CSF lactic acid has been proposed as a potential marker distinguishing between infection and inflammation.⁹ The measurement of CSF lactate by a portable lactate meter similar to a glucometer can give quick results.

CSF lactate in BM originates from different sources. Bacterial pathogens themselves produce varying amounts of lactate, accounting for 10% of total CSF lactate in patients with BM.⁶ The main source of lactate in BM is brain tissue, including neurons and glia cells, which produce lactate by distinct mechanisms.¹⁰ BM is associated with generalized brain edema, causing a reduction of global cerebral blood flow and inflammatory involvement of the vasculature, with loss of auto-regulatory mechanisms, vasospasms, and thrombosis.^{2,11,12,13} This leads to cerebral ischemia and consequently to glycolysis by means of anaerobic metabolism. In addition, cytokines that flood the brain in meningitis reduce tissue oxygen uptake and cause a shift toward anaerobic metabolism, thus increasing lactate production.^{10,14} Because lactate penetrates the blood-brain barrier at a very low rate, measurement of CSF lactate is a useful index of cerebral metabolism.¹⁴ In addition, cytokines also mediate invasion of neutrophils into the subarachnoid space, which may also contribute to the rise in CSF lactate level by glycolysis.¹⁵

Recent studies have indicated that CSF lactate shows a certain degree of diagnostic accuracy for differentiating between postoperative bacterial meningitis and aseptic meningitis.¹⁶ However, no systematic evaluations have investigated this aspect. In recent years, it has been proposed that CSF lactate may be a good marker that can differentiate bacterial meningitis (> 6 mmol/l), from partially treated meningitis (4 to 6 mmol/l) and aseptic meningitis (< 2 mmol/l).¹⁷

However, other researchers have suggested that CSF lactate offers no additional clinically useful information over conventional CSF markers.^{18,19} Other markers, such as C-reactive protein (CRP)²⁰ and pro-calcitonin²¹, heparin-binding protein²², sCD163²³ may allow differentiation of patients with bacterial meningitis from those with aseptic meningitis. However, neither of these markers is routinely

used in clinical practice. The CSF lactate exam is simple, objective and affordable.² The exam is not affected by blood contamination of the CSF.^{14,22} Many researchers also reported that the CSF lactate concentration was not related to the neutrophil count.^{2,23,24} The test can be performed at the bedside, and the results can be received immediately. Additionally, a rapid decrease in the CSF lactate level following antibiotic treatment could suggest a relatively good prognosis. Therefore, CSF lactate may play a significant role in the diagnosis of post-neurosurgical bacterial meningitis. In this study, CSF lactate accuracy for PNBM diagnosis (proven and presumed) was investigated prospectively.

Methods and Materials

It is a prospective observational study done with purposive sampling. This study was conducted at the Department of Neurosurgery. Ethical clearance was obtained from the Institutional Review Board. Duration of the study was one year. All patients who developed meningeal syndrome following cranial surgery from January 2016 to December 2016 were included in the study after prior informed consent.

CSF analysis of patients who underwent either elective or emergency cranial surgery and developed meningeal syndrome was done. CSF lactate of the same sample was also sent. Patients with clinically suspected BM were categorized according to the following preset criteria:

- (1) For proven BM, a positive bacterial CSF culture and a leukocyte count of >250/mL
- (2) For presumed BM, 1,000 WBCs/mL with >50% neutrophils or (if the patient was treated with steroids and/or antibiotics at the time of the first lumbar puncture) >250 WBCs/mL with 50% neutrophils
- (3) for non-BM(NBMS), a negative CSF culture and <250 WBCs/mL with <50% neutrophils.

Criteria for the clinical categories were established prior to the evaluation.

