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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

Devraj Yadav, Omender Singh, Deven Juneja, Amit Goel, Sahil Kataria, Anisha Beniwal

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Devraj Yadav, Omender Singh, Deven Juneja, Amit Goel, Sahil Kataria, Anisha Beniwal, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, 1, Press Enclave Road, New Delhi 110017, India. devenjuneja@gmail.com

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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ORCID number: Devraj Yadav 0000-0002-0833-6698; Omender Singh 0000-0002-3847-4645; Deven Juneja 0000-0002-8841-

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ORIGINAL ARTICLE

Prospective Study

Bedside ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure in nontraumatic neuro-critically ill patients

Madhura Bhide, Omender Singh, Deven Juneja, Amit Goel

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Madhura Bhide, Omender Singh, Deven Juneja, Amit Goel, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, 1, Press Enclave Road, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

BACKGROUND

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes. Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical intensive care unit (ICU) where the spectrum of disease is different.

AIM

To validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

METHODS

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was corelated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

RESULTS

There was significant association between raised ONSD and raised ICP on imaging ($P < 0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82% respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The area under the receiver operating characteristic curves was 0.844. Using Youden's index the best cut off value for ONSD was 5.75 mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer Glasgow Coma Scale ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas no statistically significant association

was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

CONCLUSION

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Key Words: Intracranial pressure; Intensive care unit; Neuro-critical care; Optic nerve sheath diameter; Ultrasonography

Core Tip: Raised intracranial pressure (ICP) maybe present in a significant proportion of neuro-critically ill patients and any delay in its management may lead to poor outcomes. Even though the gold standard for measuring raised ICP is the intraventricular catheter, it is invasive, not widely available, requires expertise in insertion and maintenance and may be associated with many risks. Hence, non-invasive methods like computed tomography scan or magnetic resonance imaging are being increasingly used to diagnose raised ICP. However, their utility is also restricted by logistical issues and have limited repeatability. Bedside ultrasonography measuring optic nerve sheath diameter (ONSD) can be used as a screening test to detect raised ICP and as a trigger to initiate further management. ONSD can also be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

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INTRODUCTION

Raised intracranial pressure (ICP) is a dreaded complication in the intensive care unit (ICU) which may occur either as a result of a primary neurological disorder or as a secondary complication in patients admitted due to other causes. A delay in detecting raised ICP can lead to poor clinical outcomes and increased mortality. The latest Brain Trauma Foundation guidelines now recommend a cut off 22 mmHg to initiate ICP-lowering therapies[1]. Gold standard for measuring raised ICP is the intraventricular catheter. However, it is not widely available, requires expertise in insertion and maintenance and may be associated with many risks like infection, collapse of ventricles and haemorrhage[2]. Hence, non-invasive methods like computed tomography (CT) scan or magnetic resonance imaging (MRI) are increasingly used to diagnose raised ICP. However, they are associated with transport risk and radiation exposure, in the case of CT scans, leading to logistical issues and limited repeatability.

Determination of optic nerve sheath diameter by ultrasonography (US-ONSD) is a simple bedside test with a rapid learning curve, low intra and interobserver variation and good repeatability[3,4]. Studies have shown good accuracy even when performed by non-radiologists[5]. In modern ICUs, bedside ultrasonography is integrated into routine clinical examination and is readily available. Optic nerve sheath diameter (ONSD) is frequently used across neuro-surgical ICUs as a tool for ICP monitoring and is particularly useful in patients in whom invasive ICP monitoring criteria are not met or are contraindicated. However, the spectrum of disease and comorbidities of patients admitted to neuro-medical ICUs are distinct from neurosurgical ICUs. There need to be more practical bedside screening tools to detect raised ICP in neuro-medical ICUs timely; hence, we aimed to validate ONSD in neuro-medical ICU patients.

MATERIALS AND METHODS

We conducted this study to determine the diagnostic accuracy of ONSD in adult non-traumatic neuro-critically ill patients after approval from the institutional ethics committee (TS/MSSH/MHIL/SKT/-

MHEC/CC/20-16). Our inclusion criteria were patients older than 18 years admitted to the neuro-medical ICU with signs and symptoms suggestive of raised ICP. Our exclusion criteria were previously known history of neurological conditions like chronic hydrocephalus, in situ ventriculoperitoneal shunt, known ocular mass, ocular trauma, conjunctival oedema, orbital oedema, cavernous sinus pathology or arachnoid cysts, and patients having optic nerve disease. Additionally, patients in whom CT/MRI could not be performed within 24 hours of US-ONSD were excluded from the analysis.

For the prospective study, the sample size required was calculated according to the following formula: $Z\alpha 2 \times SN \times (1 - SN)$, $n = 2 \times P$. Where, n = required sample size Z = SNV at α = 5% = 1.96. S.N.SN = Anticipated Sensitivity. d = Absolute precision desired on either side P = Expected prevalence in the population or based on the previous/pilot studies.

For this study, a 95% confidence level with an appropriate effect size and a statistical power of 80% was taken. In a previous study by Salahuddin *et al*[6], the expected prevalence of non-traumatic raised ICP in a medical ICU was 30.4%[6]. The pooled sensitivity of ONSD to determine raised ICP was 90%, as determined by a systematic review and metanalysis by Dubourg *et al*[3]. Keeping these values for the calculation of the sample size, our required sample size was 114.

We serially enrolled patients who fulfilled the inclusion criteria. After written informed consent was obtained, ocular USG was done by critical care specialists trained in critical care ultrasonography, using a 7-15 MHz ultrasound probe in B mode to determine the ONSD three mm distal to the optic disc in both eyes. A fibrous trabecular network connects the optic nerve and its sheath. Studies have shown a greater degree of mesh 6 to 12 mm behind the globe, whereas there is a lesser degree of mesh 3 mm behind the globe. Therefore, 3 mm behind the globe expands to a greater degree than 6 to 12 mm behind the globe, with the maximum expansion dependent on the individual's trabecular density[7]. Hansen *et al*[8] first validated ONSD and standardized the method to document it by B mode ultrasonography by measuring it 3 mm behind the globe. Two readings were taken for each eye, and a mean value was calculated to represent the final ONSD. ONSD more than 5.7 mm was taken as a threshold for determining raised ICP[3]. CT/MRI scans of the brain were done within 24 h of US-ONSD, and the images were reviewed for signs of raised ICP. Raised ICP or non-traumatic radiographic cerebral oedema [NTRCE] was defined on imaging as significant brain oedema, midline shift, compression of basal cisterns or ventricles, effacement of sulci, insufficient grey/white differentiation and transalpine herniation. Clinical history, general and systemic examination findings, SOFA and APACHE 2 scores and patient outcomes were recorded.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analyzed and statistically evaluated using the SPSS-PC-25 version. Quantitative data were expressed in mean ± standard deviation or median with interquartile range, and depending upon normality distribution, the difference between two comparable groups was tested by student's *t*-test (unpaired) or Mann Whitney 'U' test. Qualitative data were expressed in percentages, and statistical differences between the proportions were tested by the chi-square or Fisher's exact test, as appropriate. For all statistical tests, a *P* value less than 0.05 was taken as valid evidence for the statistical significance of the data.

The performance of the diagnostic tests was estimated using 2 × 2 contingency tables to calculate sensitivity, specificity, overall diagnostic accuracy, positive and negative predictive value, likelihood ratios (LRs) and 95% confidence intervals (CI). Post-test probability was determined using Bayes's nomogram. Discrimination was tested using the receiver operating characteristic (ROC) curves. The best cut-off value for ONSD was calculated by using Youden's index.

RESULTS

114 patients with signs and symptoms suggestive of raised ICP were included in the analysis. Out of these, raised ONSD (> 5.7 mm) was found in 45 (39.5%) patients. The mean age of patients in our study cohort was 64.05 (± 16.80) years, with a predominantly male population (59.3%). Table 1 shows that the patient comorbidities, clinical symptoms and signs, except Glasgow Coma Scale (GCS), on admission were comparable across both groups. Lower GCS was significantly associated with raised ICP (P = 0.009). Raised ICP on imaging was seen in 49 patients (43%). The most common feature of raised ICP on imaging was diffuse cerebral oedema (38.1%) followed by effacement of sulci (32.7%), insufficient grey/white differentiation (30.1%), compression of ventricles (21.2%), midline shift (20.4%) and transfalcine herniation (1.8%).

There was a statistically significant correlation between raised ONSD and increased ICP features on CT/MRI scans (P < 0.001). As shown in Table 2, the sensitivity, specificity, and positive and negative predictive values at this cut-off were 77.55%, 89.06%, 84.44% and 83.82%, respectively. The AUROC was 0.844. The best cut-off value for ONSD calculated using Youden's index was 5.75 mm.

The commonest diagnosis was septic/metabolic encephalopathies (27.4%). Other diagnoses were acute intracranial bleeding (21.2%), acute ischaemic stroke (20.4%), meningoencephalitis (13.3%), super

Table 1 Patient comorbidities and clinical features on admission

	Variables	Overall (*n* = 114), %	Normal ONSD (*n* = 69), %	Raised ONSD (*n* = 45), %	*P* value
Comorbidities	Hypertension	54 (47.8)	37 (68.5)	17 (31.5)	0.083
	T2DM	35 (31.0)	21 (60.0)	14 (40.0)	0.979
	CKD	20 (17.7)	14 (70.0)	6 (30.0)	0.323
	CAD	10 (8.8)	4 (40.0)	6 (60.0)	0.193
	OAD	8 (7.1)	7 (87.5)	1 (12.5)	0.142
	Malignancy	7 (15.0)	12 (70.6)	5 (29.4)	0.341
	Others	30 (26.5)	19 (63.3)	11 (36.7)	0.680
	No comorbidities	26 (23.0)	12 (46.2)	14 (53.8)	0.096
Symptoms on admission	Headache	30 (26.5)	18 (60.0)	12 (40.0)	0.982
	Vomiting	19 (16.8)	12 (63.2)	7 (36.8)	0.771
	Blurring of vision	10 (8.8)	4 (40.0)	6 (60.0)	0.193
	Seizures	30 (26.5)	18 (60.0)	12 (40.0)	0.982
	Altered sensorium	103 (91.2)	60 (58.3)	43 (41.7)	0.311
General examination	GCS, mean ± SD	9.39 ± 4.09	10.21 ± 3.97	8.16 ± 3.99	0.009[a]
	Bradycardia	34 (30.1)	18 (52.9)	16 (47.1)	0.303
	Hypertension	31 (27.4)	19 (61.3)	12 (38.7)	0.882
	Neck stiffness	33 (29.2)	20 (60.6)	13 (39.4)	0.952
	Focal neurological deficit	70 (61.9)	41 (58.6)	29 (41.4)	0.656

[a]Denotes Statistical significance

CAD: Coronary artery disease; CKD: Chronic kidney disease; GCS: Glasgow coma scale; OAD: Obstructive airway disease; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

Table 2 Accuracy of optic nerve sheath diameter at cut-off of 5.7 mm with raised raised intracranial pressure on brain imaging

	Values	95%CI
Sensitivity	77.55	63.38-88.23
Specificity	89.06	78.75-95.49
Positive likelihood ratio	7.09	3.47-14.50
Negative likelihood ratio	0.25	0.15-0.43
Disease prevalence	43.36	34.07-53.01
Positive predictive value	84.44	72.64-91.73
Negative predictive value	83.82	75.36-89.78
Accuracy	84.07	76.00-90.28

refractory status epilepticus (4.4%), newly diagnosed space-occupying lesion (1.8%), cerebral venous sinus thrombosis (CVST) (1.7%) and hypoxic-ischaemic encephalopathy (1.7%). Of the 31 patients presenting with septic/metabolic encephalopathy, 26 (83.9%) had a normal ONSD.

