SODIUM LEVELS AS A PREDICTOR FOR MORTALITY AND MORBIDITY IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND

This study was conducted to determine the usefulness of sodium levels in predicting the mortality and morbidity following acute myocardial infarction.

MATERIALS AND METHODS

Institutional ethics committee approved the study and 177 consenting patients satisfying the inclusion criteria were enrolled. History, demographic, clinical, biochemical, echocardiographic and ECG findings were recorded in semi structured questionnaire. Plasma sodium levels were estimated during admission. Parameters of outcome were death, heart failure, reinfarction, stroke, and arrhythmia which were followed up clinically and by echocardiogram. Data analysis was done by SPSS®. Tests of significance and bivariate logistic regression analysis were done to find out relationship between hyponatraemia and mortality and also the factors which are strongly correlated for the development of hyponatraemia.

RESULTS

Mean age of the study participants was 52.8 years and was predominantly composed of males. Statistically significant mortality was noticed in hyponatraemia (23.3%) when compared with participants with normal sodium levels (12.1%) (OR-2.2; 95% CI 1 - 4.9). Diabetes was more common in hyponatraemia (68.6%) and 49.5% were diabetic among participants with normal sodium levels (OR-2.2; 95% CI 1.2 -4.1). Hypertension was more common in hyponatraemia (60.5%) and 22% were hypertensive among participants with normal sodium levels (OR-5.4; 95% CI 2.8 -10.5). Heart failure was more common among participants with hyponatraemia when compared to those with normal sodium levels (39.5% versus 23%) (OR-2.2; 95% CI 1.1 - 4.2). Ejection fraction <45% was more common in participants with hyponatraemia (53.5%) and in participants without hyponatraemia (15.4%) (OR-6.4; 95% CI 3.1-12.9). Of the 54 participants who had anterior wall myocardial infarction, 41.9% had hyponatraemia on admission and 19.8% having normal sodium levels (OR-2.9; 95% CI 1.5-5.7).

CONCLUSION

The presence of hyponatraemia during admission for acute myocardial infarction is a strong predictor of mortality and heart failure after 60 days of follow up. hyponatraemia is strongly correlated with male sex, diabetes mellitus, hypertension, anterior myocardial infarction.

KEYWORDS

Myocardial infarction, hyponatraemia, diabetes mellitus, hypertension.

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BACKGROUND

Myocardial infarction is a very common cause of mortality and morbidity among all age groups, and is the contributor of mortality of one third of all causes of mortality in patients over 35 years. The terms cardiovascular disease (CVD), coronary artery disease (CAD) and acute coronary syndrome (ACS) has been used interchangeably even though these terms indicate different medical conditions. The term CVD indicates disease of either heart or blood vessels (those supplying vital organs), CAD denotes the atherosclerotic changes in the coronary blood vessels and ACS is a category of CAD which always presents with symptoms.[1] The terms CAD and Coronary heart disease (CHD) can be used interchangeably. Over the past three decades there has been a decline in incidence and prevalence of CVD, CAD and myocardial infarction in developed countries[1] and the incidence and prevalence has been increasing in the same time period in the developing nations.[2] Indian reports suggest an increase in prevalence of coronary heart disease (CHD) from 1% to 9% in urban areas and < 1% to 4% in rural areas.[3] Currently 17 % of the total deaths and 26% of the adult deaths in India are accountable to CHD.[3]

Myocardial infarction is the death of cardiac myocytes due to long standing ischemia to myocardium and occurs