Lactate Scout+ is a device manufactured by Sens lab (an EKF diagnostic company) from Germany. (Fig 1) It uses disposable lactate sensors to determine the level of lactate in the body fluid. The sample volume needed is 0.2µl. The measuring range is 0.5-25 mmol/l. The readings below and above that range are shown as "LO" and "HI" respectively. CSF cytology (TC/ DC) are calculated microscopically. CSF sugar and protein are calculated automatically with Erba Mannheim XL200 using spectrometry.

Clinical parameters examined were age, sex, type of surgery, presence and type of a foreign device, postoperative day on which lumbar puncture was performed, the antibiotic and/or steroid regimen initiated

before and at the time of lumbar puncture, and organism(s) identified by CSF culture.

Inclusion criteria

Patients suspected of postoperative bacterial meningitis and who underwent CSF analysis within 40 days of surgery were included for our study. Patients who had Sepsis syndrome due to causes other than Bacterial meningitis were excluded from the study.

Sample size:

The formula for sample size: $n = z^2 p (1-p) / d^2$

n= required sample size

z = confidence interval (1.96 for 95% confidence interval)

p = estimated prevalence

d = margin of error (0.05 for 5 % error)

$n = 1.96 \times 1.96 \times p \times (1-p) / 0.05 \times 0.05 = 59$

Statistical Analysis

Statistical analyses were performed using IBM SPSS 20.0. (IBM Inc., New York, NY). For descriptive statistics, Microsoft word and Excel were used to generate diagrams, graphs and tables. Descriptive statistics of quantitative data were presented as mean and standard deviation. Uni variate analysis was done with the Chi-square test/Fisher exact test. Continuous data were analyzed by One-way ANOVA test. Area under the ROC curve has been used to find the Diagnostic and predictive value of preoperative score for predicting the preoperative outcome based on easy and difficult binary outcome. If $p < 0.001$ then the variable was called highly significant, if $p \leq 0.01$ then strongly significant and $0.01 < p \leq 0.05$, then the variable was called moderately significant.

Result

Demographic characteristics

The data was collected from January 2016 to December 2016. A total of 65 patients fulfilled the inclusion criteria and thus participated in the study. The median age of the patients in the study was 18 months ranging from 1 month to 70 years. There was female predominance, female 52% vs. male 47%. Different clinical conditions for which patients were managed have been tabulated in table 1. Most of the patients were in the pediatric group as the incidence of VP shunt and ensuing infections are high in this group.

The prevalence of bacterial meningitis was 20 (30.8%). Non-bacterial meningitis syndrome was seen in 38(58.46%) and presumed bacterial meningitis in 7 patients (10.76%). Among 20 confirmed bacterial meningitis

patients, Staphylococcus aureus was isolated in 35%, Klebsiella pneumonia in 20%, Pseudomonas aeruginosa in 15%, Acinetobacter sp. in 10%, Burkholderia sp. in 10% and Citrobacter freundii in 10%. This shows a trend towards increasing gram negative shunt infections.

Biochemical characteristics

The CSF analysis revealed that 19 patients with bacterial meningitis had lactate level more than 4 mmol /L except one who had CSF lactate 2.85 mmol/l. In patients with NMBS, none except one (4.54 mmol/L) had lactate level > 4 mmol/l. The results of culture, neutrophil count, WBC count, along with culture results and CSF lactate level were documented.

Table 2 presents the correlation between CSF WBC count and CSF lactate level. The result here shows that the CSF lactate level is positively correlated to WBC count as the significance level is < .0001 and correlation coefficient is 0.540. They have a strong positive correlation. ($r = 0.40$ to 0.69)

From the table 3, we can conclude that CSF lactate level was significantly higher($p < 0.0001$) in patients with bacterial meningitis as compared to patients with non-bacterial meningitis syndrome ($p < 0.005$). There was significant difference in the mean CSF lactate level among three groups. ($f 79.82$, $df 2$, $p < 0.001$).

ROC Curve

The area under the curve is 0.96 (table 4) which is in between 0.90 and 1 that indicate the experiment has a very high level of specificity and the significance level is <0.001. The cut off point is 4.0, the sensitivity at that point is 90% and specificity is 87%. The positive predictive value is 75% and the negative predictive value is 95.12%.