Patient outcomes, including ICU length of stay (LOS) and ICU mortality, were comparable across both groups, as shown in Table 3. Raised ONSD had a statistically higher requirement of surgical intervention (P = 0.006). The surgical procedures were decompressive craniotomy in 6 patients, ventriculoperitoneal shunt (VP shunt) in 3 patients and extra-ventricular drain (EVD) insertion in 2 patients. One patient underwent EVD followed by a VP shunt with Omaya reservoir.

Table 3 Hospital course across normal and raised optic nerve sheath diameter groups

		Overall (*n* = 114)	Normal ONSD (*n* = 69)	Raised ONSD (*n* = 45)	*P* value
Hospital course	SOFA, median [IQR]	5 [3-8]	5 [3-8]	5 [3-8]	0.409
	APACHE II score, median [IQR]	20 [14-26]	21 [14-26]	20 [14-26]	0.569
	Hospital LOS, median [IQR]	17 [7-27.5]	15 [7-28]	18 [8-25]	0.688
	ICU LOS, median [IQR]	10 [5-21]	10 [5-20]	10 [5-21]	0.609
Surgical intervention	Yes	11 (9.7)	2 (18.2)	9 (81.8)	0.006[1]
	No	102 (90.3)	66 (64.7)	36 (35.3)	
Discharged or Death	Discharged	64 (56.6)	41 (64.1)	23 (35.9)	0.335
	Death	49 (43.4)	27 (55.1)	22 (44.9)	

[1]Denotes statistical significance.

APACHE: Acute physiology and chronic health evaluation; IQR: Inter quartile range; LOS: Length of stay; ONSD: Optic nerve sheath diameter; SOFA: Sequential organ failure assessment.

DISCUSSION

Invasive ICP monitoring is not widely available across the ICUs, especially in resource-limited settings. An internet-based survey of critical care physicians in India in 2013 showed that only 36.42% had access to exclusive neurocritical care units, and 63.4% of consultants did not monitor ICP. Amongst the physicians who monitored for raised ICP, 60.32% used CT/MRI scans, 28.57% intraventricular catheter with external transducer, and 11.11% used Codman microsensor[9]. This shows the extent of the deficit in terms of advanced neuro-monitoring facilities across ICUs in resource-limited settings. US-ONSD provides a lucrative alternative to the available methods for ICP monitoring. We conducted a prospective study with the primary objective of validating ONSD by bedside ultrasound compared to features of raised ICP on the CT/MRI brain. Our study found a significant association between raised ONSD (> 5.7 mm) and findings of raised ICP on imaging. The sensitivity and specificity, at this cut-off, were 77.55% and 89.06%, with an AUROC were 0.844. The positive and negative predictive values were 84.44% and 83.82%, respectively. The best cut-off value for ONSD determined by Youden's index was 5.75 mm.

Physical findings of raised ICP are nonspecific and lack accuracy in diagnosing raised ICP. Diagnosis of raised ICP is essential as it may be associated with poor clinical outcomes. Early intervention using osmotherapy with hypertonic saline or mannitol has been shown to be effective in lowering ICP[10-12]. GCS is commonly used for monitoring neuro-critically ill patients. Poor motor performance has been associated with raised ICP and poor prognosis[13]. In our study, the most common symptom in patients with suspected raised ICP was altered mental status, and poor GCS score was significantly associated with raised ONSD. This was in accordance with a study of patients with traumatic brain injury where raised ONSD was compared to three groups of GCS 3-5, 6-8, > 8 and a statistical significance was found between poor GCS and raised ONSD[14]. In patients whose GCS cannot be assessed due to ongoing sedatives or paralytic agents, raised ONSD can be used as an indicator for raised ICP warranting further evaluation. However, further studies are required to establish any linear relationship between deteriorating GCS and increasing ONSD.

Out of our entire study population, 49 patients (42.98%) showed the presence of NTRCE. In a study in general medical ICU by Salahuddin *et al*[6], NTRCE was found in 30.4%[9]. Higher prevalence of NTRCE in our study can be explained by the fact that it was done in neuro-medical ICU patients with suspected raised ICP, as opposed to the study mentioned above, which was done in a general medical ICU.

For over 10 years, the upper limit of normal for US-ONSD was considered to be 4.5 to 5.0 mm. However, recent studies have shown a higher threshold. Geeraerts *et al*[15] reported that an ONSD cut-off of 5.7 to 5.8 mm could exclude raised ICP with sensitivity and a negative predictive value of > 90%. If the ONSD was < 5.7 mm, the probability of ICP above 20 mmHg was less than 5%. Another study on 100 stroke patients with mass effect compared US-ONSD with signs suggestive of raised ICP on a brain CT scan and showed that an ONSD cut-off of > 5.7 mm positively correlated with CT scan findings[14]. In the present study, we found the best cut-off for ONSD using Youden's index as 5.75 mm, per the recent data[16].

Our study found a statistically significant association between raised ONSD (> 5.7 mm) and raised ICP on CT/MRI brain. Raised US-ONSD was a good screening tool for raised ICP with a sensitivity and specificity of 77.55% and 89.06%, respectively, and AUROC was 0.844. However, the terms sensitivity and specificity do not account for disease prevalence and are more applicable at a population level. LRs

depend on disease prevalence and can be used to quantify the probability of disease in an individual patient. In our study, the positive and negative LR was 7.09 and 0.25, respectively. The disease prevalence (raised ICP) in our study was 43%. Baye's nomogram suggests that if ONSD is more than 5.7 mm, there is an 84% probability of a patient having raised ICP. On the other hand, if ONSD is less than 5.7 mm, the probability of raised ICP is only 16% (CI: 10%-24%). Hence, in neuro-medical ICUs where raised ICP has a high prevalence, ONSD is a good screening test to detect raised ICP but may need to be more accurate to rule out raised ICP. When the same LRs are applied to a low prevalence population, like in a study by Tayal *et al*[5] where raised ICP was found to be prevalent in only 14% of patients presenting to the emergency department with a suspected acute head injury requiring CT, the positive post-test possibility was 54%, and negative post-test probability was less than 4%. Therefore, in a population with a low prevalence of raised ICP, the ONSD may be good for ruling out the diagnosis of raised ICP.

Most studies on ICP monitoring and US-ONSD have been conducted in neurosurgical ICUs, where trauma and strokes form the bulk of the disease. Primary pathology of neurocritical illness is different in medical ICUs[3,4]. A previous study of ONSD in a medical ICU found that the common causes of coma were septic or metabolic encephalopathy (25.4%) followed by new intracranial vascular event (17.6%), anoxic brain injury (4.9%), hepatic encephalopathy (21.5%), intracranial malignancy (8.8%) and others (intracranial infection, reversible posterior leukoencephalopathy syndrome, subclinical seizures) in 21.5%[9]. Similarly, our study also found septic/metabolic encephalopathy to be the commonest cause, with the majority (83.9%) of these patients having a normal ONSD. As septic/metabolic encephalopathy forms a large cohort of patients with altered sensorium in a medical ICU, it would be worthwhile to conduct an adequately powered study to validate ONSD in these patients. This gives an insight into the spectrum of diseases causing signs and symptoms of raised ICP in a neuromedical ICU.

There was no statistically significant difference between raised ONSD and SOFA scores and APACHE II scores. The severity of the disease seems to have no impact on ONSD. The hospital LOS, ICU LOS, and ICU mortality did not show any statistical correlation with ONSD. Hence, ONSD may not be a good test for prognostication in a neuro-medical ICU. However, patients with raised ONSD had a statistically higher rate of surgeries in our study and raised ONSD may indicate a greater likelihood for surgical intervention.

There are several strengths in our study. We included a reasonably large number of patients. This was a prospective study with a well-defined study protocol. The study was done in a single centre, so the ICU admission protocol and management strategies were uniform and standardized. We used CT/MRI brain as the gold standard for comparison with US-ONSD. We acknowledge the inferiority of CT/MRI to invasive gold standard measures of raised ICP. However, as invasive ICP monitoring is not readily available, CT/MRI shows a more real-life situation and may have better external validity, especially in resource-poor settings. Limitations were that all data were obtained from a single centre database, which may result in concerns regarding the generalization of the conclusions. We did not perform serial ONSD measurements or ONSD pre and post-treatment or procedures undertaken for raised ICP. Hence, the effect of therapeutic strategies on delta ONSD is not available.

CONCLUSION

Given the good sensitivity, positive LR and AUROC, ONSD can be used as a screening test to detect raised ICP in a medical ICU and future potential as a threshold trigger to escalate the management of raised ICP. This can help decrease the time gap between the episode of raised ICP and the initiation of treatment.

ARTICLE HIGHLIGHTS

Research background

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes.

Research motivation

Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical intensive care unit (ICU) where the spectrum of disease is different.

Research objectives

We conducted this study to validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

Research methods

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was correlated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

Research results

There was significant association between raised ONSD and raised ICP on imaging ($P < 0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82%, respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The AUROC was 0.844. Using Youden's index the best cut off value for ONSD was 5.75 mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer GCS ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas, no statistically significant association was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

Research conclusions

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Research perspectives

Large scale studies need to be performed to assess the utility of ONSD in specific sub-groups of critically ill patients with neurological derrangements.

FOOTNOTES

Author contributions: Bhide M and Juneja D designed the study. Bhide M and Goel A collected the data. Bhide M and Juneja D analysed the results, performed the majority of the writing, and prepared the tables; Singh O, and Goel A provided the inputs in writing the paper and reviewed the manuscript.

Institutional review board statement: The study was approved by the institutional review board of Max Super Speciality Hospital, Saket (TS/MSSH/MHIL/SKT/MHEC/CC/20-16).

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

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ORCID number: Madhura Bhide 0000-0001-5054-7969; Omender Singh 0000-0002-3847-4645; Deven Juneja 0000-0002-8841-5678; Amit Goel 0000-0002-9509-5705.

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SYSTEMATIC REVIEWS

Clonidine use during dexmedetomidine weaning: A systematic review

Sanu Rajendraprasad, Molly Wheeler, Erin Wieruszewski, Joseph Gottwald, Lindsey A. Wallace, Danielle Gerberi, Patrick M Wieruszewski, Nathan J Smischney

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Sanu Rajendraprasad, Department of Pulmonary & Critical Care, Mayo Clinic, Rochester, MN 55905, United States

Molly Wheeler, Erin Wieruszewski, Patrick M Wieruszewski, Department of Pharmacy, Mayo Clinic, Rochester, MN 55905, United States

Joseph Gottwald, Nathan J Smischney, Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Lindsey A. Wallace, Critical Care Medicine Independent Multidisciplinary Program, Mayo Clinic, Rochester, MN 55905, United States

Danielle Gerberi, Mayo Medical Libraries, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan J Smischney, MD, MS, Associate Professor, Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

Abstract

BACKGROUND

Dexmedetomidine is a centrally acting alpha-2A adrenergic agonist that is commonly used as a sedative and anxiolytic in the intensive care unit (ICU), with prolonged use increasing risk of withdrawal symptoms upon sudden discontinuation. As clonidine is an enterally available alpha-2A adrenergic agonist, it may be a suitable agent to taper off dexmedetomidine and reduce withdrawal syndromes. The appropriate dosing and conversion strategies for using enteral clonidine in this context are not known. The objective of this systematic review is to summarize the evidence of enteral clonidine application during dexmedetomidine weaning for prevention of withdrawal symptoms.

