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Hyponatremia in sepsis and its association with SOFA score: An observational cross sectional study

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Abstract

Background: Sepsis is the one of the leading causes of hospital admissions and death in India and hyponatremia in sepsis is known to be an independent risk factor for mortality. Aim of the study was to determine the prevalence of hyponatremia in sepsis and its association with SOFA (sequential organ failure assessment) score.

Methodology: This is an observational cross-sectional study in a tertiary hospital of New Delhi India. A total of 95 patients with sepsis and more than 18 years of age were enrolled in the study over 18 months period. Blood samples were drawn for estimation of serum sodium and other investigations within 24 hours of admission of patients presenting with sepsis or diagnosis of sepsis if it develops during the hospital stay.

Results: Prevalence of hyponatremia in sepsis patients were 69.47% (n=95). No significant association was seen in SOFA with severity of hyponatremia (p value >.05).

Conclusion: No statistically significant correlation was observed between SOFA score and presence of hyponatremia or the severity of hyponatremia in the study subjects. Hyponatremia is a common in sepsis patient.

Keywords: sepsis; hyponatremia; SOFA score; severe sepsis; hyponatremia in ICU

Introduction

Sepsis is a major cause of intensive care unit (ICU) admission and mortality worldwide. In India, severe sepsis accounts for 6% of admissions in a hospital and 56% of ICU mortality [1]. Various prediction models are available to assess the severity of sepsis in clinical practice [2]. One such score is the sequential organ failure assessment (SOFA) score, which provides potentially valuable prognostic information on in-hospital survival when applied to patients with severe sepsis with evidence of hypoperfusion at the time of Emergency Department presentation [1, 2]. The SOFA score is a very simple and objective score. It helps in estimations of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) and it can also estimate individual or aggregate organ dysfunction.

Hyponatremia is a common electrolyte disturbance occurring in critically ill patients. Various studies have shown that the 30-40% of all ICU admissions have hyponatremia [3]. Hyponatraemia associated with sepsis is known to have an increased morbidity and mortality because of osmotically induced cerebral oedema. Many studies have been conducted to evaluate the causes of hyponatremia and has shown its association with infective diseases. Although most cases of hyponatremia are mild, but its significance lies in the fact that it causes

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high mortality and morbidity particularly in patients with other co-morbid medical conditions and further in the patients of chronic hyponatremia. Inappropriate rapid correction of hyponatremia can lead to serious neurological deficits and even death. Numerous studies have shown the association between hyponatremia and mortality. Wald et al showed in a large cohort study (n=53236) that increased in-hospital mortality was present in those with even mild hyponatremia, and for every 1 mmol/L decrease in serum sodium level there was an increase in risk of death by 2.3% [4].

Data from various international studies have shown that hyponatremia in sepsis has been associated with increased morbidity and ICU deaths [5, 6]. However, there are only few studies in Indian scenario. Hence this study was conducted to assess the prevalence of hyponatremia in sepsis patient and show any association of hyponatremia with SOFA score. The main objectives were (i) to study prevalence of hyponatremia in sepsis, and (ii) to study association of severity of hyponatremia with SOFA score

Materials and methods

An observational cross- sectional study was conducted in the Department of Medicine and in intensive care unit at Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi. The study was approved by the Institutional Ethics Committee.

Sample size was calculated taking into consideration the prevalence of hyponatremia (56.67%) in septic patients by Muthulakshmi S et al [7]. Taking this value as reference, the minimum required sample size with 10% margin of error and 5% level of significance is 95 patients. Formula used is: $N \geq ((p\ (1\ -p))/(ME/z\alpha)2$.

Where Zα is value of Z at two sided alpha error of 5%, ME is margin of error and p is prevalence rate.

A total of 95 patients with age more than 18 years and fulfilling the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3) criteria for sepsis were enrolled. Patient with primary electrolyte disorders, on drugs associated with electrolytes disturbance and medical conditions causing sodium disturbances were excluded from the study.

After obtaining written informed consent from patients or their legal guardians, patients who fulfil the inclusion criteria were included in the study. A detailed history was taken and a thorough physical examination and investigations was done. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3) as a life threatening organ dysfunction caused by a dysregulated host response to infection and for clinical purpose organ dysfunction is represented by an increase in SOFA score by 2 or more points (Table 1).

