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The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

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ORIGINAL ARTICLE

Observational Study

Role of cerebrospinal fluid lactate in diagnosing meningitis in critically ill patients

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Abstract

BACKGROUND

Meningitis is a life-threatening clinical condition associated with high mortality and morbidity. Early diagnosis and specific treatment may improve outcomes. Lack of specific clinical signs or tests make the diagnosis challenging.

AIM

To assess the efficacy of cerebrospinal fluid (CSF) lactate in diagnosing meningitis in critically ill patients.

METHODS

A prospective, observational cohort study was carried out in a neuro-medical intensive care unit (ICU) over a 22 mo period. Adult patients, with suspected meningitis admitted in ICU, were serially recruited. Patients who refused consent, those with peripheral sensorineural deficit, or with any contraindication to lumber puncture were excluded. CSF cytology, bio-chemistry, lactates, culture and polymerase chain reaction based meningo-encephalitis panel were evaluated. Patients were divided in two groups based on clinical diagnosis of meningitis. The efficacy of CSF lactate in diagnosing meningitis was evaluated and compared with other tests.

RESULTS

Seventy-one patients were included and 23 were diagnosed with meningitis. The mean values of CSF total leucocyte count (TLC), proteins and lactates were significantly higher in meningitis group. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve of 0.81 (95% confidence interval: 0.69-0.93), sensitivity of 82.6%, and specificity 72.9%. These values were comparable to those of CSF TLC and protein. Twelve patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8

mmol/L), $P = 0.006$.

CONCLUSION

CSF lactate may be used to aid in our diagnosis of meningitis in ICU patients. CSF lactate (> 2.72 mmol/L) showed good accuracy, sensitivity, and specificity in diagnosing meningitis and may also help to differentiate between bacterial and non-bacterial meningitis.

Key Words: Encephalitis; Cerebrospinal fluid; Critically ill; CSF lactates; Meningitis

Core Tip: We conducted a prospective, observational cohort study to assess the efficacy of cerebrospinal fluid (CSF) lactate in diagnosing meningitis in critically ill patients. 71 patients were included and 23 were diagnosed with meningitis. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve (AUC) of 0.81, sensitivity 82.6%, and specificity 72.9%. These values were comparable to those of CSF total leucocyte count (TLC) and protein. Twelve patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8 mmol/L), $P = 0.006$. To conclude, CSF lactate may be used to aid in our diagnosis of meningitis in critically ill patients.

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INTRODUCTION

Meningitis is a life-threatening condition associated with high mortality and morbidity and may affect any patient's age group[1]. Patients with meningitis may present with headache, photophobia, and neck stiffness and may develop confusion and coma in the later stages[2]. Older patients are more prone to have altered mental status and focal neurologic deficits rather than neck stiffness and headache[3,4]. However, these are non-specific; hence, a high index of suspicion is required to make the correct diagnosis. As early diagnosis and specific treatment may improve outcomes, every attempt must be made to make an early etiological diagnosis to institute specific therapy[5].

The most common form of meningitis is aseptic meningitis. These cases are primarily viral, and enterovirus is the most common etiological organism reported in immune-competent individuals[6,7]. Aseptic and bacterial meningitis are similar in clinical presentation, but patients with bacterial meningitis appear more ill clinically. All patients with symptoms suggestive of meningitis should undergo lumbar puncture (LP) at the earliest and cerebrospinal fluid (CSF) assessment for definitive diagnosis and appropriate treatment. On cytological and biochemical analysis of CSF, lymphocytic pleocytosis with normal glucose level and a normal to slightly elevated protein level are seen in aseptic meningitis. Whereas bacterial meningitis characteristically has an elevated and predominantly neutrophilic pleocytosis with low glucose level, decreased CSF/serum glucose ratio (< 0.4), and a high protein level. The reported sensitivity and specificity of CSF total leucocyte count (TLC), proteins, and sugars for diagnosing meningitis are 80%, 89%; 97%, 85%; 93%, and 49%, respectively[8].

CSF Gram and acid-fast bacilli stains are quick methods of detecting the organism, but they lack sensitivity (50% to 80%). CSF cultures, which are positive in, at best, 80% of cases of bacterial meningitis, have a long turn-around time of 48 h and may be falsely negative in patients already on antibiotics. The sensitivity of CSF Gram stain and cultures is less than 50% in such patients[9]. A real-time polymerase chain reaction (rt-PCR) based meningoencephalitis panel is useful for the etiological diagnosis of meningitis. Even though it has good sensitivity and specificity, its application is restricted due to its limited availability and high cost. Hence, there is a need for a readily available test that is easy to apply and can diagnose meningitis and differentiate between bacterial and non-bacterial causes of meningitis.