AIM

To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

METHODS

This was a systematic review of enteral clonidine used during dexmedetomidine weaning in critically ill adults (≥ 18 years). Randomized controlled trials, prospective cohorts, and retrospective cohorts evaluating the use of clonidine to

wean patients from dexmedetomidine in the critically ill were included. The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal. Other secondary outcomes included prevalence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU length of stay.

RESULTS

A total of 3427 studies were screened for inclusion with three meeting inclusion criteria with a total of 88 patients. All three studies were observational, two being prospective and one retrospective. In all included studies, the choice to start enteral clonidine to wean off dexmedetomidine was made at the discretion of the physician. Weaning time ranged from 13 to 167 h on average. Enteral clonidine was started in the prospective studies in a similar protocolized method, with 0.3 mg every 6 h. After starting clonidine, patients remained on dexmedetomidine for a median of 1-28 h. Following the termination of dexmedetomidine, two trials tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, 12h, and 24 h, followed by clonidine discontinuation. For indicators of enteral clonidine withdrawal, the previously tolerable dosage was reinstated for several days before resuming the taper on the same protocol. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

CONCLUSION

Enteral clonidine is a strategy to wean critically ill patients from dexmedetomidine. There is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Key Words: Clonidine; Dexmedetomidine; Intensive care unit; Withdrawal; Weaning

Core Tip: In this systematic review of enteral clonidine use during dexmedetomidine weaning in critically ill patients, an association of increased withdrawal symptoms and agitation with the use of a clonidine taper and no difference in intensive care unit length of stay with or without clonidine taper was observed. However, varied techniques and a small total sample size restrict utility of the findings.

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INTRODUCTION

In critically ill patients, agitation and delirium lead to poor clinical outcomes, such as prolonged mechanical ventilation, intensive care unit (ICU), and hospital length of stay (LOS)[1,2]. To optimize outcomes related to sedation in ICU patients, the 2018 Society of Critical Care Medicine practice recommendations suggest avoiding benzodiazepines[3]. Dexmedetomidine and propofol are the most commonly used sedatives in this group[3]. They have resulted in a shorter duration of mechanical ventilation as compared to benzodiazepines[3-6].

Dexmedetomidine, an intravenous (IV) alpha-2A adrenergic agonist provides cooperative sedation, sympatholysis, and analgesic-sparing effects without inducing respiratory depression and is frequently used in critically ill patients to treat pain, agitation, and delirium[7,8]. Due to a lack of central depression, dexmedetomidine is an attractive sedative clinically for weaning from mechanical ventilation and awake sedation in non-intubated patients. Dexmedetomidine was licensed by the Food and Drug Administration as a sedative with a 24-h time limit; however, studies have shown that it is safe and effective for up to 5 d with bradycardia and hypotension being the most commonly reported adverse effects[4,9-11]. Other drawbacks have included the cost of drug acquisition and availability only in an IV formulation[12-14]. Sudden cessation of the drug can lead to withdrawal symptoms such as agitation, tachycardia, hypertension, and other hypersympathetic conditions[15]. Clonidine, a

structurally comparable alpha-2A that is widely used as an antihypertensive, sedative, and sympatholytic, could be an alternate enteral medication for patients transitioning from dexmedetomidine[16].

The use of enteral clonidine may be a potential strategy for weaning from dexmedetomidine to prevent withdrawal syndromes[17,18]. However, dexmedetomidine has an eight-fold higher affinity for central alpha-2A receptors than clonidine; as a result, the best dosing and conversion strategies for clonidine in this context are unknown[8]. The purpose of this systematic review was to summarize the available evidence regarding the use of enteral clonidine to prevent withdrawal symptoms during dexmedetomidine weaning.

MATERIALS AND METHODS

This was a systematic review designed to assess the use of enteral clonidine to prevent withdrawal syndromes in critically ill adults weaning from dexmedetomidine. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines[19]. The protocol was *a priori* registered in the PROSPERO database (No. CRD42022330666).

Data sources and eligibility criteria

The systematic search was designed and executed by a skilled medical librarian (DJG). We searched for the concepts of enteral clonidine and dexmedetomidine combined with variant keywords and standardized index terms. The search was performed in April 2022 and included the electronic databases Ovid Evidence-Based Medicine Reviews, Ovid Embase, Ovid Medline, Scopus, and Web of Science Core Collection. The search was limited to the English language and did not include animals or pediatrics. The full search strategy is detailed in the Supplementary Table 1.

Eligible studies to be included were those that reported randomized-, crossover-, or parallel-designed clinical trials, prospective and retrospective longitudinal (cohort) studies, and cross-sectional studies (non-longitudinal studies) that reported on the use of enteral clonidine specifically for the purposes of weaning from dexmedetomidine to avoid withdrawal syndromes. Studies were excluded if they reported on pediatric patients (age < 18 years), animal or other non-clinical experiments, case reports, case series, review articles, editorial, and book chapters. Studies using intravenous clonidine or oral alpha-2A agonists other than clonidine were also excluded. No restrictions were placed on date of publication. In addition, a relevant search was performed by Reference Citation Analysis database (https://www.referencecitationanalysis.com/) to supplement and improve the highlights of the latest cutting-edge research results.

Article selection and data extraction

Article titles and abstracts were screened by two independent reviewers (SSR, MEW) for inclusion based on the pre-defined inclusion and exclusion criteria. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. The full text files of the candidate articles were randomly assigned to the two independent reviewers (SSR, MEW) to screen for final inclusion. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. All article screening was performed using Covidence software (Melbourne, Australia).

The data from the final articles meeting inclusion criteria were abstracted from full-text documents by two independent abstractors (JAG, LAW). Disagreements were adjudicated by discussion between the abstractors, and consultation of an adjudicator (EDW) when agreement was unattainable with consultation of a senior investigator (PMW) if necessary. The data abstracted included details regarding the publication information, study design, demographic data, details regarding the dosing schema and protocols, and outcomes information.

Risk of bias assessment

The Risk of Bias in Non-randomized Studies of Interventions tool was used to assess for risk of bias[20]. The tool was applied by two independent assessors (JAG, LAW) and disagreements were adjudicated by the senior investigators (PMW, NJS). The risk of bias information was summarized using R version 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2022) and the robvis version 0.3.0 package[21].

Outcomes and data analysis

The primary outcomes of interest were the dosing and titration schema of enteral clonidine and dexmedetomidine. Secondary outcomes included risk factors for dexmedetomidine withdrawal, incidence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU LOS. The data were summarized in descriptive format. No inferential analysis was performed.

RESULTS

Trial inclusion

The initial search identified 3427 studies. Following removal of duplicates and excluded records, 29 full-text articles were assessed for eligibility. Three (10.3%) of these met the inclusion criteria and were included in the analysis[22-24]. The results of the systematic search are summarized in Figure 1.

Trial and patient characteristics

Two of the included studies were prospective with one double cohort observational study and the other an observational pilot study[22,23]. The third was a retrospective observational study[24]. A total of 88 participants were included across the 3 studies. All studies were performed in the United States, and publication dates spanned from 2015 to 2020. Characteristics of all the studies included are detailed in Table 1. Males outnumbered females in all studies, with the most common initial diagnosis on admission being respiratory or heart disease, followed by sepsis, gastrointestinal disorders, trauma, neurological issues, and substance abuse. Indications of dexmedetomidine and enteral clonidine taper use were agitation, delirium, substance abuse, post procedural and intolerance of other sedatives.

Dosing and titration schema

The decision to initiate enteral clonidine to wean dexmedetomidine was per clinician discretion in all included studies (Table 2). Bhatt *et al*[22] required at least 72 h of dexmedetomidine prior to enteral clonidine initiation for study inclusion with a median of 167 h [interquartile range (IQR) 115-217.1]; over the entire dexmedetomidine course patients received a mean dose of 0.9 mcg/kg/h and standard deviation of 0.3. Patients in the Gagnon *et al*[23] study had shorter median dexmedetomidine duration prior to enteral clonidine initiation of 33 h (IQR 21-47.5) at a median rate of 1 mcg/kg/h (IQR 0.7-1.2). Dexmedetomidine duration prior to enteral clonidine was shortest in the Terry *et al*[24] study with a median of 24 h (IQR 14.5-39) for patients who had dexmedetomidine discontinued within 8 h of clonidine initiation with a median dose at time of clonidine initiation of 0 mcg/kg/h (IQR 0-0.25). The group requiring more than 8 h of enteral clonidine to wean dexmedetomidine received a median of 13 h (IQR 4-32) of dexmedetomidine at a rate of 0.7 mcg/kg/h (IQR 0.45-0.7). Enteral clonidine was initiated in a similar protocolized fashion by Gagnon *et al*[23] and Bhatt *et al*[22], starting with 0.3 mg every 6 h. Patients with a dexmedetomidine rate < 0.7 mcg/kg/h, weight < 100 kg, or age > 65 years were initiated on 0.2 mg at the same interval. The doses were reduced by 0.1 mg for bradycardia and hypotension and increased by 0.1 mg for agitation. Dexmedetomidine dose was weaned by 25% every 6 h if no agitation requiring rescue medications had occurred. Terry *et al*[24] initiated enteral clonidine at 0.1 mg with non-protocolized uptitration every 6-8 h until the Richmond Agitation-Sedation Scale (RASS) goal was met, or hemodynamics prohibited further uptitration. Dexmedetomidine was weaned as soon as patients responded to clonidine as assessed by RASS, Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), and hemodynamics without a defined protocol.

Patients spent a median of 19 h (IQR 9.5-23) on dexmedetomidine after enteral clonidine initiation in the Bhatt *et al*[22] study. Dexmedetomidine was utilized for a median of 23 h (IQR 2-53) for patients in the Gagnon *et al*[23] study after enteral clonidine was started. Terry *et al*[24] separately evaluated patients able to wean off dexmedetomidine within 8 h of enteral clonidine initiation from those requiring more than 8 h. Of 26 patients included, 17 (65%) were weaned off dexmedetomidine within 8 h with a median transition time of 1 h (IQR 0.5-4.25). Patients requiring more than 8 h to wean off dexmedetomidine after clonidine initiation had a median transition time of 28 h (IQR 20-56.5).

After dexmedetomidine discontinuation, Bhatt *et al*[22] tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, then 12h, then 24 h, followed by clonidine discontinuation without any individual dose reduction. Gagnon *et al*[23] also increased the dosing interval in the same manner every 24-48 h without dose reduction. For signs of clonidine withdrawal, the previously tolerated dose was reinitiated for several days and then an attempted taper resumed on the same protocol. Terry *et al*[24] did not describe any subsequent enteral clonidine taper.