Table 1: Sequential [Sepsis-related] Organ Failure Assessment score.

System	*Score*				
	0	*1*	*2*	*3*	*4*
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular					
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, (mL/d)				<500	<200

Blood samples were drawn for estimation of serum sodium and other investigations within 24 hours of admission of patients presenting with sepsis or diagnosis of sepsis if it develops during the hospital stay. Serum sodium was estimated by ISE module of Beckman Coulter AU system. Hyponatraemia will be defined as a serum sodium concentration < 135 meq/l. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then non parametric test was used.

Statistical tests were applied as follows

Quantitative variables were compared using independent t test for normally distributed data set and Mann - Whitney U test was used when the data sets were not normally distributed between the two groups and ANOVA/Kruskal Wallis test between three groups. Qualitative variables were associated by using chi-square test. A p value of <0.05 was considered statistically significant. The data was entered in MS excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 95 patients who were above 18 years of age and with SOFA score of at least 2 was enrolled in the study. The table 2 shows the baseline characteristics of the study population.

Table 2: Demographic profile of the study participants.

		Frequency (n-95)	*Percentage*
Age (in years)	18-30	19	20.00%
	31-50	44	46.32%
	51-70	25	26.32%
	>70	7	7.37%
	Mean ± SD	45.34 ± 17.1	
Gender	Male	37	38.95%
	Female	58	61.05%

In present study, 69.47% of patients had hyponatremia. Out of 66 patients with hyponatremia, 50.00% of patients had mild hyponatremia followed by moderate hyponatremia (27.27%). Severe hyponatremia was present in 15 out of 66 patients (22.7%) (Figure 1). Mild hyponatremia was defined as 130-134 meq/l, moderate as 125-129 meq/l and severe as <125meq/l.

Table 3 shows the Mean ±SD and Median (IQR) of platelets, PaO2/FiO2, total bilirubin, mean arterial pressure, Glasgow coma scale and serum creatinine levels in both patients of hyponatremia and in normal blood sodium levels. There was no association found between individual SOFA score components and hyponatremia.

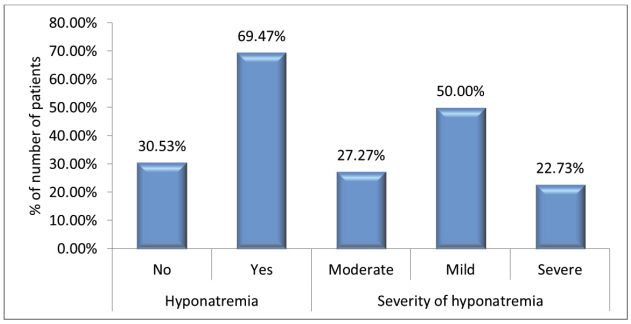

Figure 1: Distribution of hyponatremia and severity of hyponatremia of study subjects.

The mean value of SOFA score of study subjects was 6.18 ± 2.38 patients. Though the SOFA score was more among patients with severe hyponatremia, however the overall SOFA score for sepsis showed no statistically significant association with hyponatremia or its severity (Table 4).

Discussion

Sepsis is a systemic inflammatory response syndrome, characterised by release of numerous cytokines and inflammatory mediators due to documented or presumed infection [8]. It causes high morbidity and mortality ranging from 16% to 50% in septic shock [8]. Hence it is necessary to develop an easily available and reproducible clinical parameter which can monitor and predict the prognosis of sepsis [7]. Serum sodium level is one such parameter which can be used in monitoring of patients with sepsis, and critically ill patients admitted to the ICU [8-11].

In this study the mean age of patients with hyponatremia was 44 years whereas mean age of patients without hyponatremia was 48 years. In addition, severity of hyponatremia showed no association with demographic characteristics (age and gender). Similar were the findings in other studies done on adult patients where hyponatremia was unaffected by age and gender [8-11].