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due to the imbalance between coronary arterial blood flow and oxygen demand of myocardium[4] causing a threat to circulatory homeostasis. After an event of myocardial ischemia, compensatory mechanisms get activated which include an increase in sympathetic tone, increased activity of both circulating and local renin-angiotensin systems (RAAS), and deranged endothelial function causing vasoconstriction in both coronary and systemic blood vessels. Activation of RAAS cause further detrimental effects such as vasoconstriction (arteries and veins) by angiotensin II, sympathetic neurotransmitter release by angiotensin II via action on AT1 receptors in sympathetic autonomic ganglia and aldosterone causing sodium and water retention by its action on collecting tubule. These neuro-humoral mechanisms are activated to cope up with the immediate threat to circulation, which together lead to increase in both preload and afterload. The increased circulating levels of sympathetic neurotransmitters (norepinephrine, epinephrine), angiotensin II and aldosterone determine the magnitude of myocardial damage (replacement of cardiac myocytes with fibroblasts). Cardiac remodeling is a group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury.[5] Remodeling is also influenced by electrolyte disturbances like hyponatraemia and hypokalaemia. There has been contradicting reports of sodium levels in both tissue and serum during an event of acute myocardial infarction. There are previous reports of reduced plasma sodium levels,[6] increase in serum and hair sample sodium[7] and elevated tissue levels of sodium with contrast enhanced Magnetic Resonance imaging (MRI)[8] during an event of acute myocardial infarction. Hence this study is conducted to evaluate the usefulness of sodium levels in predicting the mortality and morbidity such as heart failure, reinfarction and arrhythmia following acute myocardial infarction.

MATERIALS AND METHODS

Our prospective cohort study enrolled 177 participants who were admitted in intensive care units with acute myocardial infarction in Government Medical College Trivandrum during a period of 1 year between 2015 and 2016. Study subjects were those of age < 65 years, having characteristic electrocardiographic (ECG) changes, those with chest pain > 20 minutes and those with Troponin T positivity were included in the study. Participants who were not willing to participate in the study, participants with history of previous myocardial infarction, participants with secondary causes of hyponatraemia were excluded from the study. Sample size was calculated using the formula, $n = (Z\alpha/2)^2 \times PQ/ (d \times d (s + c - 1)^2)$ where P is the proportion of myocardial infarction patients undergoing bad outcome, Q is 100 - P, d is 20% of P, s is the sensitivity of hyponatraemia undergoing bad outcome, c is the specificity of hyponatraemia causing bad outcome. The study commenced after obtaining Institutional Ethics Committee approval (IEC No.: 02/49/2015/MCT) and written informed consent was obtained from all study participants. Data was collected in semi structured proforma after interview with the patient and bystanders. Detailed history, examination findings, 2-D echocardiogram, ECG reports and serum sodium levels were the variables used in the study. Ejection fraction (EF) and regional wall motion abnormality (RWMA) was detected using 2-D echocardiogram. Diagnosis of hyponatraemia was considered when serum sodium levels were <135 meq/L. Each patient was followed up for a period of 60 days and the outcome parameters taken into consideration were death, heart failure, arrhythmia and reinfarction. Patients were followed up clinically and by echocardiogram and ECG. Data was analysed using SPSS software®™ version 15, Chi square test was used to determine the association between parameters and logistic regression was used to determine the viability of using serum sodium as a predictor in myocardial infarction. Odds ratio (OR) and confidence interval (CI) were used to express 2 x 2 tables. All values are rounded off to the nearest decimal point and p value < 0.05 was considered statistically significant.

RESULTS

Our prospective cohort study enrolled 177 participants in the age range of 30 to 65 years. The mean age of the study participants were 52.8 years and maximum proportion of the study participants were in the age group 55 - 60 years (n = 73, 41.2%) followed by 50 - 54 years (n = 52, 29.4%). The age distribution of study participants is demonstrated in table 1. Among the study participants 66.7% (n = 118) were males and 33.3% (n = 59) were females. Among the study participants 48.6% (n = 86) were having hyponatraemia during the course of admission and 17.5% (n = 31) participants expired during the course of the study. We found significant association between gender and hyponatraemia (p = 0.001) and also between diabetes mellitus and hyponatraemia (p = 0.01) which is demonstrated in table 2 and table 3 respectively.

Age (years)	n (%)
< 40	11 (6.2)
40 – 44	4 (2.3)
45 – 49	25 (14.1)
50 – 54	52 (29.4)
55 – 60	73 (41.2)
> 60	12 (6.8)

Table 1. Age Distribution Among Study Participants

Gender	Hyponatraemia		Total
	Yes	No	
Male	68	50	118
Female	18	41	59
Total	91	86	177

Table 2. Association between Gender and hyponatraemia

There was significant association between gender and hyponatraemia (Chi square p = 0.001; OR – 3.1; 95% CI –

1.6 - 6) which indicates a 3.1 higher Odds of male participants to develop hyponatraemia.

