Brief Communication

Association of hyponatremia with in-hospital outcomes in infective endocarditis: A 5-year review from an Indian Intensive Care Unit

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Abstract

Hyponatremia is commonly noted with cardiovascular disorders, but its role in infective endocarditis (IE) is limited to being a marker of increased morbidity in IE patients with intravenous drug use. This was a 5-year retrospective review from an Indian Intensive Care Unit (ICU). Patients >18 years with IE and available serum sodium levels were included in the study. Pediatric and pregnant patients were excluded from the study. Hyponatremia was defined as admission sodium <135 mmol/L. Detailed data were abstracted from the medical records. Primary outcomes were need for invasive mechanical ventilation, ICU length of stay, and in-hospital mortality. Secondary outcomes included development of acute kidney injury, acute decompensated heart failure (ADHF), acute respiratory distress syndrome, stroke, and severe sepsis in the ICU. Two-tailed $P < 0.05$ was considered statistically significant. Between January 2010 and December 2014, 96 patients with IE were admitted to the ICU with 85 (88.5%) (median age 46 [34.5–55] years, 51 [60.0%] males) meeting our inclusion criteria. The comorbidities, echocardiographic, and microbiological characteristics were comparable between patients with hyponatremia (56; 65.9%) and eunatremia (29; 34.1%). Median sodium in the hyponatremic cohort was 131 mmol/L (127.25–133) compared to the eunatremic cohort 137 mmol/L (135–139) ($P < 0.001$). The primary outcomes were not different between the two groups. Hyponatremia was associated more commonly with ADHF (12 [21.4%] vs. 0; $P = 0.007$) during the ICU stay. Hyponatremia is commonly seen in IE patients and is not associated with worse hospital outcomes. ADHF was seen more commonly in the hyponatremic patients in comparison to those with eunatremia.

Keywords: Heart failure, hospital outcomes, hyponatremia, India, infective endocarditis

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Introduction

Hyponatremia is one of the most common electrolyte disorders and is associated with increased mortality in the general population.[1] Cardiovascular conditions such as heart failure, myocardial infarction, pulmonary arterial hypertension, and pulmonary embolism have been noted to have worse outcomes with hyponatremia, but its role in infective endocarditis (IE) is lesser understood.[1-4] Prior studies have demonstrated hyponatremia to be associated with higher incidence of bacterial IE and mortality in patients with intravenous

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drug use (IVDU).[5-7] However, the role of hyponatremia has not been systematically evaluated in non-IVDU IE, especially in the Intensive Care Unit (ICU).

Subjects and Methods

This is a 5-year retrospective study of all IE cases at a tertiary care academic medical center from January 2010 to December 2014. The Institutional Ethics Committee approved the study and waived the need for informed consent. All patients >18 years admitted to the ICU with a diagnosis of IE as defined by the modified Duke criteria and available sodium level at admission were included in this study. Pediatric patients, patients discharged against medical advice (AMA), and pregnant females were excluded. Hyponatremia was defined as admission serum sodium <135 mmol/L.[2,3] Details on demographic characteristics, comorbidities, examination, and microbiological data were abstracted from the medical records. Charlson age-adjusted comorbidity index (CACI) was used to evaluate baseline characteristics. Echocardiographic variables, vegetation details, and clinical course were obtained from the ICU records. Acute kidney injury (AKI) was defined as rise in serum creatinine >0.3 mg/dL over a 7-day period and acute decompensated heart failure (ADHF) was diagnosed using Framingham criteria. Sepsis and septic shock were defined using the American College of Chest Physicians/Society of Critical Care Medicine consensus statement criteria and acute respiratory distress syndrome (ARDS) per the revised American/European consensus statement.[8,9] Apriori selected primary outcomes included need for invasive mechanical ventilation, ICU length of stay, and in-hospital mortality. Secondary outcomes included development of AKI, ADHF, ARDS, cerebrovascular accident, and severe sepsis/septic shock in the ICU.