In our study hyponatremia occurred in 66 (69.47%) of adult sepsis patients, with a mean sodium value of 132.98 ± 9.02. Most of them were categorized as mild (50%), while rest of them were moderate [n=18 (27.27%)] and severe [n=15 (22.73%)]. The prevalence of hyponatremia in our study was slightly higher as compared to the study by Muthulakshmi S et al., in which hyponatremia was seen in around 50% (n=60) sepsis patients though their sample size was smaller [8]. In another study by Otniel W et al., out of 328 sepsis patients hyponatremia was seen in 68% which was comparable to our study [9]. In their study also, most of

Table 3: Association of components of SOFA score with hyponatremia.

Components of SOFA score		*Hyponatremia present (n=66)*	*Hyponatremia absent(n=29)*	*Total*	*P value*
Platelets	Mean ±SD	120010.45 ± 108999.71	112629.52 ± 103868.69	117757.33 ± 106962.02	0.868
	Median (IQR)	78000(34250-188500)	81000(30000-177000)	81000(33850-188000)	
PaO2/FiO2 (mmHg)	Mean ±SD	426.35 ± 192.88	468.97 ± 194.97	439.36 ± 193.49	0.277
	Median (IQR)	402.5(286.75-557.5)	452(345-600)	412(297-582)	
Total bilirubin (mg/dL)	Mean ± SD	2.21 ± 4.39	2.45 ± 3.37	2.28 ± 4.09	0.463
	Median (IQR)	1.05(0.5-2.25)	1.2(0.6-2.4)	1.1(0.5-2.4)	
Mean arterial pressure (mmHg)	Mean ± SD	95.08 ± 19.12	96.07 ± 20.78	95.38 ± 19.53	0.82
	Median (IQR)	93(83.5-108)	94(83-109)	93(83-108.5)	
Glasgow coma scale score	Mean ± SD	11.38 ± 4.21	11.07 ± 4.61	11.28 ± 4.31	0.821
	Median (IQR)	13(8-15)	12(8-15)	13(8-15)	
Serum creatinine (mg/dL)	Mean ± SD	2.27 ± 2.81	2.58 ± 3.12	2.36 ± 2.89	0.509
	Median (IQR)	1.5(0.5-2.825)	1.2(0.8-3.3)	1.2(0.55-2.9)	
Overall SOFA	Mean ± SD	6.05 ± 2.41	6.48 ± 2.34	6.18 ± 2.38	0.409
	Median (IQR)	6(4-7)	6(4-8)	6(4-8)	

Table 4: Association of SOFA with severity of hyponatremia.

SOFA score	*Mild hyponatremia (n=33)*	*Moderate hyponatremia (n=18)*	*Severe hyponatremia (n=15)*	*Total*	*P value*	*Test performed*
Mean ± SD	5.85 ± 2.11	5.39 ± 2.43	7.27 ± 2.71	6.05 ± 2.41	0.121	Kruskal Wallis test; Chi square =4.217
Median(IQR)	6(4-7)	5.5(3-7)	7(5-8)	6(4-7)		
Range	2-10	2-10	4-13	2-13		

the patients had mild hyponatremia (29.87%) followed by 22.25% with moderate and 15.85% with severe hyponatremia. 22.86% had normonatremia and 9.14% had hypernatremia [9], whereas in another study on 610 patients of pneumonia, 47 patients (7.7%) were found to have hyponatraemia [12].

Very few studies have addressed the hyponatremia in adult patients with sepsis moreover studies on hyponatremia in critically ill patients with sepsis are even fewer. In study by Padhi et al., hyponatremia was found to be 34.3% and severe sepsis was the second most common etiology for hyponatremia whereas in study by Nicolini et al., out of 1599 critically ill patients, 152(9.5%) had sepsis and among them 22(14.2%) patients had hyponatremia [10, 11]. The low incidence of sepsis and hyponatremia among their study was may be because they included only surgical patients admitted to the ICU in the post-operative period instead of all sepsis patients admitted in the hospital [11].