Diabetes Mellitus	Hyponatraemia		Total
	Yes	No	
Yes	59	45	104
No	27	46	73
Total	**86**	**91**	**177**

Table 3. Association between Diabetes Mellitus and hyponatraemia

There was significant association between diabetes mellitus and hyponatraemia (Chi square p = 0.01: OR – 2.2; 95% CI – 1.2- 4.1) which indicates a 2.2 higher odds among diabetic participants to develop hyponatraemia.

We found significant association between hypertension and hyponatraemia (p < 0.001), but we did not find any association between smoking and hyponatraemia (p = 0.5), alcoholism and hyponatraemia (p = 0.09) and these are demonstrated in table 4, table 5 and table 6 respectively.

Hypertension	Hyponatraemia		Total
	Yes	No	
Yes	52	20	72
No	34	71	105
Total	**86**	**91**	**177**

Table 4. Association between Hypertension and hyponatraemia

There was significant association between hypertension and hyponatraemia (Chi square p < 0.001: OR – 5.4; 95% CI – 2.8-10.5) which indicates a 5.4 higher Odds among hypertensive participants to develop hyponatraemia.

Smoking	Hyponatraemia		Total
	Yes	No	
Yes	43	50	93
No	43	41	84
Total	**86**	**91**	**177**

Table 5. Association between Smoking and hyponatraemia

No significant association was observed between smoking and hyponatraemia (Chi square p = 0.5: OR – 0.8; 95% CI – 0.5-1.5).

Alcoholism	Hyponatraemia		Total
	Yes	No	
Yes	7	15	93
No	79	76	84
Total	**86**	**91**	**177**

Table 6. Association between Alcoholism and hyponatraemia

No significant association was observed between alcoholism and hyponatraemia (Chi square p = 0.09: OR – 0.8; 95% CI – 0.4-1.2).

We found significant association between ejection fraction and hyponatraemia (p <0.001) when participants were categorized into those with normal ejection fraction and reduced ejection fraction. We did not find any association between hyponatraemia and regional wall motion abnormality (RWMA) (p = 0.4), and between hyponatraemia and reinfarction (p = 0.8). These findings are demonstrated in table 7, table 8 and table 9 respectively.

Ejection Fraction (%)	Hyponatraemia		Total
	Yes	No	
< 45	46	14	93
> 45	40	77	84
Total	**86**	**91**	**177**

Table 7. Association between Ejection Fraction and hyponatraemia

There was significant association between ejection fraction and hyponatraemia (Chi square p < 0.001: OR – 6.3; 95% CI – 3.1-12.9) which indicates a 6.3 higher Odds among participants with EF < 45% to develop hyponatraemia.

RWMA	Hyponatraemia		Total
	Yes	No	
Yes	82	89	93
No	4	2	84
Total	**86**	**91**	**177**

Table 8. Association Between Regional Wall Motion Abnormality (RWMA) and hyponatraemia

No significant association was observed between RWMA and hyponatraemia (Chi square p = 0.4: OR – 0.5; 95% CI – 0.1-2.6).

Reinfarction	Hyponatraemia		Total
	Yes	No	
Yes	4	5	93
No	82	86	84
Total	**86**	**91**	**177**

Table 9. Association between Reinfarction and hyponatraemia

No significant association was observed between reinfarction and hyponatraemia (Chi square p = 0.8: OR – 0.8; 95% CI – 0.2-3.2).

We found significant association between heart failure and hyponatraemia (p = 0.01) but we did not find any association between arrhythmia and hyponatraemia (p = 0.09) and also between mortality and hyponatraemia (p = 0.05) and are demonstrated in table 10, table 11 and table 12 respectively.

Heart Failure	Hyponatraemia		Total
	Yes	No	
Yes	34	21	93
No	52	70	84
Total	**86**	**91**	**177**

Table 10. Association between Heart Failure and hyponatraemia

There was significant association between heart failure and hyponatraemia (Chi square p = 0.01: OR – 2.2; 95% CI – 1.1-4.2) indicating a 2.2 higher Odds of participants with heart failure to develop hyponatraemia.