Figure 1: Lactate Scout + machine used to get point of care lactate level.

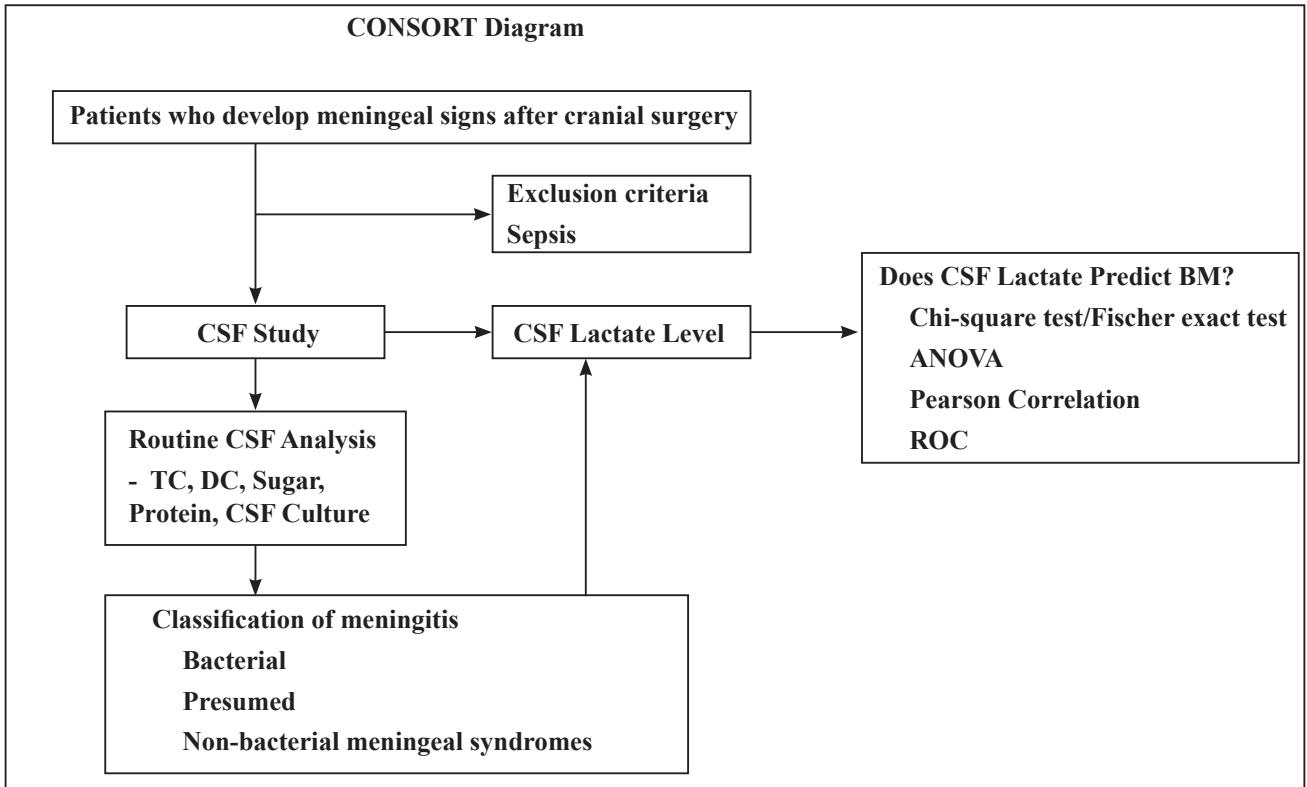


Figure 2: CONSORT diagram.

