PROGNOSTIC IMPORTANCE OF HYPONATRAEMIA IN ACUTE ST-ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND

In patients with heart failure, hyponatraemia has been shown to be a predictor of cardiovascular mortality. In fact, the neurohormonal activation that accompanies acute myocardial infarction is similar to that which accompanies heart failure. Hence, we aimed to investigate the prognostic importance of hyponatraemia in the setting of acute ST-elevation MI and to determine its usefulness in predicting short-term survival.

MATERIALS AND METHODS

This is a prospective observational study of 100 patients presenting with acute ST-elevation myocardial infarction admitted in ICCU, Department of Medicine, KIMS, Hubli, during the period of 1st December 2009 to 30th November 2010 were studied. Detailed history and clinical examination has been done. Plasma sodium concentrations were taken on admission and at 24, 48 and 72 hours thereafter. The primary end point has been taken as mortality within 30 days following myocardial infarction.

RESULTS

In this study, significant proportion of patients who presented with acute ST-elevation myocardial infarction were having hyponatraemia at time of admission or developed hyponatraemia after admission. The odd's ratio for 30-day mortality was found to be high in the hyponatraemic groups compared to normal group. There was a significant linear relationship between severity of hyponatraemia and mortality. Multivariate analysis was done, which showed hyponatraemia on admission or early development of hyponatraemia as a significant independent predictor of 30-day mortality.

CONCLUSION

In this study, we concluded that presence of hyponatraemia on admission or early development of hyponatraemia in patients with acute ST-elevation myocardial infarction is an independent predictor of 30-day mortality. Plasma sodium levels may serve as a simple marker to identify patients at risk.

KEYWORDS

Acute Myocardial Infarction, Hyponatraemia.

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BACKGROUND

Myocardial infarction is one of the most fatal diseases that may strike any individual during the most productive years and can have profound deleterious, psychological and economic ramifications.

Despite impressive studies in the diagnosis and management over the past 4 decades, acute MI continues to be a major public health problem in the industrialised world and is becoming an increasingly important problem in developing countries. With the decline in infectious disease related death accompanied by accelerated economic development and lifestyle change promoting atherosclerosis, developing countries especially India are expected to experience a sharp increase in ischaemic heart disease and AMI.

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Given the wide disparity of available resources to treat AMI in developing countries, major efforts are needed to strengthen primary prevention programmes at community level.[1]

Hyponatraemia is one of the common electrolyte disorder amongst hospitalised patients,[2] more so in postoperative period[3] and in patients with heart failure, nephrotic syndrome or cirrhosis.[4,5] In patients with heart failure, hyponatraemia has been shown to be a predictor of cardiovascular mortality.[6,7] Neurohormonal activation that occurs in acute myocardial infarction is similar to that which occurs in heart failure.[8] Hyponatraemia happens frequently after MI and clinical improvement happens by rise in plasma sodium concentration.[9]

However, while the prognostic value in hyponatraemia in chronic heart failure is well established,[10,11] data on the prognostic importance of hyponatraemia in the setting of acute myocardial infarction are lacking.

This study was done to determine the prognostic importance of hyponatraemia in the setting of acute ST-elevation MI and to determine its usefulness in predicting short-term survival.

Aims and Objectives

1. To find out the incidence of hyponatraemia in acute ST-elevation myocardial infarction.

2. To find out the prognostic importance of hyponatraemia in acute ST-elevation myocardial infarction.

Review of Literature

Several systemic metabolic changes have been reported following acute myocardial infarction in man. These are increased plasma concentration of catecholamine, cortisol, glucose, glycerol and cyclic adenosine phosphate, decreased triglyceride concentrations and initial fall in plasma insulin concentration followed by early return to normal values. Flear CT and Hilton P in their study of 235 consecutive patients admitted to a coronary care unit have concluded that hyponatraemia, hypochloraemia and uraemia were common in patients with confirmed myocardial infarctions and the degree of infarctions correlating well with all the above indices of severity. They also found higher in-hospital mortality rates among patients with minimal plasma sodium levels < 130 mmol/L.[9]

Hyponatraemia is common after infarction and clinical improvement is accompanied by a rise in the plasma sodium concentration. These findings are similar to the systemic biochemical changes that occur after injury. Hyponatraemia occurs more often and is more pronounced in patients who die in hospital than in others. It is an epiphenomenon and should not be treated directly with, for example saline. A low plasma sodium concentration is more appropriate to circumstances attending infarction than a so-called normal concentration would be. Hypoxia and ischaemia increase the permeability of sarcolemma to sodium- for example, Flear et al found a considerable increase in sodium permeability during elective ischaemic anoxic arrest during heart surgery.

