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Research Article

HYPONATREMIA IN ACUTE MYOCARDIAL INFARCTION AND SHORT-TERM CLINICAL OUTCOME: A CROSS-SECTIONAL STUDY

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ABSTRACT

Objectives: Neurohumoral activation in acute myocardial infarction (MI) causes hyponatremia and is associated with poor outcome. We aimed to establish a relationship between hyponatremia in acute ST-elevation MI (STEMI) and its complications.

Methods: Patients with acute STEMI were included. The patients were monitored for serum sodium at admission; at 24, 48, and 72 h; and echocardiographic evaluation at admission and at 72 h. Complications such as left ventricular (LV) failure and mortality during hospital stay were noted.

Results: In the acute setting of STEMI, hyponatremia was observed in 86% of patients aged >60 years (p=0.001). In patients with moderate LV dysfunction, 91% had hyponatremia at 24 h after admission, with persistent hyponatremia in 66.7% at 72 h (p=0.02). Within 24 h of admission, when the patient had normal serum sodium, the risk of complications was 16%, with mild hyponatremia the risk was 66.7%, with moderate hyponatremia the risk was 85.7%, and with severe hyponatremia the risk was 100% (p=0.001).

Conclusion: Elderly individuals are prone to hyponatremia following acute MI. LV dysfunction is associated with hyponatremia following MI. Moderate-to-severe hyponatremia is associated with a high risk of complications.

Keywords: Acute myocardial infarction, Elderly, Hyponatremia, Left ventricular dysfunction.

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INTRODUCTION

Coronary artery disease (CAD) is the third leading cause of death globally and is associated with 17.5 million death annually [1]. The incidence and prevalence of CAD are still increasing and becoming a global burden in the past two to three decades, as per studies conducted worldwide and in India [2]. Numerous studies have provided sufficient information regarding the correlation between hyponatremia and myocardial infarction (MI) and its outcomes [3]. Previous studies have shown that the neurohumoral activation observed in acute MI and heart failure causes hyponatremia and is associated with worse outcomes [4]. In our study, we attempted to establish a relationship between hyponatremia in acute ST-elevation MI (STEMI) and its complications.

METHODS

Study design

This was a cross-sectional, observational study. Patients admitted to the intensive care unit from June 2021 to September 2022 in Government Dharmapuri Medical College and Hospital with acute STEMI were included in the study and were observed for 72. STEMI was diagnosed by the detection of a rise or fall in cardiac troponins, with one value above the upper reference limit and new ischemic electrocardiogram (ECG) changes of ST-segment elevation >1 mm in two contiguous leads or new-onset left bundle branch block. The study data were collected by detailed history, clinical examination, 12-lead ECG (including right-sided and posterior leads taken for patients with inferior wall MI), and blood samples for sugar, creatinine, and electrolytes collected at the time of admission and sodium at 24, 48, and 72 h after admission. 2D echocardiography was performed to assess left ventricular (LV) systolic function at the time of admission and 72 h after admission. The ejection fraction (EF) was calculated using the Simpson's method. According to this method, normal EF is 56–70%, mildly reduced is 45–54%, moderately reduced is 30–44%, and severely reduced EF is <30%. Serum sodium concentration was determined using an ion-selective electrode auto-analyser (Roche OMNIC). Hyponatremia was defined as a corrected serum sodium level (plasma Na+ 0.024*[plasma glucose (mg/dL)–100]) of <135 mmol/L. We defined hyponatremia as mild if the plasma Na was 130–134 mEq/L, moderate if it was 125–129 mEq/L, and profound or severe if it was <125 mEq/L [5].

Inclusion criteria

All adults above 18 years of age admitted with STEMI, as per the above definition.

Exclusion criteria

Any history of known heart disease, thyroid disorders, clinical volume overload status, renal failure, acute and chronic liver failure, adrenal insufficiency, hypertension on diuretics, malignancy, and other electrolyte abnormalities [6]. Patients who fulfilled the inclusion criteria and did not meet any of the exclusion criteria were included in this study.

Statistical analysis

The collected data were analyzed with IBM Statistical Package for the Social Sciences statistics software 23.0 version. Descriptive statistics, frequency analysis, and percentage analysis were used for categorical variables, whereas means and standard deviations were used for continuous variables. Pearson's correlation coefficient was used to assess the relationships between the variables. The Chi-square test was used to determine the significance of categorical data. In both the above statistical tools, a probability value of <0.05 is considered significant.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee (GDMCH 01/04/2021). Written informed consent was obtained from all participants.