The mean value of SOFA score of study subjects was 6.18 ± 2.38 patients. Though the SOFA score was more among patients with severe hyponatremia, however the overall SOFA score for sepsis showed no statistically significant association with hyponatremia or its severity. This may be because most of the patients in our study had mild hyponatremia. In contrast, Nzerue CM et al. found significant association of sepsis and hyponatremia [13]. Padhi et al. also found contrasting results as the patients with hyponatremia had higher APACHE scores as compared to those with normal sodium levels (31±8.98 vs 26 ±7.68, p<0.01), though their study included all critically ill patients and not just patients with sepsis [10]. Other studies have shown a significant association of hyponatremia with increasing mortality however whether its due to increasing severity of sepsis or other causes was not determined [8, 9]. We were also not able to confirm it because we did not assess the outcome and mortality among sepsis patients. However, future studies must be conducted to assess severity of both

hyponatremia and sepsis and their association with the patient outcomes to have a better understanding.

Otniel et al. found a significant association of sepsis (specific and non-specific) with severity of hyponatremia with specific identified sepsis being more in mild hyponatremia and unspecified sepsis being more with severe hyponatremia signifying that the unknown nature of the sepsis may be severe enough to cause more hyponatremia [9]. Our study lacked any such association which may be due to the fact that we had very less number of severe hyponatremia cases.

In sepsis, dysregulation of cytokine release causes endothelial dysfunction, vasodilation, increased capillary permeability resulting in cellular leakage syndrome that interferes with fluid regulation and causes intravascular hypovolemia, cellular dysfunction, and finally tissue death. The dysregulation of the intra- and extra- vascular volumes lead to electrolyte disturbances such as hyponatremia [9]. Further, hemodynamic changes in sepsis are directly related to endothelial disorders, tissue hypoxia, mitochondrial dysfunction, decreased oxygen delivery, and changes in blood flow [14]. Impaired renal function and the effects of fluid loss play important roles in the increase of BUN and creatinine [15].

Abnormalities in serum sodium indicate a disturbance in the body's water balance. This can cause serious clinical manifestations including seizures, coma and even death [16]. Hyponatremia lower extracellular osmolality and promotes movement of water into cells, hence severe, and sometimes fatal, cerebral oedema may occur. It occurs more frequently when hyponatremia develops in <48h [17].

In our study, patients with severe hyponatremia had lower minimum GCS scores, higher TLC, lower PaO2/FiO2 (hypoxia), and higher levels of bilirubin, which are clinical indicators of a more severe brain injury and greater degree of pro-inflammation but all these parameters showed no statistically significant association with hyponatremia or its severity [18]. Our findings were in line with an observational cohort study based in the Netherlands, where hyponatremia was a common and benign complication in adults with bacterial meningitis. They also found no association of hyponatremia with either the severity of disease or outcomes [19].

Other studies have shown contrasting results since their study determined the association of these parameters with the sepsis outcomes in patients with hyponatremia. Hypoxia (lower PaO2/FiO2) as a significant predictor of mortality in sepsis was shows in the study by Nzerue et al [13]. The underlying mechanism may be that hypoxia interferes with cerebral adaptive responses to hyponatremia [20, 21].

In a cohort of children with bacterial meningitis, Zheng et al found a significant association of severe hyponatremia with impaired consciousness and low GCS scores [18]. The results were in contrast to the present study but their study group was children, though we still cannot ignore the importance of decreasing consciousness among hyponatremia patients which subsequently have an adverse effect on the outcome of the patients.

Limitation of the study

While this study addresses some interesting clinical questions, it also has several limitations that warrant discussion. Critically, the association of sepsis severity with hyponatremia severity was not statistically significant in our study which may be due to small number of patients included in the study. This may have prevented our ability to draw more definitive association regarding the same. Moreover we were also not able to investigate mortality associated with degree of hyponatremia.

Conclusion

Sodium is one of the active solutes and a major extracellular electrolyte. Sepsis affects the fluid balance of the body and results in hyponatremia. Increasing severity of hyponatremia in sepsis may trigger rapid changes in serum osmolality resulting in hypoxia, consciousness disturbances, deranged kidney functions and blood pressure variations. In our study the prevalence of hyponatremia was 66 (69.47%). No statistically significant correlation was observed between SOFA score and presence of hyponatremia or the severity of hyponatremia in the study subjects. Also, no statistically significant association was observed between hyponatremia and individual components of the SOFA score.

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Conflicts of interest

Authors declare no conflicts of interest.

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