Outcomes

Dexmedetomidine re-initiation: No patients had dexmedetomidine restarted for documented enteral clonidine failure, albeit transition failure was identified as inability to wean dexmedetomidine after 8 h (Table 3)[24]. Failed transition had a median transition time of 28 h (IQR = 20-56.5). Patients who failed transition had alcohol withdrawal, septic shock, endocarditis, lung transplant and aortic valve replacement[24]. None of the patients were restarted on dexmedetomidine in the observation pilot trial [23]. Bhatt *et al*[22] showed 93% of patients were able to stop dexmedetomidine within 24 h of enteral clonidine initiation. No explicit details on re-initiation were provided.

Duration of mechanical ventilation: Seventeen (37%) patients were mechanically ventilated of the 2 studies that reported this data[23,24]. Gagnon *et al*[23] reported duration of mechanical ventilation of 3.5 d (IQR 0-10.5) and mechanical ventilation free days of 24.5 (IQR 15.3, 28)[23]. One study, despite having the bulk of its patients admitted with respiratory diagnosis to the ICU, did not provide data regarding

Table 1 Trial characteristics

Ref.	Type of study	Study dates	Total patients studied	ICU	Admitting diagnosis	Mechanical ventilation	Age (yr)	Sex	Weight (kg)	BMI (kg/m²)	APACHE score
Terry *et al* [24], 2015	Single-center, retrospective, observational study	February 1, 2013-February 28, 2014	26	Cardiac surgery 21 (80.7%), thoracic 3 (11.5%), neurology 1 (3.8%), surgical 1 (3.8%)	Respiratory 4 (15.4%), cardiac 20 (76.9%), trauma 1 (3.8%), substance abuse 1 (3.8%)	4 (14.8%)	54.4 ± 16.9[1]	Male: 17 (63%), female: 9 (37%)	NR	32 ± 3.1[1]	18 (14-22)[2]
Gagnon *et al*[23], 2015	Single-center prospective observational pilot study	January, 2014-March, 2014	20	Mixed medical, surgical, neuro ICU	Respiratory 12 (60%), neurologic 1 (5%), trauma 2 (10%), substance abuse 2 (10%), other 3 (15%)	13 (65%)	62 (54-73)[2]	Male: 13 (65%), female: 7 (35%)	NR	29.9 (26.5-33.1)[2]	62 (54-80)[2]
Bhatt *et al* [22], 2020	Single-center, prospective, double cohort observational study	November, 2017-December, 2018	42	Medical-surgical 10 (67%) *vs* 13 (48%), cardiothoracic 3 (20%) *vs* 8 (30%), neurosurgical 2 (13%) *vs* 6 (22%)	Respiratory 16 (38.1%), cardiac 12 (28.6%), gastroenterological 5 (11.9%), neurologic 2 (4.8%), trauma 1 (2.4%), sepsis/shock 6 (14.3%)	NR	Clonidine taper: 58 (43-66[2] *vs* no taper: 54 (45-66)[2] (P = 0.93)	Male: 27 (64%), female: 15 (36%)	Clonidine taper: 86.9 (67.3-94.1)[2] *vs* no taper 91.6 (78.9-101.1)[2] (P = 0.19)	NR	NR

[1]Data reported as mean ± SD.

[2]Data reported as median (interquartile range).

NR: Not reported; ICU: Intensive care unit; BMI: Body mass index, APACHE: Acute physiology and chronic health evaluation.

the need for supplemental oxygenation or ventilation[22].

ICU LOS: All three studies reported ICU LOS; two of the studies appear to have similar ICU LOS in patients that had weaning protocol with no comparison[23,24]. Only one study specifically evaluated and found no statistically significant difference in ICU LOS between enteral clonidine taper *vs* no taper (22.7 d *vs* 17 d; P = 0.3) and time to discharge after dexmedetomidine wean in either group (7.2 d *vs* 7 d; P = 0.69)[22].

Adverse events: Terry *et al*[24] did not specify symptoms associated with enteral clonidine withdrawal. Gagnon *et al*[23] discovered that only one patient met withdrawal criteria (blood pressure > 180/120 mmHg) after stopping enteral clonidine despite a 6-d taper; this patient was also tapering off methadone and clonazepam. Bhatt *et al*[22] provided significant withdrawal data as defined by ³2 of: heart rate > 90, CAM positive, RASS > 1, systolic blood pressure > 140, or Withdrawal Assessment Tool Version 1 (WAT-1) > 2. Patients who experienced at least two withdrawal symptoms from dexmedetomidine during a single assessment during the wean period were not significantly different between the two groups (73% for patients who were given an enteral clonidine taper and 59% for patients who were weaned off dexmedetomidine alone; P = 0.27). The most common symptoms reported by both groups on the WAT-1 were loose stools, fever, and agitation. Those on enteral clonidine taper had more withdrawal symptoms, notably agitation (RASS > 1), than patients on

Table 2 Dosing schemes reported in study methods

Ref.	Formal protocol	Dexmedetomidine indication	Threshold for clonidine use	Initial clonidine dose	Dexmedetomidine wean	Clonidine taper
Terry *et al*[24], 2015	No	Primarily for sedation after cardiac surgery	No standard	No standard. 0.1 mg three times daily commonly used	No standard	No standard
Gagnon *et al*[23], 2015	Yes	Agitation: 12 (60%); Alcohol withdrawal: 3 (15%); Delirium: 2 (10%); Intolerance to other sedatives: 3 (15%)	Hemodynamically stable patients; Favorable response to DEX for 12-24 h	0.2-0.5 mg every 6 h; Start at 0.2 mg with DEX doses of < 0.7 μg/kg/h, weight < 100 kg or age > 65 yr; Start with 0.5 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline within 6 h of clonidine administration (as long as no rescue meds were needed for agitation)	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation
Bhatt *et al*[22], 2020	Yes	No clear selection criteria; patients with substance withdrawal were excluded	Variable; Clonidine taper and DEX wean started together	0.3 or 0.2 mg every 6 h; Start at 0.2 mg with DEX < 0.7 μg/kg/h, weight < 100 kg, age > 65 yr old; Start with 0.3 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline from 0 h to 6 h, and continue dose reduction by 25% every 6 h while on clonidine	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation

DEX: Dexmedetomidine.

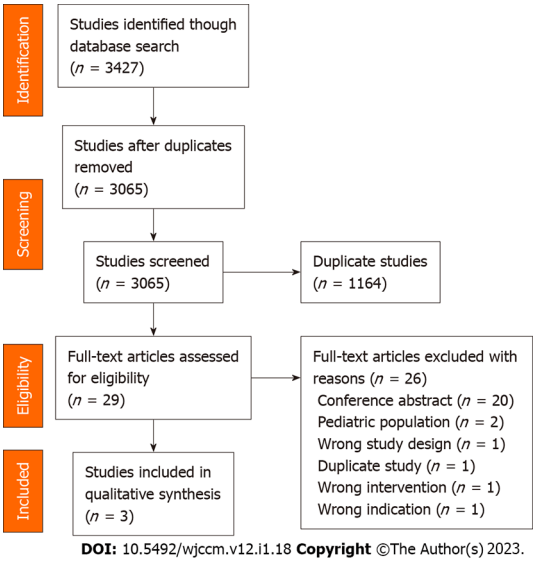

Figure 1 Study flow diagram.

dexmedetomidine taper (40% *vs* 11%; $P = 0.05$). During the weaning period, there was no difference in the use of propofol, antipsychotics, benzodiazepines, or ketamine between groups. Patients on enteral clonidine taper had a higher average daily dexmedetomidine rate (mcg/kg/h) than patients on a dexmedetomidine alone taper, although the total infusion dose in g/h was not significantly different between groups[22].

Socioeconomic factors: Gagnon *et al*[23] reported an estimated $15360-$52140 cost reduction with enteral clonidine usage based on drug acquisition cost alone assuming a minimum of 24 h of enteral clonidine in place of dexmedetomidine per patient and a maximum of substituting the entire enteral clonidine course with continuous dexmedetomidine[23]. Bhatt *et al*[22] reported an average cost savings of $1553 per patient, also based solely on drug acquisition costs. Gagnon *et al*[23] reported 25% (5/20) of the patients were discharged on enteral clonidine with 20% (4/20) receiving instructions to taper off the medication. Terry *et al*[24] discovered 54% (14/26) of patients were continued on enteral clonidine at ICU transfer with 23% (6/26) of patients being discharged home on clonidine unintentionally.

Risk of bias: In the risk of bias assessment, two studies[22,23] were deemed to be moderate risk and one study[24] was deemed to be serious risk (Figure 2). The primary reasons for a serious risk of bias were

Table 3 Outcomes data

Outcomes data	Terry *et al*[24], 2015	Gagnon *et al*[23], 2015	Bhatt *et al*[22], 2020
Breakthrough withdrawal	NR	1[1]	Taper 11 (73%); No taper 16 (59%)[2]
Discharged on clonidine	Out of ICU: 14 (54%); Out of hospital: 6 (23%)	5 (25%)	NR
Use of other agents			
Propofol	NR	No individual data	Taper: 5 (33%); No taper: 8 (30%)
Ketamine	NR	NR	Taper: 1 (6.7%); No taper: 6 (22.2%)
Benzodiazepines	Clonidine: 2 (22%); No clonidine: 5 (29%)	No individual data	Taper: 3 (20%); No taper: 3 (11%)
Antipsychotics	Clonidine: 4 (44%); No clonidine: 3 (18%)	DEX maintenance dose	Taper: 9 (60%); No taper: 10 (37%) (P = 0.2)
Opioids	Clonidine: 7 (78%); No clonidine: 13 (76%)	No individual data	No individual data
Hemodynamic changes			
Tachycardia	NR	NR	Taper: 12 (80%); No taper: 20 (74%)
Hypertension	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 0; Clonidine taper final day: 0; Post clonidine: 1 (6%)	Taper: 6 (40%); No taper: 8 (30%)
Bradycardia	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 1 (5%); Clonidine taper final day: 1 (6%); Post clonidine: 0	0
Hypotension	Clonidine: 4 (44%); No clonidine: 6 (35%)	DEX maintenance dose: 8 (40%); Transition: 7 (35%); Clonidine maintenance: 4 (20%); Clonidine taper final day: 2 (12%); Post clonidine: 2 (25%)	0
Sedation assessment score	RASS; Clonidine: 0 (-2 to 2); No clonidine: 0 (0-2)	SAS Score outside the goal of 3-4; DEX maintenance: 10 (50%); Transition: 10 (50%); Clonidine maintenance: 9 (45%); Clonidine taper final day 13 (76%); Post clonidine: 2 (25%)	NR
CAM ICU	Clonidine: 4 (44%); No clonidine: 3 (18%), P = 0.036	DEX maintenance: 10 (50%); Transition: 11 (55%); Clonidine maintenance: 9 (45%); Clonidine taper final day: 13 (76%); Post clonidine: 3 (38%)	Taper: 11 (73%); No taper: 17 (63%)
Duration of mechanical ventilation (d), median (IQR)	NR	3.5 (0, 10.5)	NR
Hospital length of stay (d), median (IQR)	8 (4, 10.5)	16.5 (10.5, 29.5)	NR
ICU length of stay (d), median (IQR)	12.5 (7, 28)	9.5 (5, 16.5)	Taper: 22.7; No taper: 17
Mortality	0	2 (10%)	NR

[1]Systolic blood pressure (SPB) > 180/120 after stopping despite 6-d taper, but was also tapering off methadone and clonazepam so causality if not clear.
[2]Significant withdrawal as defined by paper (≥ 2 heart rate > 90, Confusion Assessment Method positive, Richmond Agitation-Sedation Scale > 1, SBP > 140, Withdrawal Assessment Tool Version 1 > 2).
DEX: Dexmedetomidine; NR: Not reported; SAS: Sedation-Agitation scale.

confounding, participant selection, and deviations from the intended interventions given the observational nature of the design[24]. Additionally, confounding, participant selection, and outcomes measurements were common reasons for a moderate risk of bias in the other studies[22,23].