Continuous data are presented as median (interquartile range [IQR]) and categorical data as totals (percentages). The continuous and categorical variables were assessed using unpaired *t*-test (or Mann–Whitney U-test) and Chi-square test (or Fisher's exact test), respectively. Two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP statistical software version 10.0.1 (SAS Institute Inc., Cary, NC, USA). A portion of the findings was presented as a poster presentation at the American Thoracic Society International Conference 2016, San Francisco CA.[10]

Results

During this 5-year period, 96 patients with IE were admitted to the ICU of which 11 (11.5%) patients (9 left AMA, 2 had no sodium levels) were excluded. In the remaining 85 patients, median age was 46 (34.5–55) years with 51 (60.0%) males. Hyponatremia was noted in 56 (65.9%) patients with median sodium 131 mmol/L (IQR 127.25–133) versus 137 mmol/L (IQR 135–139) in eunatremic patients ($P < 0.001$). Baseline characteristics of the cohorts are detailed in Table 1. CACI >4 was seen in 8 (14.3%) and 3 (10.3%) patients with and without hyponatremia ($P = 0.74$). No patient had IVDU history. The two cohorts were not different in their history of chronic heart failure (CHF), CKD, and alcohol abuse. The two cohorts had comparable left ventricular ejection fraction, right ventricular systolic pressure, and significant (≥Grade II) mitral and aortic regurgitation [Table 1]. Large vegetations (>1.0 cm) (24 [66.6%] vs. 17 [70.8%]; $P = 0.56$), multiple valve involvement (5 [10.2%] vs. 2 [7.7%]; $P = 1.00$), and prior prosthetic valves (4 [7.1%]

Table 1: Baseline characteristics of cohorts

Parameter	Hyponatremia (*n*=56)	Eunatremia (*n*=29)	*P*
Demographics			
Age (years)	50 (35-59.5)	42 (33-50.5)	0.07
Male gender	37 (66.1)	14 (48.3)	0.16
Comorbidities			
Hypertension	14 (25.0)	7 (24.1)	1.00
Diabetes	6 (10.7)	5 (17.2)	0.50
Congestive heart failure	4 (7.1)	2 (6.9)	1.00
Prior infective endocarditis	11 (19.6)	6 (20.7)	1.00
Chronic kidney disease	2 (3.6)	3 (10.3)	0.33
Cerebrovascular accident	11 (19.6)	5 (17.2)	1.00
CACI	2 (1-2.8)	1 (0.5-3)	0.55
Alcohol abuse	10 (19.6)	10 (35.7)	0.17
Examination			
Fever	24 (51.1)	18 (64.3)	0.34
Heart rate (bpm)	83 (80-100.5)	87 (80-98)	0.83
MAP (mmHg)	83.3 (83.3-93.3)	81.7 (73.3-96.7)	0.32
New murmur	47 (87.0)	22 (75.9)	0.23
Vascular phenomenon	14 (25.5)	3 (10.7)	0.15
Immunological phenomenon	5 (9.1)	0 (0.0)	0.16
Laboratory:			
Hemoglobin (g/dL)	10.1 (7.5-11.8)	11.0 (7.9-12.8)	0.61
Leukocytes ($\times 10^3$/mm^3)	8.3 (7.0-10.7)	8.1 (7.2-9.0)	0.15
Platelets ($\times 10^3$/mm^3)	221.5 (168.0-285.3)	240.0(164.0-311.0)	0.55
Creatinine (mg/dL)	1.0 (0.7-1.3)	1.2 (1.0-1.6)	0.08
Alanine transaminase (U/L)	27 (13-50)	22 (15.3-37.8)	0.58
Positive blood cultures	32 (57.1)	20 (69.0)	0.35
Echocardiography			
LVEF (%)	65 (61-68)	64 (62-67)	0.92
RVSP (mmHg)	39.0 (35.0-50.0)	35.0 (31.8-47.2)	0.22
Vegetation	44 (80.0)	25 (86.2)	0.56
Mitral regurgitation ≥Grade II	36 (64.3)	16 (55.2)	0.48
Aortic regurgitation ≥Grade II	23 (41.1)	11 (37.9)	0.82

Median (IQR) or number (percentage). CACI: Charlson age-adjusted comorbidity index; LVEF: Left ventricular ejection fraction; MAP: Mean arterial pressure; RVSP: Right ventricular systolic pressure; IQR: Interquartile range

vs. 4 [13.8%]; P = 0.44) were comparable between groups.