Blood lactate is tested in almost all critically ill patients in intensive care units (ICUs) and has been used to guide treatment and predict prognosis. In contrast, CSF lactate is rarely tested. Normal CSF lactate levels are 1.2-2.1 mmol/L, but they may range from 0.6-3.1 mmol/L[10]. Anaerobic glycolysis of brain tissue due to decreased cerebral blood flow and oxygen uptake may increase lactate concentration in CSF patients with meningitis[11]. Hence, CSF lactate has been suggested as an excellent marker to diagnose meningitis and may be a better marker than CSF TLC, sugar, and proteins[12,13]. In addition,

it is inexpensive, has high test-retest reliability and is also readily available even in the resource-poor world, where neurological imaging may be difficult to obtain. However, most of the studies have been done on post-neurosurgical and brain trauma patients, and there is a dearth of data regarding its accuracy in critically ill medical patients with suspected meningitis.

MATERIALS AND METHODS

A prospective, observational cohort study was carried out in a neuro-medical ICU of a tertiary care hospital in India from December 2019 to October 2021. Institutional Human Ethics Committee approval was obtained before the commencement of the study (Reference number: TS/MSSH/MHIL/SKT-1/MHEC/CC/20-17). After explaining the study protocol, written informed consent was obtained from all the participants. Those patients fulfilling inclusion criteria, patients older than 18 years, admitted with suspected meningitis in ICU, were serially recruited. Patients who refused to consent to the study, those with a peripheral sensorineural deficit, and those with any contraindication to the LP procedure were excluded. Trained intensivists performed LP with full aseptic precautions per the clinical protocols, and samples were sent immediately to the hospital laboratory in sterile containers. CSF cytology, biochemical parameters, culture and polymerase chain reaction (PCR) -based meningoencephalitis panel, were evaluated. CSF lactate levels were measured in all the patients. The final diagnosis of meningitis was made based on the clinical picture, CSF analysis, culture and PCR reports. The sensitivity, specificity, and positive and negative predictive value of CSF lactate, to diagnose meningitis were calculated. The efficacy of CSF lactates was compared with other commonly employed tests like CSF TLC, proteins, and sugar levels. Correlation of CSF lactate with CSF culture and PCR was also performed. CSF lactates were also compared in patients with bacterial *vs* non-bacterial causes of meningitis. Hospital and ICU length of stay (LOS), need for invasive mechanical ventilation, and ICU mortality were also recorded.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, IL, United States). Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the chi square test or Fisher's exact test, as appropriate. Area under receiver operating characteristics (AUROC) analysis was calculated to determine optimal cut-off values for CSF TLC, protein and sugar and lactate levels. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

Seventy-one patients, who fulfilled the inclusion criteria were included in the final analysis and divided in two groups, meningitis and non-meningitis groups, based on the clinical diagnosis of meningitis. Their basic characteristics, clinical parameters and hospital course are given in the Table 1.

The mean values of CSF TLC, proteins and lactates were significantly higher in meningitis group whereas mean value sugar levels were significantly higher in non-meningitis groups (Table 2). There was a significant correlation of CSF lactate levels with CSF cultures; meningo-encephalitis PCR based panel, and a combination of both (CSF cultures and meningo-encephalitis panel) with P value < 0.05.

As shown in Table 3, CSF lactate cut-off point for the diagnosis of meningitis, obtained by analyzing the ROC curve, was > 2.7 mmol/L with AUC of 0.81 (95% confidence interval: 0.69-0.93). Sensitivity was 82.6%, specificity 72.9%, positive predictive value 59.4%, negative predictive value 89.7% and accuracy 76.1%.

Causes of meningitis and the final diagnosis of patients in the non-meningitis group is given in Table 4. Out of 23 patients of meningitis patients, 12 patients had bacterial meningitis and 11 patients had non-bacterial meningitis. CSF lactate levels were significantly higher in bacterial meningitis (8.9 ± 4.7) than non-bacterial meningitis (4.2 ± 3.8), P = 0.006.