DISCUSSION

This systematic review of the literature summarized the use of enteral clonidine for weaning of parental dexmedetomidine in the critically ill, dosing and titration schema of enteral clonidine and

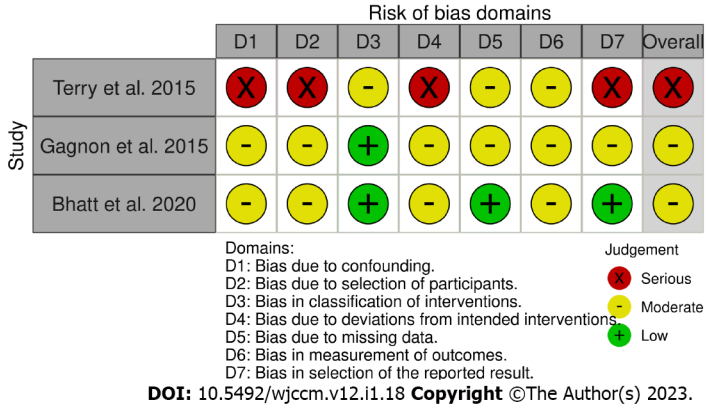

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Figure 2 Risk of bias assessment.

dexmedetomidine, prevalence of adverse events associated with clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation and ICU LOS. Meta-analysis was not feasible due to differences in methodology, patients, and procedures that led to variation in the reported results between studies.

Weaning off dexmedetomidine with enteral clonidine has gained much attention for the potential benefits of reduced ICU LOS and costs. Clonidine has shown promise in minimizing the withdrawal symptoms associated with cessation of prolonged dexmedetomidine[25]. Clonidine, like dexmedetomidine, is a centrally acting alpha 2 agonist and has a longer half-life (8-12 h *vs* 2 h); however, dexmedetomidine has an eight-fold higher affinity for central alpha receptors than clonidine[8]. Clonidine is thought to reduce central nervous system hyperactivity after dexmedetomidine withdrawal due to its alpha 2 agonist actions and decreased affinity for the alpha 2 receptors. Our review focusing on enteral clonidine for dexmedetomidine weaning in adults resulted in three studies, two prospective and one retrospective. Importantly, no randomized controlled trials were identified.

The results of this systematic review leave many unanswered questions regarding the optimal utility of enteral clonidine in the setting of dexmedetomidine weaning. It is difficult to draw comparisons among the available data from the three studies due to the heterogeneity of the groups studied. There seems to be a common dosing scheme for enteral clonidine in the setting of weaning from dexmedetomidine based on Gagnon *et al*[23] and their institutional experience with the medication. However, the process of determining who received enteral clonidine in the reviewed studies was largely left to clinician discretion, limiting the ability to draw conclusions about the impact of clonidine. For example, although Bhatt *et al*[22] demonstrated a higher incidence of agitation and rescue antipsychotic dosing in the patient group receiving enteral clonidine, potential confounders include unknown patient factors that led to higher dexmedetomidine dosing and the clinician's need to provide clonidine as a treatment rather than to evaluate its comparative effect vs. dexmedetomidine taper alone.

Dexmedetomidine is typically restricted to use in areas with critical care personnel and monitoring available such as the ICU and the perioperative care area. While it is valuable to have a study design with an inclusive patient population, the inclusion of both medical and postoperative patients in the studies reviewed pose challenges to the generalizability of the findings. For example, the sedation needs for a cardiac surgery patient in a rapid recovery protocol and the rapidity of sedation and mechanical ventilation liberation is often quite different than the medical patient requiring both treatment and stability after an acute cardiorespiratory insult requiring escalation to critical care needs. Terry *et al*[24] was highly skewed toward a post cardiac surgery population, whereas Gagnon *et al*[23] and Bhatt *et al*[22] included more mixed medical-surgical patients. The numerically lower total duration of dexmedetomidine in Terry *et al*[24] may have allowed for a lower general dose of enteral clonidine (*i.e.* 0.1 mg per dose) compared to the standard 0.2-0.3 mg clonidine doses used in the other two studies. However, given the lack of detail regarding exact dosing plan and the liberty clinicians were allotted regarding dosing selection, it is difficult to draw specific conclusions beyond the generalities offered in the study methods.

Adverse events from dexmedetomidine withdrawal included anxiety, agitation, decreased sleep, loose stools, emesis, tremors, and increased secretions[26]. Similarly, well-described phenomenon attributed to cessation of adrenal catecholamine secretion blockade and a subsequent surge in their circulating levels is associated with clonidine withdrawal resulting in rise in blood pressure, agitation, insomnia, and palpitations[27]. Risk factors for withdrawal are not known and were not identified in the studies reviewed. Further understanding of the risk factors for withdrawal and targeting appropriate patients for weaning could help minimize harm and improve quality of care. Patients on the enteral clonidine taper appeared to have more withdrawal symptoms than patients on dexmedetomidine taper. Re-initiation of dexmedetomidine was not explicitly addressed in any of the studies for withdrawal and should be an area of further investigation.

Although cost-effectiveness data is limited, the anticipated cost savings from drug acquisition ranged from $819 to $2338 per patient in two of the studies that reported data[22,23]. This price solely includes the drug acquisition cost and excludes the additional costs associated with dexmedetomidine, such as a dedicated ICU service line, monitoring, and titration. As a result, the shorter time on dexmedetomidine infusion following clonidine commencement may be greatly understated by these values.

Notably, in the two studies that reported information on enteral clonidine continuation at discharge from the hospital, approximately 25% of patients were still taking the medication[23,24]. Terry *et al*[24] also reported over half of patients were still taking enteral clonidine upon transfer from the intensive care unit. Several medications started in the ICU to expedite discharge, including antipsychotics and midodrine, are frequently prolonged without proper indication during transfer and upon discharge[28,29]. An order set and medication reconciliation during transitions of care may be helpful techniques for preventing the unintentional continuation of clonidine.

Strengths of this systematic review include the identification of a feasible enteral clonidine dosing strategy protocolized by Gagnon *et al*[23] that has been applied to other institutions as evidenced by Bhatt *et al*[22] and the elucidation of areas that could be optimized when utilizing enteral clonidine for dexmedetomidine weaning such as appropriate discontinuation prior to hospital discharge and the potential association of increased hypersympathetic withdrawal symptoms with its use. This systematic review has several limitations. All three studies have insufficient sample sizes, preventing the detection of withdrawal symptoms. Only one study had a matched control group, despite selection bias based on withdrawal risk assessment, which was not reported in any of the studies. Indications for weaning protocol varied according to the patient group and ICU site. There was heterogeneity of the research and data regarding the start date of clonidine weaning. The broad use of clinician discretion in the determination of enteral clonidine use and dosing limits the ability to systematically evaluate the available literature. Lastly, due to the heterogeneity in the reporting of the outcomes, quantitative meta-analysis was not possible.

CONCLUSION

Enteral clonidine has been utilized as a strategy to wean patients from parenteral dexmedetomidine due to similar mechanisms of action and potential for reduced costs and shorter ICU requirements. However, guidance on an appropriate taper strategy and resultant outcomes is limited. This systematic review investigated the literature related to weaning dexmedetomidine with and without an enteral clonidine taper. While there are some patterns in dosing schedules among the studies included, there is no consensus regarding an ideal taper strategy and the decision to utilize an enteral clonidine taper is left to clinical judgment. There may be an association of increased withdrawal symptoms and agitation with the use of an enteral clonidine taper, however we did not observe any appreciable difference in ICU LOS with or without a clonidine taper. Further research into risk factors for withdrawal, dose, and duration of dexmedetomidine use followed with appropriate clonidine dose and taper is needed.

ARTICLE HIGHLIGHTS

Research background

Clonidine, an enterally available alpha-2A adrenergic agonist, may be a suitable agent to taper off parenteral dexmedetomidine (centrally acting alpha-2A adrenergic agonist) and reduce withdrawal syndromes. This could lead to reduced intensive care unit (ICU) length of stay (LOS), among other outcomes. However, limited data exist on this topic.

Research motivation

To determine if oral clonidine is useful to wean off parenteral dexmedetomine and reduce ICU LOS.

Research objectives

To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

Research methods

This was a systematic review of randomized controlled trials, prospective and retrospective cohorts, on the use of enteral clonidine during dexmedetomidine weaning in critically ill adults (≥ 18 years). The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal.

Research results

Three observational studies were included (two prospective and one retrospective). Weaning time ranged from 13 to 167 h on average. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

Research conclusions

Enteral clonidine is a strategy to wean critically ill patients from parenteral dexmedetomidine. However, there is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Research perspectives

It is unclear if oral clonidine is useful in weaning from dexmedetomidine. More data are needed in terms of both dosing schedule and outcomes.

FOOTNOTES

Author contributions: Rajendraprasad S, Wieruszewski P, and Smischney N designed the research; Rajendraprasad S, Wheeler M, and Wieruszewski E performed the research; Gottwald J and Wallace L analyzed the data; Rajendraprasad S, Wheeler M, Gottwald J, Wallace L, Wieruszewski P, and Smischney N drafted the paper; All authors reviewed and edited the manuscript and approved the final version.

Conflict-of-interest statement: All authors declare no conflicts of interest.

PRISMA 2009 Checklist statement: The study followed the PRISMA guidelines. The protocol was *a priori* registered in the PROSPERO database (No. CRD42022330666).

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ORCID number: Patrick M Wieruszewski 0000-0002-5871-5186; Nathan J Smischney 0000-0003-1051-098X.

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CASE REPORT

Severe hypernatremia in hyperglycemic conditions; managing it effectively: A case report

Maulik K Lathiya, Praveen Errabelli, Susan M Cullinan, Emeka J Amadi

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Maulik K Lathiya, Susan M Cullinan, Department of Emergency, Mayo Clinic Health System, Eau Claire, WI 54703, United States

Praveen Errabelli, Department of Nephrology, Mayo Clinic Health System, Eau Claire, WI 54703, United States

Emeka J Amadi, Hospital Internal Medicine, Mayo Clinic Health System, Eau Claire, WI 54703, United States

Corresponding author: Maulik K Lathiya, MBBS, Research Fellow, Department of Emergency, Mayo Clinic Health System, 1221 Whipple Street, Eau Claire, WI 54703, United States. lathiya.maulik@mayo.edu

Abstract

BACKGROUND

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are common acute complications of diabetes mellitus with a high risk of mortality. When combined with hypernatremia, the complications can be even worse. Hypernatremia is a rarely associated with DKA and HHS as both are usually accompanied by normal sodium or hyponatremia. As a result, a structured and systematic treatment approach is critical. We discuss the therapeutic approach and implications of this uncommon presentation.