RESULTS

A total of 100 patients were included in this study. Among them, 73% (73) were male. The mean age of the male and female patients was 52±8.8 and 55±7.8 years. All patients were aged between 28 and 70 years old. According to age group, 8% (8) were below 40 years and all were male, 30% (30) were between 41 and 50 years, 48% (48) were between 51 and 60 years, and 14% (14) were more than 60 years. The comorbidities among the patients were hypertension in 54% (54), diabetes mellitus in 42% (42) and either hypertension or diabetes in 74% (74). The most common presentations were anterior wall MI in 38 patients, anterolateral MI in 24, and anteroseptal MI in 14.

The prevalence of hyponatremia at 72 h was 18% (18), when compared to 40% (40) at admission and 44% (44) at 24 h. At 24 h, hyponatremia was observed in 25% (2/8) of patients aged <40, 27% (8/30) of patients aged 41–50, 46% (22/48) of patients aged 51–60, and 86% (12/14) of patients aged >60 years (p=0.002). As age increases, hyponatremia becomes more common in the acute setting of STEMI (Table 1).

Mean serum sodium level in relation to LV function at admission: The mean sodium level at admission in patients with normal LV function was 138.38, with mild LV dysfunction was 134, and moderate LV dysfunction was 129.09 (p=0.001). The mean serum sodium level at 72 h in patients with normal LV function was 140.85, with mild LV dysfunction was 138.35, and moderate LV dysfunction was 133.27 (p=0.001). There was a significant association between the severity of LV dysfunction at admission and mean serum sodium level, with the lowest mean serum sodium levels in those with moderate LV dysfunction.

The EF at admission was normal in 26% (26), mild dysfunction in 52% (52), and moderate dysfunction in 22% (22) patients, respectively. Among them, four reverted to normal LV function and six progressed to severe LV dysfunction at 72 h. All four patients reverted from mild LV dysfunction to normal LV function had serum sodium in the normal range at admission and at 24, 48, and 72 h. Among the six patients who progressed to severe LV dysfunction at 72 h, four presented with severe hyponatremia within 24 h, and two progressed from mild-to-moderate hyponatremia within 72 h.

Patients with normal LV function at admission had normal serum sodium levels at admission and 24 h after admission. Patients with mild LV dysfunction at admission, 42.3% (22/52) had hyponatremia at admission and 46% (24/52) had hyponatremia at 24 h and those with moderate LV dysfunction, 81.8% (18/22) had hyponatremia at admission and 91% (20/22) had hyponatremia at 24 h (p=0.002). Hyponatremia persisted in 66.7% at 72 h in those with moderate LV dysfunction. The proportion of patients with hyponatremia was higher in those with moderate LV dysfunction than in those with normal LV function (Table 2). Hyponatremia normalized in 75% (18/24) with mild LV dysfunction and 40% (8/20) with moderate LV dysfunction at 72 h (p=0.02) (Fig. 1).

The mean serum sodium level in relation to complications of STEMI: The mean serum sodium levels at admission, 24 h, 48 h, and 72 h, were significantly lower in those with complications (129.88, 131, 132.14, and 135.33 mEq/L, respectively, vs. 137.92, 138.38, 139 and 140.23 mEq/L), when compared to those without complications following STEMI (p=0.001). A significant association was observed between hyponatremia and STEMI complications.

The prevalence of moderate to severe hyponatremia was 26% (26) within 24 h of acute MI. The severity of hyponatremia in patients without complications following STEMI was mild in 15.4% (8/52) and moderate in 3.8% (2/52). All the ten patients had normal serum sodium levels within 72 h. All the eight patients with mild hyponatremia had EF more than 50% at admission. The two patients with moderate hyponatremia had EF <50% at admission and had hypertension as comorbidity. Four patients died during hospitalization. Among those four patients, two had mild hyponatremia and moderate LV dysfunction at admission and progressed to moderate hyponatremia and severe LV dysfunction at 72 h. Two other patients presented with moderate hyponatremia and mild LV dysfunction at admission and progressed to severe hyponatremia within 24 h. Cardiogenic shock was noted in six patients who presented with severe hyponatremia at admission. Among them, two had progressed from mild to moderate LV dysfunction, two had progressed from moderate to severe LV dysfunction, and the remaining two had persistent moderate LV dysfunction within 72 h of admission. As the severity of hyponatremia increases in acute STEMI, there is a greater risk of complications, such as LV failure, shock, heart block, and mortality (Table 3).