Arrhythmia	Hyponatraemia		Total
	Yes	No	
Yes	11	5	93
No	75	86	84
Total	**86**	**91**	**177**

Table 11. Association between Arrhythmia and hyponatraemia

No significant association was observed between arrhythmia and hyponatraemia (Chi square p = 0.09: OR – 2.5; 95% CI – 0.8-7.6).

Mortality	Hyponatraemia		Total
	Yes	No	
Yes	20	11	93
No	66	80	84
Total	**86**	**91**	**177**

Table 12. Association between Mortality and hyponatraemia

No significant association was observed between mortality and hyponatraemia (Chi square p = 0.05: OR – 2.2; 95% CI – 0.9-4.9).

We found significant association between territory of infarction and hyponatraemia (p = 0.001)

Location of infarct	Hyponatraemia		Total
	Yes	No	
AW	36	18	93
Others	50	73	84
Total	**86**	**91**	**177**

Table 13

There was significant association between location of infarct and hyponatraemia (Chi square p = 0.001: OR – 2.9; 95% CI – 1.5-5.7) indicating a 2.9 higher Odds among participants with anterior wall myocardial infarction to develop hyponatraemia.

Multivariate analysis of binary logistic regression model for sodium status as dependent variable and the predictors as gender (p = 0.02, OR-2.4; 95% CI – 1.1 - 5.3), diabetes mellitus (p = 0.04, OR-2.2; 95% CI – 1 – 4.5), hypertension (p < 0.001, OR-3.7; 95% CI – 1.8 – 7.6) and Ejection Fraction (p < 0.001, OR-5.4; 95% CI – 2.5 – 11.8).

DISCUSSION

Our study is a prospective cohort study enrolled 177 participants presenting with acute myocardial infarction. The mean age of the participants was ~ 53 years which was higher compared to study from the same setting reported a mean age of ~ 39 years with maximum number of participants in the age groups of 40 – 44 years and 35 to 39 years.[9] Higher proportion of the participants were males (66.7%) which can be explained on the basis of previous reports of men being at high risk of developing myocardial infarction in earlier age groups due to the protective effects of female hormones on the heart preventing any acute coronary events.[10] hyponatraemia was seen ~ 49 % of the study participants, which is higher than previous reports where 12.5% participants were having hyponatraemia with 24 hours of admission and 19.9% within 72 hours of admission.[11] This higher prevalence of hyponatraemia among our study participants could be explained on the basis of higher mean age. As age increases renal function declines and gastrointestinal motility and absorbing capacity reduces leading to increase in urinary excretion of sodium and reduced gastrointestinal absorption predisposing them to hyponatraemia. Males (79.1 %) were predominant among participants with hyponatraemia, this has been previously demonstrated by Chiari Lazzeri et al in their study named usefulness of hyponatraemia in the acute phase of ST elevation myocardial infarction as a marker of severity.[12] Among the study participants, 58.8% were diabetics and 41.2 % were non diabetics which is higher than previous reports of 28% prevalence of diabetes mellitus among patients with acute myocardial infarction.[13] This could be an indicator of the pandemic of diabetes mellitus and other life style diseases among Keralites. Diabetes mellitus has been shown to increase the risk of cardiovascular risk by 2-4 fold and is considered an equivalent risk as previous history of myocardial infarction by increasing the utilization of fatty acids in a setting with hyperglycaemia, endothelial dysfunction, dyslipidaemia, inflammation pro coagulability and impaired fibrionolysis.[14] 68.6 % of the participants with diabetes mellitus were having hyponatraemia which was shown to be significantly associated (p = 0.01). Diabetes mellitus has been known to produce dysnatraemias (both hypo and hypernatremia) via the osmotic properties of glucose leading to movement of fluid from the cell to the vascular compartment leading to haemodilution and subsequent hyponatraemia, uncontrolled diabetes mellitus produce osmotic diuresis and urinary loss producing hyponatraemia, ketoacidosis obligate the urinary loss causing hyponatraemia.[15] 40.7% of the study participants were hypertensives and 59.3% were non hypertensives. Hypertension and myocardial infarction have strong co-relation probably due to the involvement of common factors and pathological processes in both these disease.[16] Overactive sympathetic nervous system, renin angiotensin aldosterone system plays important role in development of hypertension which could lead to peripheral vasoconstriction and increase the preload of the heart predisposing it to infarction. Additionally, hypertension contributes to