CASE SUMMARY

A 62-year-old man with no known past medical history presented to emergency department with altered mental status. Initial work up in emergency room showed severe hyperglycemia with a glucose level of 1093 mg/dL and severe hypernatremia with a serum sodium level of 169 mEq/L. He was admitted to the intensive care unit (ICU) and was started on insulin drip as *per* DKA protocol. Within 12 h of ICU admission, blood sugar was 300 mg/dL. But his mental status didn't show much improvement. He was dehydrated and had a corrected serum sodium level of > 190 mEq/L. As a result, dextrose 5% in water and ringer's lactate were started. He was also given free water *via* an nasogastric (NG) tube and IV Desmopressin to improve his free water deficit, which improved his serum sodium to 140 mEq/L.

CONCLUSION

The combination of DKA, HHS and hypernatremia is rare and extremely challenging to manage, but the most challenging part of this condition is selecting the

correct type of fluids to treat these conditions. Our case illustrates that desmopressin and free water administration *via* the NG route can be helpful in this situation.

Key Words: Diabetic ketoacidosis; Hyperglycemic hyperosmolar state; Hypernatremia; Hyperglycemia; Desmopressin; Case repot

Core Tip: Hyperglycemia is usually associated with hyperkalemia, but it is rare to see hypernatremia with hyperglycemia as hyperglycemia is usually seen with pseudohyponatremia. Correcting hypernatremia with hyperglycemia is challenging because of the complex fluid requirements in this situation. We are describing a case here with severe hyperglycemia and severe hypernatremia. In our case, we have used free water flushes *via* nasogastric access and desmopressin to correct the free water deficit, which hasn't been described previously in the literature. This makes our case unique.

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INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are common acute complications of diabetes mellitus (DM) with a high risk of mortality. DKA is more common in patients with type 1 diabetes (T1DM), whereas HHS is more common in patients with type 2 diabetes. However, symptoms of DKA and HHS can sometimes overlap and result in a combined laboratory presentation of both conditions[1]. When it comes to managing this overlap presentation, glucose levels, electrolyte levels, and the patient's hemodynamics are all closely monitored because DKA and HHS can cause serious complications like brain edema, rhabdomyolysis, thrombosis[1]. When combined with hypernatremia, the complications can be even worse[2]. Hypernatremia is a rare condition associated with DKA and HHS as both can be accompanied by normal sodium or hyponatremia. As a result, a structured and systematic treatment approach is critical.

CASE PRESENTATION

Chief complaints

We present a case of successfully treated severe hypernatremia in an adult with DKA-HHS.

History of present illness

A 62-year-old male, who has not seen a physician for more than a decade presented to a local Emergency Department (ED) as a tele-stroke activation following a fall at home. A few days prior to the event he started having excessive thirst, dry mouth, and urinary frequency. He consumed large volumes of water, and when that did not quench his thirst, he started drinking V8 vegetable juice and Kool-Aid powdered drink mix. He was consuming approximately 16 to 18 cans of V8 (11.5 ounces each) and several Kool-Aid packets daily. Each 11.5-ounce V8 can contains 960 mg of sodium and each Kool-Aid packet contains 25 mg of sodium. His symptoms worsened, becoming increasingly fatigued, with multiple falls. Though, He did not suffer significant injury from the fall, however due to slurring of speech and altered mental status he was brought to the ED for evaluation.

History of past illness

He has no known prior medical history.

Personal and family history

Not a known alcoholic or a smoker. No history of illicit substance use. No family history of any chronic medical conditions.

Physical examination

He was evaluated in the ED and workup was negative for neurologic findings.

Laboratory examinations

His initial workup revealed sodium 169 mEq/L (Corrected sodium for hyperglycemia is 193 mEq/L), chloride 124 mEq/L, blood glucose 1093 mg/dL, bicarbonate 16 mEq/L, anion gap of 29, serum creatinine 2.27 mg/dL (baseline creatinine was 0.7), and potassium 4.6 mEq/L. Urine osmolality was 751 mOsm/kg, while serum osmolarity was 438 mOsm/kg (Figure 1). In the emergency department, HbA1c was > 18%, Serum lactate was 4.6 and the pH of venous blood gas was 7.33. During hospitalization, his serum bicarbonate, serum lactate, and anion gap were also elevated (Table 1). His arterial blood gas levels were determined during his hospitalization (Table 2). In addition, we have added his fluid balance and diuresis in the period of the first 5 d (Table 3).

FINAL DIAGNOSIS

DKA and Hyperosmolar hyperglycemic syndrome with hyperglycemia-induced hypernatremia were the definitive diagnoses in the case described.

TREATMENT

He was started on an insulin drip *per* DKA protocol and was admitted to the intensive care unit (ICU). On initial evaluation, his calculated serum sodium at this point was > 170 mEq/L and his free water deficit was close to 29 L. After 12 h of admission, the blood sugar was corrected to 300 mg/dL, but serum sodium remained elevated at > 170 mEq/L. Urine output remained suboptimal at 1.09 mL/kg/hr. He was hyperventilating and blood gas showed a PH 7.51, and a PCO_2 of 26. Creatine phosphokinase was 6300 U/L. He became increasingly confused and obtunded. He had multiple temperature spikes. Blood cultures were drawn, and empirical antibiotics were initiated. Given worsening mental status in the setting of acute kidney injury and severe hypernatremia, aggressive fluid resuscitation by increasing 5% dextrose solution (D5W) to 200 mL *per* hour and Ringer's lactate to 250 cc/h was undertaken. With nephrology consultation, dialysis was considered but withheld as it would correct his sodium too rapidly and might have adverse consequences. In addition to aggressive IV fluid resuscitation, a nasogastric tube (NG tube) was placed, and he was started on free water administration at 250 cc every 4 h. He was also started on desmopressin 0.2 g twice daily. Serum sodium was monitored every 4 h (Figure 1B).

Twenty-four hours after above interventions, serum sodium slowly dropped to 167 mEq/L (Figure 1B), creatinine improved to 1.9 mg/dL (from 2.27 mg/dL) and urine output improved. Desmopressin was continued until serum sodium corrected to 140 mEq/L. At this point his mental status had returned to baseline and NG tube free water replacement was discontinued. Patient eventually recovered with normalization of electrolytes and renal function at the time of discharge. He was discharged on insulin for newly diagnosed DM and atorvastatin for newly diagnosed hyperlipidemia with dietary recommendations.

OUTCOME AND FOLLOW-UP

After 24 h, we were able to achieve the desired decline in sodium level, improvement in both serum creatinine and urine output, improvement in urine and serum osmolarity (Figure 1A) and improvement in the mental status of the patient, suggesting that the altered mental status was driven by his severe hypernatremia.

DISCUSSION

Complications associated with undiagnosed and untreated DM can be disastrous, especially over an extended duration. The onset and development of this complex disease in our patient is particularly difficult to track due to a prolonged period of health care avoidance. However, the critical state of the patient upon presenting to the ED highlights the severity of several consequences, namely hypernatremia.

Hypernatremia, an elevated level of serum sodium, can be attributed to multiple processes, including hypertonic fluid gain, hypotonic fluid loss, or general water depletion. No matter the origin, the increased extracellular osmolality drives water outward from cells, resulting in cell shrinking. Although

Table 1 Initial work up at presentation (day 1) in the Emergency Department and subsequent hospitalization

Indicator	Normal value	In the Emergency Department day 1	Hospital day 2	Hospital day 3	Hospital day 4	Hospital day 5
Serum sodium (Na)	135-145 mmol/L	169				
Serum chloride (Cl)	98-107 mmol/L	124				
HCO3-	22-29 mmol/L	16	24	26	24	21
Glucose	70-140 mg/dL	1093				
Serum creatinine (Cr)	0.74-1.35 mg/dL	2.27				
Serum potassium (K)	3.6-5.2 mmol/L	4.6				
Serum lactate	5.2-2.2 mmol/L	4.1	4.6	3.9	1.6	
Serum osmolarity	276-306 mOsm/kg	438				
Urine osmolarity	150-1150 mOsm/kg	751				
HbA1c	5.7%-6.4%	> 18%				
pH venous blood Gas	7.32-7.43	7.33				
Anion gap	7-15	29	24	16	10	12
Fio2/Spo2	96%-99%/95%-100%	None/92%	2 Liter (nasal cannula)/92%-98%	Room Air/94%-100%		

Table 2 Blood gas studies during intensive care unit stay after initial resuscitation

Arterial blood gas	Normal range	Hospital day 1	Hospital day 2
PH	7.35-7.45 pH	7.43; 7.45; 7.48	7.51
PCO_2	35-48 mmHg	30; 28; 25	26
PO_2	28-108 mmHg	78; 73; 72	78

Table 3 His fluid intake and output during hospital period (fluid balance and diuresis during hospital period)

Day (Hospital period)	Fluid intake (mL)	Fluid output (mL)
1	5381	950
2	6200	2935
3	2650	1900
4	1900	1205
5	3987	1925

an ionic osmolytic response serves to counter these dangerous effects, long-term damage is nearly inevitable. Such impairments manifest in various organ systems leading to short-term mortality rates between 50% and 60%[3]. Our patient's initial measured sodium level of > 170 mEq/L that later progressed to > 200 mEq/L indicated a precarious and time-sensitive situation requiring urgent intervention.

The development of hypernatremia in this patient should be considered in both DKA and HHS, in addition to the combination of these conditions. The appearance of hypernatremia in DKA can be attributed to a fluid imbalance. As significant volumes of free fluid are lost (most commonly by polyuria), electrolyte loss (through vomiting and diarrhea) may lag behind, leading to a very unusual occurrence of hypernatremia with osmolytic imbalance[4]. Although such cases of DKA-induced hypernatremia are infrequent, a 2019 paper reviews the cases of two female patients found to be

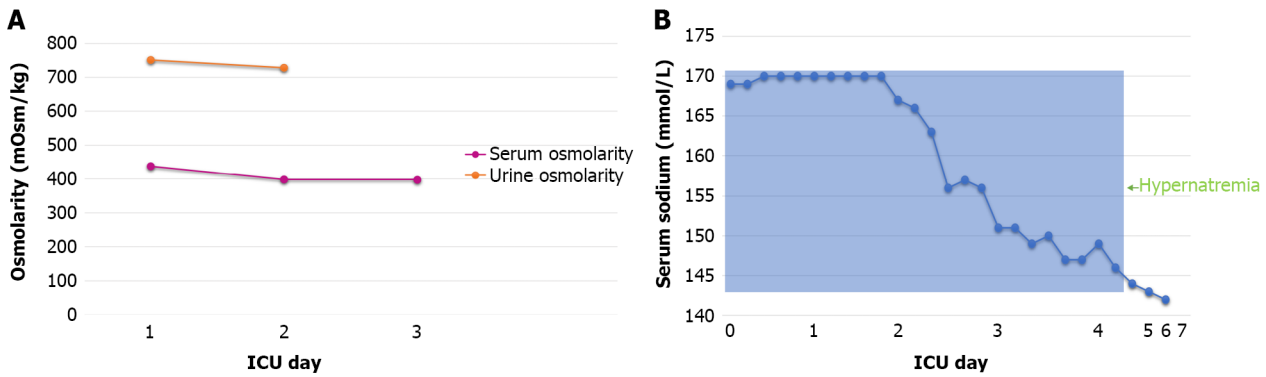

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Figure 1 Critical care admission. A: Urine and serum osmolarity throughout critical care admission; B: Serum sodium throughout critical care admission. ICU: Intensive care unit.

suffering from hypernatremia secondary to DKA after complaints of altered mental status and other symptoms[5]. Additionally, a 2020 study describes an altered male T1DM patient with a largely unknown medical history suffering from DKA and severe hypernatremia; aggressive treatment of DKA and fluid management yielded a positive outcome. While DKA and HHS diverge in incidence, mechanism, and prognosis, the rare occurrence of hypernatremia in HHS arises for similar reasons: A free water deficit develops through osmotic diuresis. A 2020 case report discusses a female patient with no known history of DM that presented to the ED for confusion amongst many other progressive symptoms. Investigations revealed extremely elevated blood glucose and sodium levels, which led to a diagnosis of HHS[6]. Our case differs from previous literature in that the patient was diagnosed with DKA, HHS, and acute hypernatremia. While a combination of these three constituents is detailed in a 2020 paper referencing two pediatric patients, this combination, to our knowledge, has not been identified in an adult patient[1].