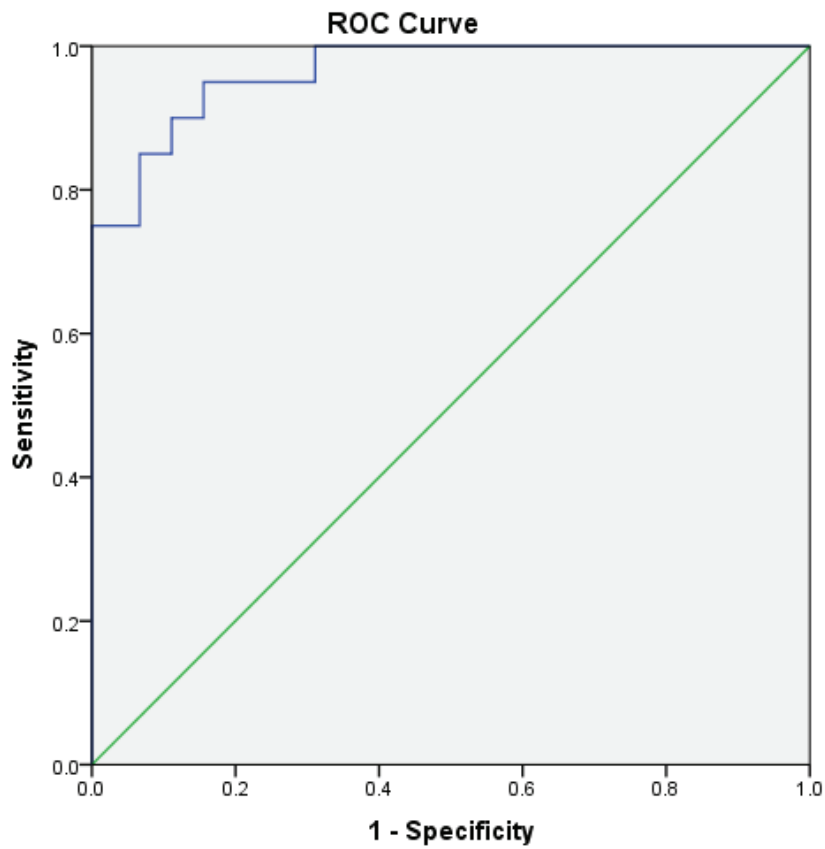


Figure 3: Area under curve.

	Type of surgery	Frequency (n)
1	VP(Ventriculo peritoneal) Shunting	37
2	EVD(External ventricular Drain)	9
3	ETV(Endoscopic Third Ventriculostomy)	7
4	Shunt Revision	5
5	VP Shunt exteriorization	4
6	Subtotal tumor excision + VP Shunting	1
7	Tumor excision	1
8	Cervical Meningomyelocele excision	1
Grand total		65

Table 1: Surgical characteristics of patients enrolled.

		WBC count
Level of CSF lactate	Pearson correlation	.540*
	Sig. (2-tailed)	.000

*correlation is significant at the 0.01 level (2 tailed)

Table 2: Relationship between WBC count and Level of lactate in CSF.

Variable	CSF lactate level (Mean ± SD)
Bacterial Meningitis (n=20)	8.4 ±3.0 mmol/l (p<0.0001)
Presumed bacterial meningitis (n=7)	4.8 ± 0.99 mmol/l (p<0.005)
Non Bacterial Meningitis syndrome (n=38)	2.08 ± 0.822 mmol/l(p<0.001)

Table 3: Significance difference in types of meningitis (BM, Presumed and NBMS).

Test Result Variable(s): Level of CSF Lactate

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
.964	.021	.000	.924	1.000

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 4: Area under curve to show specificity.

	Cut-off value	PPV of lactate	NPV of lactate	Sensitivity	Specificity	Area Under ROC
Leib et al ²	4.0mmol/l	96%	94%	88%	98%	NA
Travares et al ²⁸	5.4mmol/L	75%	95%	86%	90.5%	0.85
Grille et al ²⁹	5.9mmol/L	77%	97%	87%	94%	0.92
Maskin et al ²⁷	4.0mmol/L	70%	100%	100%	78%	0.96
Li et al ³⁰	3.45mmo/L	69.2%	95.6%	90%	84.4%	0.94
Our study	4.0mmol/L	75%	95.12%	90%	87%	0.96

Table 5: Comparison of sensitivity and specificity as per various studies.