Table 1: Age and serum sodium

Serum sodium	Age in years				p-value
	<40	41–50	51–60	>60	
At admission					
>135	4	24	30	2	0.001
<135	4	6	18	12	
At 24 h					
>135	6	22	26	2	0.002
<135	2	8	22	12	
At 48 h					
>135	6	26	26	6	0.001
<135	2	4	22	8	
At 72 h					
>135	6	28	40	8	0.032
<135	2	2	8	6	

Table 2: Ejection fraction at admission and serum sodium

Time frame	Serum sodium	EF at admission			p-value
		>55	45–54	30–44	
At admission	>135	26	30	4	0.001
	<135	0	22	18	
At 24 h	>135	26	28	2	0.002
	<135	0	24	20	
At 48 h	>135	24	32	8	0.001
	<135	2	20	14	
At 72 h	>135	26	46	10	0.032
	<135	0	6	12	

EF: Ejection fraction, EF>55% – normal, EF 45–54% – mild LV dysfunction, EF 30–44% – moderate LV dysfunction. LV: Left ventricular

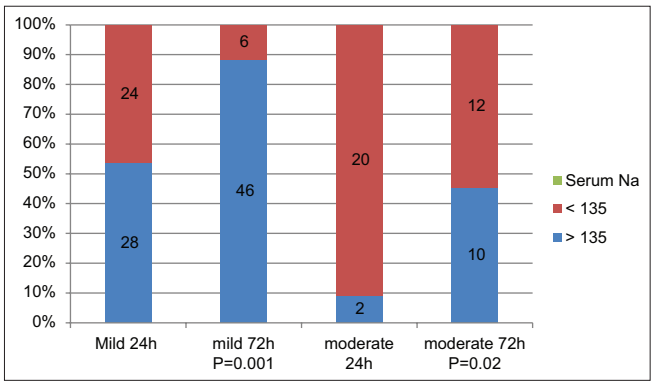

Fig. 1: Left ventricular dysfunction and hyponatremia at 24 h and 72 h

Table 3: Hyponatremia and complications of STEMI

Serum sodium within 24 h	Complications of STEMI				
	Nil	LV failure	Shock	Heart block	Death
>135 mEq/L	42	4	0	4	0
130–134 mEq/L	8	14	0	0	2
125–129 mEq/L	2	8	0	4	0
<125 mEq/L	0	4	6	0	2
Total	52	30	6	8	4

STEMI: ST-elevation myocardial infarction

Table 4: Hyponatremia at 24 h and complications of STEMI

Serum sodium at 24 h	Complications of STEMI		
	Present	Absent	p-value
>135 mEq/L	8	42	0.001
130–134 mEq/L	18	8	
125–129 mEq/L	12	2	
<125 mEq/L	12	0	

STEMI: ST-elevation myocardial infarction

Within 24 h of admission, when the patient had normal serum sodium, the risk of complications was 16% (8/50); with mild hyponatremia, the risk was 66.7% (16/24); with moderate hyponatremia, the risk was 85.7% (12/14); and with severe hyponatremia, the risk was 100% (12/12) (p=0.001) (Table 4).

DISCUSSION

Hyponatremia is a common electrolyte disorder in hospitalized patients, with the prevalence of 11–23% in both STEMI and non-STEMI and is associated with poor outcomes in both the short and long term [7,8]. In our study, the prevalence of moderate-to-severe hyponatremia was 26% within 24 h. In the early period of MI, there is intense sympathetic neural hyperactivity in response to myocardial ischemia and anoxia, which results in the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems [4]. There was a rapid increase in catecholamine, angiotensin II, aldosterone, and arginine vasopressin (AVP) levels. Reduced cardiac output in patients with acute STEMI leads to a reduced effective circulating volume and causes non-osmotic release of AVP. Neurohumoral activation causes more proximal tubular reabsorption and less distal delivery to the diluting segment, whereas AVP acting on the collecting duct causes more water reabsorption, predisposing the patient to hyponatremia [9]. The other temporary factors operating in the setting of acute MI that causes AVP release include stress, pain, and nausea. In patients with STEMI, there is a negative correlation between plasma AVP and serum sodium levels [3]. The clinical and laboratory variables more closely associated with neurohumoral activation after acute MI were the Killip class, LV EF, age, and diuretic drug use [10].

Older individuals are prone to hyponatremia due to a reduced glomerular filtration rate, reduced renal prostaglandins, and a reduction in the percentage of total body water content [11]. Since, serum sodium is a function of total exchangeable sodium plus potassium in total body water, reduced total body water in older individuals, predisposes them to hyponatremia even with minimal excess water. The ability of the kidney to conserve salt and water reduces with age, with an increased AVP response to both osmotic and non-osmotic stimuli [12].

In our study, hyponatremia was more common as age advances, with more than 80% patients older than 60 years having hyponatremia in acute MI. LV dysfunction was associated with hyponatremia. The patients with normal LV function, none had hyponatremia; the prevalence of hyponatremia was more than 80% in those who presented with moderate LV dysfunction at admission. Even though most patients had persistent LV dysfunction at 72 h, more than half had normalized serum sodium at 72 h, particularly in patients with mild LV dysfunction, because of the abatement of temporary factors and some improvement in LV function due to thrombolytic therapy.

According to Lazzeri *et al*. [13], in the short and long term, hyponatremia was not associated with an increased risk of death, indicating that hyponatremia in acute STEMI is a risk marker for more severely ill patients. According to Choi *et al*., [14] hyponatremia at discharge is associated with an increased long-term mortality risk, regardless of EF, whereas baseline serum sodium levels had no adjusted prognostic impact on long-term mortality.