The precise origin of hypernatremia in this patient is complicated by the patient's past medical history. For one, the incompleteness of his record, due to a ten-plus year hiatus from receiving even primary care, abridges available information to a matter of days before admission. Also, the polydipsia described by the patient himself led to the unintentional ingestion of excessive amounts of sodium, primarily through his beverages of choice. Nevertheless, the patient's hyperglycemia, hypernatremia, and free water deficit necessitated careful manipulation as a 2022 case series study describes the cases of DKA-HHS induced severe hypernatremia in three adolescents due to high soft drink consumption where one patient died due to development of severe hypovolemia[7]. As increased consumption of carbohydrate-rich beverages exacerbated glucose induced osmotic diuresis and resulted in worsening severe intravascular dehydration. To restore the water deficit, a large amount of fluid is needed. It is also important to choose right fluid to correct plasma sodium level with the aim of avoiding treatment-related dysnatremia. As an improper management of plasma sodium concentration and plasma osmolality during treatment has been associated with two rare potentially life-threatening complications such as hypovolemic shock, cerebral edema and osmotic demyelination syndrome. Previous literature suggests that the correction of hypernatremia is best achieved through the intravenous administration of a hypotonic solution such as D5W and safest as long as the etiology of hypernatremia is hypertonic sodium gain and treatment can be initiated at ≤ 12 h from the onset of the cause[8]. Since this patient's free water deficit was 29 L, effective fluid resuscitation required D5W, Ringer's lactate, and enteral free water for prompt change. The rate of sodium correction should be based on the type of fluid used. Although the blood glucose level was unusually high (300 mg/dL) to initiate D5W, we planned to perform fluid resuscitation with Ringer's lactate and D5W, which resulted in a slower decrease in serum sodium when compared to other isotonic or hypotonic fluids alone. In addition, we started giving free fluid *via* NG tube. According to de Vos and van der Voort[9], treating patients with ICU-induced hypernatremia with enteral free water did not result in a clinically significant decrease in serum sodium levels[9]. However, we noticed improving sodium as we combined desmopressin to conserve free water by its antidiuretic effects. After 24 h, we were able to achieve the desired decline in sodium level, improvement in both serum creatinine and urine output, improvement in urine and serum osmolarity (Figure 1A), and improvement in the mental status of the patient, suggesting the altered mental status was driven primarily by the hypernatremia.

CONCLUSION

This case report highlights three vital considerations when treating patients with hypernatremia in the DKA-HHS overlap disease state. First, the decision to treat hyperglycemia more aggressively than hypernatremia due to the intrinsic life-threatening risks. Second, at the initial stage, choosing a combination of hypotonic and isotonic fluid that contains sodium close to the lower limit of normal serum sodium allows glucose to decrease first, at the same time maintaining serum sodium at steady-state and not increasing. Third, giving water *via* oral, NG, or orogastric tube in combination with desmopressin to improve free water deficit and to prevent excessive hypotonic and/or isotonic fluid induced complications such as peripheral edema and pulmonary edema. This case report highlights the importance of understanding the management approach required for hypernatremia in DKA-HHS to prevent complications associated with these two conditions.

FOOTNOTES

Author contributions: Lathiya MK and Errabelli P contributed to the conceptualization, writing, original draft preparation, graphics, reviewing; Cullinan SM contributed to original draft preparation, reviewing and editing; Amadi EJ contributed to reviewing and editing.

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ORCID number: Maulik K Lathiya 0000-0002-3593-3850.

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CASE REPORT

Vasopressin-induced hyponatremia in an adult normotensive trauma patient: A case report

Maulik K Lathiya, Emily Pepperl, Daniel Schaefer, Hussam Al-Sharif, Adel Zurob, Susan M Cullinan, Antonios Charokopos

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Maulik K Lathiya, Emily Pepperl, Susan M Cullinan, Department of Emergency Medicine, Mayo Clinic Health System, Eau Claire, WI 54703, United States

Daniel Schaefer, Hussam Al-Sharif, Adel Zurob, Antonios Charokopos, Department of Pulmonary and Critical Care Medicine, Mayo Clinic Health System, Eau Claire, WI 54703, United States

Corresponding author: Antonios Charokopos, MD, Department of Pulmonary and Critical Care Medicine, Mayo Clinic Health System, 1221 Whipple Street, Eau Claire, WI 54703, United States. charokopos.antonios@mayo.edu

Abstract

BACKGROUND

Arginine vasopressin is a neuropeptide produced in the hypothalamus and released by the posterior pituitary gland. In addition to maintaining plasma osmolarity, under hypovolemic or hypotensive conditions, it helps maintain plasma volume through renal water reabsorption and increases systemic vascular tone. Its synthetic analogues are widely used in the intensive care unit as a continuous infusion, in addition to hospital floors as an intravenous or intranasal dose. A limited number of cases of hyponatremia in patients with septic or hemorrhagic shock have been reported previously with vasopressin. We report for the first time a normotensive patient who developed vasopressin-induced hyponatremia.

CASE SUMMARY

A 39-year-old man fell off a forklift and sustained an axial load injury to his cranium. He had no history of previous trauma. Examination was normal except for motor and sensory deficits. The Imagine test showed endplate fracture at C7 and acute traumatic disc at C7 with cortical degeneration. He underwent cervical discectomy and fusion, laminectomy, and posterior instrumented fusion. After intensive care unit admission post-surgery, he developed hyponatremia of 121-124 mEq/L post phenylephrine and vasopressin infusion to maintain blood pressure maintenance. He was evaluated for syndrome of inappropriate secretion of antidiuretic hormone, hypothyroid, adrenal-induced, or diuretic-induced hyponatremia. At the end of extensive evaluation for the underlying cause of hyponatremia, vasopressin was discontinued. He was also put on fluid restriction, given exogenous desmopressin, and a dextrose 5% in water infusion to prevent osmotic demyelination syndrome caused by sodium overcorrection which im-

proved his sodium level to 135 mmol/L.

CONCLUSION
The presentation of vasopressin-induced hyponatremia is uncommon in normotensive patients, and the most difficult aspect of this condition is determining the underlying cause of hyponatremia. Our case illustrates that, considering the vast differential diagnosis of hyponatremia in hospitalized patients, both hospitalists and intensivists should be aware of this serious complication of vasopressin therapy.

Key Words: Hyponatremia; Vasopressin; Normotensive; Therapy; Case report

Core Tip: While hyponatremia can have many causes, vasopressin-induced hyponatremia in normotensive patients is unusual. Since the coronavirus disease 2019 pandemic, vasopressin use has increased in intensive care units across the country, and vasopressin-induced hyponatremia is likely underrated. We have intervened by discontinuing vasopressin, which led to rapid overcorrection of the sodium, and thus required temporary exogenous desmopressin and a dextrose 5% in water infusion. Through his care, the patient's serum sodium returned to normal and he made a full recovery. This makes our case unique.

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INTRODUCTION

Under normal conditions, the major physiological role of vasopressin (also known as antidiuretic hormone) is the maintenance of serum osmolarity *via* the regulation of water balance, through the activation of aquaporin channels in the renal collecting duct. Vasopressin is also an important endogenously released stress hormone, particularly during shock; it exerts vasoconstrictive properties *via* arginine vasopressin receptor 1A receptors. Consequently, this hormone has been used clinically as a vasoconstrictive, norepinephrine-sparing agent in the treatment of septic shock and other forms of hypotension[1]. Furthermore, it is utilized in the treatment central diabetes insipidus, von Willebrand disease, Hemophilia A, and nocturnal enuresis. However, vasopressin therapy carries a number of serious potential side effects, including cardiac and gastrointestinal complications, anaphylaxis, cutaneous gangrene, and venous thrombosis[2]. Vasopressin-induced hyponatremia is a rare adverse effect that has only recently been identified in patients suffering from vasodilatory shock[3]. Hyponatremia is mechanistically justified based on vasopressin's mechanism of action. In this article, we will discuss a case of clinically significant vasopressin-induced hyponatremia in a normotensive patient in the Mayo Clinic Health System Intensive Care Unit (ICU).

CASE PRESENTATION

Chief complaints

We present a case of successfully treated vasopressin induced hyponatremia in normotensive patient.

History of present illness

A 39-year-old previously healthy male presented as a high acuity trauma after falling off a forklift, sustaining an axial load injury on his cranium. He was evaluated in the emergency department and workup was negative for neurologic findings. His initial vital signs in the emergency department were normal and the patient had a Glasgow Coma Scale of 15. He was protecting his airway and had bilaterally clear lung sounds without chest wall trauma. He was noted to have a scalp laceration with no active bleeding.

History of past illness

He has no known prior history of trauma and illness.

Personal and family history

He has no known prior personal and family history.

Physical examination

The patient had a loss of sensation below the level of the nipples, loss of motor function of his lower extremities, and no rectal tone. In terms of upper extremity motor function, he had good power and grip strength in right hand but decreased on the left hand. No thoracic or lumbar spine step-off nor back trauma stigmata were noted.

Laboratory examinations

To rule out hyperglycemia-induced hyponatremia, we measured serum glucose and calculated corrected sodium. In order to rule out pseudohyponatremia, we measured serum protein and lipid profiles. We also performed a complete blood count and measured urinary osmolarity, plasma osmolarity, random urine sodium level, serum cortisol level, serum adrenocorticotropic hormone level, and serum thyroid-stimulating hormone level to rule out differential diagnosis of hypoosmotic hyponatremia.

Imaging examinations

On imaging in the emergency department, a focused assessment with sonography in trauma exam was done and was negative. A computerized tomography (CT) scan of the head was negative for acute intracranial processes, as well as negative CT scans of the thoracic and lumbar spines. CT scan of the cervical spine revealed a superior endplate fracture at C7, and an magnetic resonance imaging revealed what appeared to be an acute traumatic disc at the C7 Level with cortical degeneration. Subsequent CT angiogram of the neck revealed no acute vascular injuries.