Discussion

The occurrence of bacterial meningitis after neurosurgery has been documented in up to 4% of patients.^{25,26} The diagnosis of BM relies on the isolation of bacteria from CSF samples. However, in up to 70% of clinically suspected cases,

Bacterial CSF cultures remain negative.^{1,4} The severe consequences of delayed or untreated BM, in conjunction with the lack of clear diagnostic criteria for BM occurring after neurosurgery, explain the prevailing practice of empirically treating all suspected cases with high-dose broad spectrum intravenous antibiotics. The expense and risk of unnecessary treatment of uninfected patients

Conclusion

Our results indicate that CSF lactate is reliable to distinguish between post-neurosurgical bacterial meningitis and non-bacterial meningitis syndrome. High sensitivity and negative predictive values are achieved with a cut-off value of 4 mmol/L, and this value is especially useful to rule out post neurosurgical bacterial meningitis in the adequate clinical setting.

Conflict of Interest: None

Source(s) of support: None

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call for a more specific test for the diagnosis of BM after neurosurgery.

The prevalence of bacterial meningitis was 20 (30.8%). Thirty Eight (58.46%) and 7 (10.76%) patients were diagnosed with non-bacterial and presumed bacterial meningitis respectively as shown in the table below. This was similar to the findings in the study from Lieb et. al² (34%); Maskin et. al²⁷(33%) and Traveres et. al²⁸ (25%). The high prevalence of the bacterial meningitis in our and several other studies may be due to the fact that study was done in patients who were clinically suspected to be meningitis. These are the high risk group of patients who were subjected to CSF analysis.

The cut off value of lactate is different in different studies ranging from 3.45mmol/L to 5.9mmol/L. (Table 5) In our study the area under the curve is 0.96 which is in between 0.90 and 1 that indicate the experiment has very high level of specificity and the significance level is <.001. the cut off point is 4.0, the sensitivity at that point is 90% and specificity is 87%. The positive predictive value is 75% and the negative predictive value is 95.12%. These results are comparable to other studies shown in the table.

In study of Lieb et al, they have compared lactate level to CSF/blood glucose ratio and concluded that the CSF lactate level (cutoff, 4 mmol/L) is superior to the CSF/blood glucose ratio (cutoff, 0.4) for diagnosis of BM in neurosurgical patients. Similarly, Travares et al concluded CSF cellularity, glucose and lactate can be more reliable for the diagnosis of BM than clinical parameters alone in post neurosurgical patients while comparing different CSF markers. The study of Grille et al concluded CSF lactate represents a good marker for BM following neurosurgical procedures, superior to other biochemical or cytological CSF markers such as CSF protein, glucose and CSF/blood glucose ratio. Maskin et al concluded CSF lactate as a reliable marker for distinguishing bacterial meningitis from aseptic meningitis. Li et al concluded that CSF procalcitonin and lactate are reliable markers to distinguish between PNBM and non-PNBM, and current sensitivity and negative predictive values are achieved with a cut-off value of 0.075 ng/mL for procalcitonin and 3.45 mmol/L for lactate. However, his study has better results with CSF lactate compared to procalcitonin.

Several other biochemical tests are under study to find a single biomarker to determine bacterial meningitis from aseptic meningitis. However, CSF lactate could be the one of the important markers to distinguish bacterial meningitis from aseptic meningitis. This can prevent the use of unnecessary antibiotics to patients who are suspected to have aseptic in preventing antibiotic resistance which is going to create a great problem in future. Those patients with high CSF lactate level must be started on empirical antibiotics to prevent and decrease the morbidity and mortality due to BM following cranial surgery

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