DISCUSSION

Even though central nervous system (CNS) infections account for only 2.9% of infections in ICU, they are associated with high morbidity and mortality, ranging from 17%-40%[14,15]. These patients' outcomes depend on the etiological organism and the kind of care provided[15]. Hence, making an early diagnosis and initiating specific treatment measures is imperative. In the present prospective cohort study, we found that CSF lactate had good accuracy, sensitivity and specificity in diagnosing meningitis and showed a good correlation with CSF cultures and RT-PCR-based panels. In addition, it may also aid

Table 1 Basic characteristics, clinical parameters and hospital course

Patient parameters	Overall (*n* = 71), %	Meningitis group (*n* = 23) , %	Non-Meningitis Group (*n* = 48), %	*P* value
Age, yr	58.1 ± 16	57.8 ± 15.4	58.9 ± 17.3	0.820
Males	23 (32.4)	10 (43.5)	13 (27.1)	0.167
Clinical parameters				
Headache	25 (35.2)	11 (47.8)	14 (29.2)	0.123
Seizures	46 (64.8)	17 (73.9)	29 (60.4)	0.265
Fever	50 (70.4)	16 (69.6)	34 (70.8)	0.871
Altered sensorium	70 (98.6)	23 (100)	47 (97.9)	0.486
Photophobia	5 (7)	3 (13)	2 (4)	0.171
Coma	24 (33.8)	9 (39.1)	15 (31.3)	0.511
Antibiotic exposure before CSF analysis	65 (91.5)	22 (95.7)	43 (89.6)	0.39
Traumatic brain injury	2 (3)	0 (0)	2 (4)	0.321
Neurosurgical intervention	4 (5.6)	3 (13)	1 (2)	0.061
Neurosurgical device in-situ	4 (5.6)	3 (13)	1 (2)	0.061
Glasgow coma scale	9.5 ± 4	9 ± 4	9.7 ± 4	0.508
Neck stiffness	4 (5.6)	4 (17.4)	0 (0)	0.003[a]
Focal neurological deficit	14 (19.7)	5 (21.7)	9 (18.8)	0.767
Length of stay in hospital	21.1 ± 16	21.9 ± 8.9	21 ± 18.2	0.053
Length of stay in ICU	10.4 + 8.9	12.1 ± 6.3	9.6 ± 9.8	0.005[a]
Need for any surgical intervention	20 (28.2)	10 (43.5)	10 (20.8)	0.047[a]
Need for invasive mechanical ventilation	27 (38)	13 (56.5)	14 (29.2)	0.026[a]
ICU mortality	20 (28.2)	10 (43.5)	10 (20.8)	0.047[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; ICU: Intensive care unit.

Table 2 Comparison of cerebrospinal fluid analysis between meningitis and non-meningitis groups

CSF parameters	Meningitis group (*n* = 23)	Non-meningitis group (*n* = 48)	*P* value
TLC (mean ± SD)	1223.4 ± 2611	8.1 ± 12.6	< 0.001[a]
Protein (mean ± SD)	177.1 ± 204.2	69.3 ± 61.5	0.002[a]
Sugar mg/dL (mean ± SD)	90.1 ± 98.4	102.1 ± 41	0.011[a]
Lactate levels mg/dL (mean ± SD)	60 ± 43.9	23.6 ± 11.1	< 0.001[a]
Lactate levels mmol/L (mean ± SD)	6.6 ± 4.8	2.6 ± 1.2	< 0.001[a]
Positive CSF cultures	17 (74)	0 (0)	< 0.001[a]
Positive meningo-encephalitis panel	7 (30)	0 (0)	0.001[a]
Positive CSF cultures or meningo-encephalitis panel	23 (100)	0 (0)	< 0.001[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; SD: Standard deviation.

in differentiating between bacterial and non-bacterial causes of infective meningitis.

In critically ill patients, there could be several differential diagnoses that may mimic meningitis symptoms. These include acute stroke, tumours, toxins, autoimmune and paraneoplastic diseases and cerebral or epidural abscesses. In addition, several metabolic derangements like sepsis and electrolyte disturbances may also present similarly. In the present study, these factors were the most common

Table 3 Comparison of various cerebrospinal fluid parameters for diagnosing meningitis

CSF Parameters	Cut-off	Sensitivity, %	Specificity, %	NPV, %	PPV, %	Accuracy, %	AUC	CI	*P* value
TLC (Cell/mm^3)	> 55	73.9	100	100	88.9	91.5	0.92	0.84-1	< 0.001[a]
Lactate levels (mmol/L)	> 2.7	82.6	72.9	59.4	89.7	76.1	0.81	0.7-0.9	< 0.001[a]
Protein (mg/dL)	> 104.4	56.5	87.5	68.4	80.8	77.5	0.73	0.6-0.9	0.002[a]
Sugar (mg/dL)	> 63	56.5	83.3	61.9	80.0	74.6	0.7	0.6-0.9	0.006[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; AUC: Area under the curve; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; TLC: Total leucocyte count.