irreversible hypertrophy of the ventricles replacing them with areas of non-functioning myocardium predisposing those areas to infarction. Overactive sympathetic nervous system and renin angiotensin aldosterone system cause an increase in heart rate reducing the time for coronary perfusion and thereby predisposing an event of myocardial infarction. 60.5% of the hypertensives were hyponatraemic and we found significant association between hypertension and hyponatraemia (p <0.001). The association between hypertension and hyponatraemia has not been clearly elucidated though evidence for an entity named hypertensive hyponatraemic syndrome has been reported.[17] Though published literature suggest correlation of hyponatraemia and smoking[18] we did not find any significant association between these two (p = 0.5). Chiari Lazzeri et al in their study smoking had no correlation with hyponatraemia.[12] We did not find any association between alcoholism and hyponatraemia. 53.5% of the participants with reduced ejection fraction (<45%) were having hyponatraemia and we found significant association between ejection fraction and hyponatraemia with higher Odds of developing hyponatraemia among participants with reduced ejection fraction. Ejection fraction and hyponatraemia has not been reported to be associated, though hyponatraemia is considered one of the prognostic indicators of longevity and survival in patients with cardiac failure with reduced ejection fraction.[19] Prashant Singhi et al demonstrated that hyponatraemia is strongly associated with mean ejection fraction.[20] We did not find any significant association between regional wall motion abnormality and hyponatraemia. This association has not been clearly described in already existing literature. We also did not find any association between hyponatraemia and reinfarction which was similar to previous reports of no association between hyponatraemia and risk of reinfarction.[21] 39.5% of the hyponatraemic patients developed cardiac failure during 30 days of follow up period and we found significant association between cardiac failure and hyponatraemia (p = 0.01) with 2 times higher odds of developing hyponatraemia among patients who developed cardiac failure. hyponatraemia has been associated with cardiac failure and is considered as a predictor in worsening of cardiac failure.[22] We did not find any significant association between hyponatraemia and cardiac arrhythmia though reports of severe hyponatraemia causing cardiac arrhythmia and severe heart block has been published.[23] No association was observed between hyponatraemia and mortality though reports of association between hyponatraemia and mortality have been published.[24] We found significant association between hyponatraemia and anterior wall myocardial infarction with 2.9 odds of developing hyponatraemia among patients with anterior wall myocardial infarction. hyponatraemia was shown to be significantly associated with severity, progression and outcome of myocardial infarction[25] however the association between anterior wall myocardial infarction and hyponatraemia has not been completely elucidated which requires further studies to clearly find out the association.

Logistic regression of parameters with sodium status as dependent variable and other parameters as predictors showed significant association between hyponatraemia and gender (p = 0.022; OR: 2.4, 95% CI – 1.1-5.3) indicating a 2.4 higher Odds of male participants to develop hyponatraemia, hyponatraemia and diabetes mellitus (p = 0.04; OR: 2.2, 95% CI – 1.1 - 4.5) indicating a 2.2 higher Odds among diabetic participants to develop hyponatraemia, hyponatraemia and hypertension (p < 0.001; OR: 3.7, 95% CI – 1.8 – 7.6) indicating a 3.7 higher Odds among hypertensives to develop hyponatraemia, hyponatraemia and ejection fraction (p < 0.001; OR: 5.4, 95% CI – 2.5 – 11.8) indicating a 5.4 higher Odds among participants with reduced ejection fraction to develop hyponatraemia.

CONCLUSION

The presence of hyponatraemia during admission for acute myocardial infarction is a strong independent predictor of mortality after 60 days of follow up. It is also an independent predictor of heart failure. Male gender, diabetes mellitus, hypertension, low ejection fraction are strongly associated with development of hyponatraemia.

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