In another study, early hyponatremia was an independent predictor of mortality in patients with acute STEMI. As the severity of hyponatremia increases, the risk of 30-day mortality increases more than 3 fold [15]. In a meta-analysis by Ma *et al*., [16] among 34,782 patients with acute coronary syndrome (ACS), the incidence of short-term mortality was higher when the patient had moderate-to-severe hyponatremia compared to mild hyponatremia, even though mild hyponatremia also increased the mortality risk. They also concluded that hyponatremia during ACS is associated with a risk of heart failure independent of LVEF.

In our study, four patients died; among them, two had mild hyponatremia with moderate LV dysfunction at admission and progressed to moderate hyponatremia with severe LV dysfunction within 72 h, and two had severe hyponatremia with moderate LV dysfunction within 24 h of admission. All six patients with cardiogenic shock presented with severe hyponatremia at admission. Among them, two patients had persistent moderate LV dysfunction; LV dysfunction progressed from mild to moderate in two, moderate to severe in two, within 72 h. Progression of hyponatremia from admission to 72 h was a poor prognostic marker following MI.

In an animal model, AVP, through action on the V1 receptor, promoted fibroblast proliferation and protein synthesis, leading to myocardial hypertrophy and remodeling [17]. AVP may be involved in left ventricular hypertrophy. In dogs, V1 receptor antagonists exert beneficial effects through increased cardiac output and decreased systemic vascular resistance [18]. In patients with advanced chronic kidney disease, hyponatremia occurred independently of plasma AVP but was still independently related to mortality, indicating the direct toxic effect of hyponatremia [16]. Hypotonic hyponatremia activates aquaporin-mediated cell swelling, leading to activation of the reverse mode of the sodium-calcium exchanger (NCX). The increase in intracellular calcium load through activation of the reverse mode of NCX generates reactive oxygen species and augments vulnerability to ischemia-reperfusion injury in the heart [19]. The myocardial calcium accumulation can accelerate myocardial necrosis, predispose patients to contractile failure, and trigger arrhythmias.

In a rat model of acute myocardial infarction, both tolvaptan and conivaptan effectively prevented heart failure. Tolvaptan also improved cardiac contractility [20]. In a human study, the addition of tolvaptan to standard therapy in the efficacy of vasopressin antagonism in heart failure outcome study with Tolvaptan trial, which included two-thirds of patients with ischemic heart failure, failed to show a beneficial effect on long-term mortality, despite significant beneficial effects on water retention and serum sodium [3]. The tolvaptan use in patients with increased circulating vasopressin leads to excessive stimulation of V1Rs located on cardiac myocytes, causing fibrosis and worsening of heart failure [21]. The outcome of acute decompensated heart failure did not improve with the addition of vasopressin antagonism, natriuretic peptides, or ultrafiltration to the standard diuretic regimen. The addition of the sodium-glucose-cotransporter-2 inhibitor empagliflozin to standard diuretic therapy had beneficial effects without affecting kidney function or injury in the EMPAG-HF study [22]. SGLT2i improves serum sodium levels without the risk of overcorrection in euvolemic and hypervolemic hyponatremia [23]. In the DAPA-HF trial, there was a biphasic sodium response, with a decrease in serum sodium on day 14,

followed by an increasing trend [24]. SGLT2i also causes natriuresis, counteracts sympathetic over activity on proximal tubular sodium absorption, and reduces renin angiotensin aldosterone system activity through more distal delivery. Thus, the neurohumoral mechanism of hyponatremia in acute MI is abated, favoring SGLT2i as a therapy for acute STEMI with persistent hyponatremia at discharge. A limitation of our study is that we did not monitor the discharge serum sodium level, which may have provided an opportunity to start SGLT2i in needed patients.

CONCLUSION

Hyponatremia is common in acute STEMI patients. Elderly individuals are prone to hyponatremia after an acute MI. LV dysfunction is associated with hyponatremia following MI. Hyponatremia improves within 72 h in more than half of patients following MI, particularly in those with mild LV dysfunction. Moderate-to-severe hyponatremia is associated with a high risk of complications. The progression of hyponatremia from mild to moderate within 72 h is associated with poor outcomes.

AUTHOR'S CONTRIBUTIONS

Conceptualization, Design and Data interpretation: Dr Naveen Kumar G, Dr Anandi C, Dr Seenivasn M; Data collection: Dr Naveen Kumar G, Dr Anandi C; Statistical analysis, Manuscript Preparation, Manuscript Editing: Dr Naveen Kumar G, Dr Anandi C, Dr Seenivasn M; Approval: Dr Naveen Kumar G, Dr Anandi C, Dr Seenivasn M.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this research.

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