Table 4 Etiological causes of patients in meningitis and non-meningitis groups

Meningitis group (*n* = 23), %		
Bacterial (*n* = 12)	Streptococcus pyogenes	5 (41.7)
	Staphylococcus aureus	2 (16.7)
	Haemophilus influenzae	2 (16.7)
	Enterococcus faecium	2 (16.7)
	Escherichia coli	1 (8.4)
Viral (*n* = 6)	Varicella zoster virus	3 (27.3)
	Herpes simplex virus	2 (18.2)
	Measles virus	1 (9.1)
Fungal (*n* = 2)	Candida tropicalis	1 (9.1)
	Cryptococcus neoformans	1 (9.1)
Tubercular (*n* = 3)	Mycobacterium tuberculosis complex	3 (27.3)
Non-meningitis group (*n* = 48)		
Septic and metabolic encephalopathy		34 (70.8)
Hypoxic brain injury		3 (6.3)
Guillain barre syndrome		2 (4.2)
Autoimmune encephalitis		2 (4.2)
Metastatic brain involvement		2 (4.2)
Post-ictal confusion		2 (2.1)
Hypoglycaemic coma		1 (2.1)
Demyelinating disorder		1 (2.1)
Unknown		1 (2.1)

causes of neurological derangement in the non-meningitis group. The typically described triad of headache, fever and neck rigidity is present in less than 50% of patients with meningitis; hence a high degree of suspicion is required[3].

CSF analysis remains the cornerstone for diagnosing meningitis and making the etiological diagnosis. The etiological organism causing meningitis depends on several patient conditions, including age, immunocompromised status, sinusitis or endocarditis, and any traumatic brain injury, neurosurgery or indwelling neurological devices or catheters. Streptococcus pneumoniae has been reported to be the commonest cause of bacterial meningitis, similar to the results of our study. Haemophilus influenza and Staphylococcus aureus are rare causes of meningitis in adult patients and are generally secondary to other underlying clinical conditions like sinusitis and endocarditis[16]. The reported incidence of Mycobacterium tuberculosis as a cause of acute meningitis is around 5%, but it may be higher in countries with a higher prevalence of tuberculosis[17]. Among the viral causes, the Varicella-zoster virus is most commonly implicated in immunocompromised patients and the Herpes simplex virus in

immunocompetent adults[17].

Presently, there is a need for a definitive test to enable rapid and accurate diagnosis, and hence the search for an ideal test continues. Apart from the routinely employed tests, several other CSF markers have been tested for their efficacy in diagnosing meningitis. Tests like CSF adenosine deaminase and cortisol have explicitly been evaluated for the diagnosis of tubercular meningitis, and specific other markers like CSF TNF-alpha, IL-6, IL-8 and IL-17 Levels have been tested for the diagnosis of nosocomial meningitis, with varied success[18-20].

CSF culture is still the gold standard for diagnosing bacterial meningitis, with a reported sensitivity of up to 80%. However, its efficacy in diagnosing other causes of infective meningitis is limited[21,22]. Its clinical application is also limited by a long turn-around of 48 h, thus delaying the initiation of appropriate early treatment. Moreover, its efficacy is further hampered in patients who have already received antibiotics.

Newer tests like RT-PCR-based meningitis-encephalitis panel (FilmArray PCR), a qualitative multiplex nucleic acid-based in-vitro diagnostic test, have been developed and are being increasingly used to diagnose meningitis[23]. This test has several advantages, including rapid turn-around time, good sensitivity and specificity (above 90%) and minimal effect of previous antibiotic exposure[24]. In addition, this test may help diagnose non-bacterial causes of meningitis, including viral and fungal meningitis and culture-negative cases[23]. This panel is capable of simultaneous identification of 14 different organisms, including multiple bacterial (Escherichia Coli, H. Influenzae, L. Monocytogenes, N. meningitides, Strepto. agalactiae, Strepto. pneumoniae), viral (Cytomegalovirus, Enterovirus, HSV 1; HSV 2; HHV 6, VZV) and fungal/yeast (Cryptococcus neoformans/gatti) nucleic acid directly from CSF specimen and may help diagnose complex cases too[25].