FINAL DIAGNOSIS

The definitive diagnosis in the case described is vasopressin-induced hyponatremia in a normotensive state.

TREATMENT

The patient was taken to the odd ratio where he underwent C6-C7anterior cervical discectomy and fusion, C6-C7 Laminectomy, and C4-T2 posterior instrumented fusion, as well as closure of the patient's scalp laceration.

He admitted to the critical care unit on phenylephrine postoperatively for maintenance of a mean arterial pressure (MAP) greater than 85mmHg. On day 2 and day 3 of ICU care, infusion of vasopressin was initiated with the addition of phenylephrine intermittently to maintain MAP goals of 80-85 mmHg to augment cord perfusion for 7 d from the time of his injury. His sodium level on ICU day 3 was 131 mmol/L. On day 4, he had an episode of hypoxemia and cough with a chest x-ray that revealed perihilar infiltrates concerning for possible volume overload. Furosemide was given and arterial blood gas showed minimal hypoxemia with normal pCO_2 and was managed on a high-flow nasal cannula. However, we encountered new onset hyponatremia with sodium levels 121-124 mmol/L and noted high urine osmolarity and high urine sodium. He was evaluated for syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypothyroid, adrenal-induced, or diuretic-induced hyponatremia. He was placed on fluid restriction without much improvement, so subsequently the vasopressin infusion was discontinued. After discontinuation of vasopressin, over ICU days 4 and 5, subsequent sodium levels at 6 h, 12 h, and 18 h were 124, 134, and 141 mmol/L respectively (Figure 1). Additionally, on day 5, Nephrology was consulted to manage the over-correction of hyponatremia to reduce the risk of osmotic demyelination syndrome, and he was started on exogenous desmopressin (DDAVP) and dextrose 5% in water (D5W) instead of hypertonic solution, as hypertonic solution is only used in cases of seizure or acute neurological signs and symptoms. Phenylephrine was continued to maintain MAP. On ICU day 6, the patient's sodium stabilized at 135 mmol/L overnight with DDAVP and free water was discontinued. On day 7, overnight sodium level was noted to stabilize between 135-138 mmol/L. A tertiary survey was performed and no occult injuries were identified. The patient was started on aggressive physical therapy and occupational therapy, and attempts were made to wean off phenylephrine as per Neurosurgery for spinal cord perfusion purposes. He was able to wean off vasopressors but due to orthostatic hypotension symptoms, the patient was started on a low dose of midodrine with subsequent improvement. On day 8, the patient was transferred for inpatient spinal

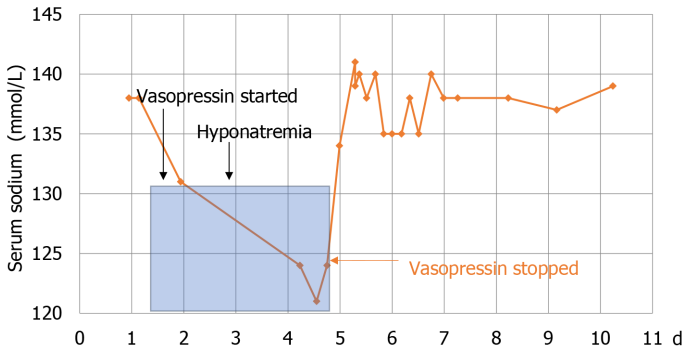

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Figure 1 Changes of serum sodium level before and after vasopressin withdrawal. After discontinuation of vasopressin, over intensive care unit days 4 and 5, subsequent sodium levels at 6 h, 12 h, and 18 h were 124, 134, and 141 mmol/L respectively.

cord rehabilitation, where he continued to demonstrate strength, functional improvement, and coordination of left upper extremity, as well as static and dynamic sitting balance and sensation to light touch and pressure in the lower extremity.

OUTCOME AND FOLLOW-UP

On 3 mo postop follow up, he showed improvement as he was upgraded from American Spinal injury Association Impairment Scale Score (ASIA) B to an ASIA C.

DISCUSSION

Vasopressin is critical for maintaining normal body osmolality and plasma volume in response to several pathways of stimuli, including osmotic and nonosmotic triggers[4-6]. Its mechanism of action begins with a cyclic adenosine monophosphate signaling cascade in the renal system and culminates with the insertion of aquaporin 2 channels into the apical membrane of the renal collecting duct. The resulting accumulation of these water channels leads to the reabsorption of water into the bloodstream [7-10]. This hormone also serves numerous related functions both when delivered endogenously and exogenously. For instance, in clinical settings, the vasoconstrictive effects of vasopressin correct depleted blood volume in patients facing vasodilatory shock[11]. In the case of this patient, the use of general anesthesia during and following a surgery to address an acute spinal cord injury required external maintenance of MAP for a stated period of seven days. Initially, phenylephrine, an α1-adrenergic receptor, was infused at a maximum dose for these purposes; vasopressin administration began concurrently with phenylephrine to continually reach goal MAPs of > 85 mmHg. Prior to the initiation of vasopressin, basic metabolic panels revealed that sodium levels were within normal limits, defined in this report as 135-145 mmol/L. After vasopressin support, the significant drop in the patient's sodium level down to 121 mmol/L indicated a state of hyponatremia, and lead to a significant risk for neurologic complications (Figure 1).

While hyponatremia is a relatively common affliction of hospitalized patients, the ramifications of unrecognized or untreated cases can be devastating for patient outcomes. With a decrease in serum sodium, the corresponding increase in intracellular osmolality can result in excess entrance of water into the cells[12,13]. This swelling of cells may engender several effects specifically secondary to brain edema, ranging from those as mild as headaches, lethargy, and nausea to ones as extreme as comas, seizures, and even eventual death[14]. Fortunately, hyponatremia can be carefully corrected *via* multiple treatments that encourage slow re-establishment of the standard osmotic gradient. Rapid overcorrection can become quickly dangerous to the patient, as brain cell dehydration leads to osmotic demyelination and numerous neurological defects[13,15]. The preferred intervention in correcting hyponatremia depends largely on the cause of this electrolyte imbalance, namely whether it can be described as isotonic, hypertonic, or hypotonic[13].

The investigation of the etiology of hyponatremia in this patient required a systematic approach to eliminating all possible causes of hyponatremia in a stable, normotensive, post-surgical trauma patient. First, it should be noted that blood glucose was within the normal range, noted as 110 mg/dL during the onset of hyponatremia, which concluded that hyperglycemia was not present. Neither hyperlipidemia nor hyperproteinemia were suspected as the serum was not lipemic, the patient did not exhibit jaundice, or have a history of plasma cell dyscrasia. These inquiries, along with a measured serum osmolality of 268 mOsm/kg, outside of defined normal limits of 276-306 mOsm/kg, suggested

hypotonic hyponatremia. His euvolemic status and elevated urine sodium level, on the other hand, made hypovolemic hyponatremia less likely, and there was no other obvious cause of SIADH. However, while encephalic trauma can cause transient changes in water-electrolyte balance, this patient's initial serum electrolytes levels, including sodium, potassium, bicarbonate, and chloride, were normal, and his urine output was also normal[16]. His urine output and lack of primary central nervous injury made cerebral salt wasting less likely. We became concerned for hyponatremia secondary to the recent vasopressin infusion[13]. In a combined diagnostic and therapeutic approach, cessation of vasopressin led to prompt improvements in serum sodium. The hyponatremia corrected too rapidly, reaching a high sodium level of 141 mmol/L. After DDAVP and D5W, this overcorrection was reversed and stabilization of sodium levels within the normal range ensued. These observed changes in sodium levels, both upon beginning and stopping vasopressin, heightened suspicions of vasopressin-induced hyponatremia.

Both in the intensive care setting and otherwise, the finding of vasopressin-induced hyponatremia, is still emerging and rare. A few previous studies have detailed cases of hyponatremia secondary to vasopressin administration in the treatment of specific conditions. For example, a 2015 study reviews the cases of two young adult ICU patients treated with vasopressin for septic shock; both patients developed hyponatremia following initiation of the medication, but quickly rebounded from hyponatremia following discontinuation of vasopressin. The aforementioned study also mentions the role of catecholamines, corticosteroids, and endotoxins in counteracting the potentially detrimental effects of vasopressin in shock patients[3]. Another study in 1984 compared the utility of intravenous somatostatin and vasopressin in cirrhotic patients with variceal bleeding; researchers discovered that a complication common only to the vasopressin group was hyponatremia[17]. Similarly, a 1995 case report follows a post-caesarean section patient that received intravenous vasopressin to control esophageal and gastric varices. This serum sodium of this patient dropped significantly following vasopressin infusion but rebounded quickly following discontinuation of the medication[18].

Following his axial loading injury, this trauma patient exhibited periods of hyponatremia while recovering in critical care. While the etiology of this deficiency was initially unknown, the vasopressin infusion’s mechanism of action was thought-provoking. Similar inductions of hyponatremia by vasopressors have been documented in patients suffering from septic shock, as well as in patients undergoing treatment for variceal hemorrhage; however, these consequences have not been examined in a stable, normotensive, adult patient[3,17,18]. Our study diverges from past literature through the patient presentation and the indication for vasopressin treatment and the lack of shock. A stable, normotensive, adult trauma patient received vasopressin post-operation to maintain MAP. The result in this case report illustrates the shared result of hyponatremia remedied through the cessation of vasopressin. As far as we are aware, potential hyponatremia complications include cerebral edema, non-cardiogenic pulmonary edema, permanent neurological damage, and death. Finding the underlying cause of hyponatremia is always necessary in order to prevent life-threatening complications. Although the majority of hyponatremia's underlying causes are treatable and reversible, rare causes such as vasopressin-induced hyponatremia should be considered. Due to the widespread use of this medication in hospitals, both critical care physicians and hospitalists should be aware of this vasopressin side effect. Ultimately, the potential for hyponatremia per vasopressin commands further study across all demographics, indications, and settings. An improved understanding of the risks and mechanisms of vasopressin-induced hyponatremia would better inform clinical decision-making and possible prophylactic salt restriction for these patients.

CONCLUSION

Vasopressin-induced hyponatremia is an overall rare occurrence, but this potential consequence should still be suspected under certain conditions to both prevent and mitigate harmful effects. While several previous studies have detailed the development of vasopressin-induced hyponatremia in pediatric, hemorrhage, and shock patients, our case study demonstrates this form of hyponatremia in an adult, normotensive trauma patient recovering in the critical care setting. In brief, our patient’s serum sodium dropped to hyponatremic levels concurrently with the administration of vasopressin and recovered promptly with the cessation of this medication. However, more research is needed to various factors that may be responsible for additive effects, such as additional comorbidities, duration of vasopressin use, dosage, and interaction with other medications.

FOOTNOTES

Author contributions: Lathiya MK, Schaefer D, Cullinan SM and Charokopos A designed and conceptualized the research; Lathiya MK and Pepperl E performed the research; Lathiya MK, Al-Sharif H, Zurob A, Cullinan SM and Charokopos A wrote the paper and assisted with graphics; Lathiya MK and Charokopos A revised the paper.

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Country/Territory of origin: United States

ORCID number: Maulik K Lathiya 0000-0002-3593-3850; Antonios Charokopos 0000-0002-8895-687X.

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