Positive blood cultures were seen in 52 (61.2%) patients with no differences between the two cohorts [Table 1]. *Streptococcus* and *staphylococcus* species were the most common bacteria – 27 (49.1%) and 12 (21.8%), respectively. Ceftriaxone (46 [54.1%]) and gentamicin (41 [48.2%]) were the most commonly used antimicrobials. Vasopressor use (8 [14.3%] vs. 2 [6.9%], P = 0.48) and need for surgical intervention (3 [5.4%] vs. 1 [3.7%]; P = 1.00) were not different between groups.

Detailed outcomes data are presented in Table 2. The two cohorts were not different in terms of their primary outcomes. Hyponatremia was associated with higher occurrence of ADHF (P = 0.007); however, the event rate was too low for a multivariate analysis. AKI incidence was lower in the hyponatremia (P = 0.03) population in comparison to the eunatremic patients.

Discussion

The major findings of our study are as follows: (a) hyponatremia is a common laboratory abnormality in patients with IE noted in nearly 66% of the ICU admissions, (b) ICU outcomes are comparable between hyponatremic and eunatremic patients, and (c) hyponatremia is associated with higher incidence of ADHF in IE patients.

In the IE population, the etiopathogenesis of hyponatremia is lesser understood.[5-7] Neurohormonal stimulation resulting in release of antidiuretic hormone (ADH) has been implicated in acute infectious and noninfectious processes for mimicking a syndrome of inappropriate ADH secretion (SIADH) like picture.[1,2,4]

Table 2: Outcomes in patients with and without hyponatremia

Parameter	Hyponatremia (n=56)	Eunatremia (n=29)	P
Primary outcomes			
IMV use	9 (16.1)	2 (7.4)	0.49
ICU LOS (days)	6.0 (3.0-12.5)	5.0 (2.5-11.0)	0.63
In-hospital mortality	7 (12.5)	2 (6.9)	0.71
Secondary outcomes			
Cerebrovascular accident	12 (21.4)	4 (14.3)	0.56
Acute kidney injury	4 (7.1)	7 (25.0)	0.03
Severe sepsis/septic shock	9 (16.1)	4 (14.3)	1.00
ADHF	12 (21.4)	0 (0.0)	0.007
ARDS	9 (16.1)	5 (18.5)	0.76

Median (IQR) or number (percentage). ADHF: Acute decompensated heart failure; ARDS: Acute respiratory distress syndrome; ICU: Intensive Care Unit; IMV: Invasive mechanical ventilation; LOS: Length of stay

Interleukin release in chronic inflammation and infectious disease has been demonstrated to trigger SIADH leading to chronic hyponatremia.[1,6] In an assessment of patients with IVDU, Levine and colleagues[7] noted hyponatremia in 32% of their 171 patients with the bacterial IE group having a higher incidence compared to the nonbacterial IE patients. Hyponatremic patients had a longer duration of pyrexia (15.8 vs. 5.0 days, P < 0.001), but had no differences in valvular involvement or hospital outcomes. The longer duration of pyrexia could have contributed to hypovolemic hyponatremia from dehydration or hypotonic hyponatremia from water consumption. Ogbuawa *et al*.[6] noted patients with IVDU and IE to have a clinical picture of SIADH, which we were unable to evaluate due to the retrospective nature of the study. In our patients, we noted hyponatremia to be strongly associated with ADHF. However, due to the retrospective nature of the study, it is challenging to evaluate the cause and effect relationship. In patients with CHF and ADHF, hypovolemic hyponatremia is a well-documented consequence of impaired water excretion due to excessive ADH release.[2,3] Due to lack of information on serum and urine osmolalities and serial serum sodium levels, an etiological diagnosis in our patients was challenging. Hyponatremia could be a direct cause, marker of severity, or an independent risk factor in IE and definitely needs further elaboration.[2] Although a difference in mortality was noted in previously published studies; this was not replicated in this cohort.

Our study has certain limitations such as its retrospective design that carry inherent informational and selection biases. We performed a single-center study and limited our outcomes to a single hospital stay, which could potentially impact the generalizability of our findings. Being a tertiary care referral center, we have a high proportion of referred cases thereby potentially affecting the generalizability to the Indian population.

In summary, we present the first study evaluating the association of admission hyponatremia with ICU outcomes in the IE population. Hyponatremia demonstrated a significant association with ADHF, which could represent either an independent or comorbid association necessitating further studies on the mechanistic aspects.

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Conflicts of interest

There are no conflicts of interest.

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