CSF lactate is now recognized as a valuable marker for diagnosing acute meningitis. It has shown to be a helpful marker in diagnosing nosocomial meningitis and has shown up to 100% sensitivity for diagnosing bacterial meningitis[19]. As it is a rapid, inexpensive and readily available tool, it may guide physicians in making an early diagnosis of acute meningitis and differentiating bacterial from other causes of meningitis. Nevertheless, it cannot be used as a standalone test but may be helpful to our routine CSF analysis. The value of CSF lactates does not depend on the serum lactate levels as ionized lactate crosses the blood-brain barrier very slowly, eliminating the need for simultaneous measurement of blood lactate levels[11]. CSF lactates have also been used for prognostication, with rapidly falling levels shown to be associated with positive outcomes[26]. It is generally advised to obtain CSF for lactate measurement before administering antibiotics, as antibiotic exposure may reduce its sensitivity [27]. However, in our patient cohort, more than 90% of patients had already received antibiotics still the sensitivity and specificity of CSF lactate remained good.

The cut-off for CSF lactate still needs to be clarified, with different authors using different cut-offs ranging from 2-3 mmol/L[28,29]. Our study observed that CSF lactates had the best accuracy at the cut-off of 2.7 mmol/L, within the generally accepted range. Moreover, it is agreed that the higher the CSF lactates, the higher the chances of it being caused by bacterial meningitis. A meta-analysis by Huy *et al* [26] reported that a CSF lactate of ≥ 3.5 mmol/L was associated with a high sensitivity ranging from 96%-99% and specificity ranging from 88-94% in diagnosing bacterial meningitis. In our study, CSF lactate levels were also significantly higher in bacterial (8.85 ± 4.66 mmol/L) *vs* non-bacterial causes of meningitis (4.15 ± 3.84 mmol/L).

There are several strengths to our study. It was a nicely designed prospective study, and we included all the available measures, including CSF cultures and PCR-based panels, to reach a diagnosis. Moreover, our study had primarily medically ill patients and was the first to show the correlation of CSF lactates with modern diagnostic techniques like PCR-based panels. The limitation of our study was that it was a monocentric study with a relatively small number of patients. Hence, it is imperative to conduct a larger multi-centre trial to improve the generalizability of our results.

CONCLUSION

CSF lactate may be used as an add-on marker to aid our clinical diagnosis of meningitis in critically ill patients. CSF lactate cut-off value above 2.72 mmol/L showed good accuracy, sensitivity, and specificity in diagnosing meningitis. High CSF lactates also help us to differentiate between bacterial and non-bacterial causes of meningitis and show a good correlation with CSF cultures and PCR-based meningo-encephalitis panel for the diagnosis of meningitis.

ARTICLE HIGHLIGHTS

Research background

Meningitis is a life-threatening clinical condition associated with high mortality and morbidity. Early diagnosis and specific treatment may improve outcomes. Lack of specific clinical signs or tests make the

diagnosis challenging, especially in critically ill patients.

Research motivation

Cerebrospinal fluid (CSF) lactate has been used to diagnose meningitis in post-operative neurosurgical patients. However, there is a dearth of data from neuro-medical patients regarding its role in diagnosing meningitis.

Research objectives

To assess the efficacy of CSF lactate in diagnosing meningitis in critically ill patients.

Research methods

A prospective, observational cohort study was carried out in a neuro-medical intensive care unit (ICU). CSF cytology, bio-chemistry, lactates, culture and polymerase chain reaction based meningo-encephalitis panel were evaluated. Patients were divided in two groups based on clinical diagnosis of meningitis. The efficacy of CSF lactate in diagnosing meningitis was evaluated and compared with other tests.

Research results

Seventy-one patients were included and 23 were diagnosed with meningitis. The mean values of CSF total leucocyte count, proteins and lactates were significantly higher in meningitis group. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve of 0.81 (95% confidence interval: 0.69-0.93), sensitivity 82.6%, and specificity 72.9%. Patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8 mmol/L), $P = 0.006$.

Research conclusions

CSF lactate may be used to aid in our diagnosis of meningitis in ICU patients. CSF lactate (> 2.72 mmol/L) showed good accuracy, sensitivity, and specificity in diagnosing meningitis and may also help to differentiate between bacterial and non-bacterial meningitis.

Research perspectives

Larger trials may assess the utility of CSF lactate in differentiating various infective meningitis like those secondary to bacterial, fungal, viral and tubercular bacilli.

FOOTNOTES

Author contributions: Yadav D, Singh O, and Juneja D designed the study. Yadav D, Kataria S, and Beniwal A collected the data, and analyzed the results. Yadav D, and Juneja D performed majority of the writing, and prepared the tables; Singh O, Goel A, Kataria S and Beniwal A provided the inputs in writing the paper and reviewed the manuscript.

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