A reduction in the plasma sodium concentration reduces the influx of sodium into cells and so limits the resultant increase in energy expenditure on sodium pump activity. It also lessens the likelihood of imbalance in transmembrane sodium exchanges and net sodium accumulation. Accumulation of sodium by myocardial cells reduces diastolic membrane potentials, impairs contraction and relaxation, and impairs or abolishes electrical coupling between cells, and in-vitro evidence attests that the heart withstands anoxia better when the sodium concentration in the medium is reduced and that an increase in fibre sodium depresses contraction when active sodium efflux is depressed.[9]

In acute myocardial infarction, non-osmotic release of vasopressin may occur due to the acute development of left ventricular dysfunction in response to pain, nausea and major stress, the most common mechanism of hyponatraemia in adults or in response to the administration of analgesics and diuretics.[12,13] In this setting, vasopressin levels increase concomitantly with the activation of other neurohormones such as renin and norepinephrine. However, vasopressin level does not correlate with serum osmolarity in myocardial infarction, suggesting that non-osmotic mechanisms are involved.[14] Activation of carotid baroreceptors has been implicated in the non-osmotic release of vasopressin due to arterial underfilling.[15] In addition, increased expression of messenger RNA for vasopressin in the hypothalamus has been described. Moreover, the renal effect of vasopressin is enhanced in heart failure, as the vasopressin-regulated water in the collecting duct is upregulated.[16]

In patients with myocardial infarction, hyponatraemia may be aggravated further by the concomitant activation of the renin-angiotensin system and increased catecholamine production.[17,18] These factors decrease the glomerular filtration rate and subsequent delivery of tubular fluid to the diluting segment of the nephron, further contributing to decreased renal water excretion.[19]

Szatalowicz VL, Arnold PE, Chaimotivz C, Bichet D, Berl T and Schrier RW- Their study has shown that Vasopressin is essential for the development of hyponatraemia and arginine vasopressin levels were detectable in 30 of 37 patients with congestive heart failure. They also found that the degree of neurohormonal activation correlates with the severity of hyponatraemia in patients with chronic heart failure.[20]

Sigurdsson A, Held P and Swedberg K in their study of 55 patients with acute myocardial infarction concluded that sustained neurohormonal activation after myocardial infarction mainly occurs in patients with clinical heart failure and is related to the magnitude of myocardial damage even in patients without heart failure.[8]

Goldberg A et al in their study of 978 patients have concluded that early hyponatraemia is a simple marker of neurohormonal activation during the acute phase of myocardial infarction and predicts the long-term development of heart failure and death.[21]

Rouleau JL et al in their study of 534 patients have concluded that neurohormonal activation at the time of hospital discharge in post infarction patients is an independent sign of poor prognosis.[22]

M Aziz, M Ullah, MG Azam and M Hossain concluded that Hyponatraemia on admission in patients with acute ST-Elevation MI is a strong independent predictor of prognosis. Plasma sodium levels may serve as a simple marker to identify patient at high risk.[23]

MATERIALS AND METHODS

Source of Data

This is a prospective observational study of 100 patients presenting with acute ST-elevation myocardial infarction admitted in ICC, Department of Medicine, KIMS, Hubli, during the period of 1st December 2009 to 30th November 2010 were studied.

Goldberg A, Hammerman H, Petcherski S, Zdorovyak A, Yalonetsky S, Kapeliovich M et al in their study at Rambam Medical Center and Rappaport Medical School, Haifa, Israel have shown incidence rates of hyponatraemia in acute ST-elevation myocardial infarction as 32%, that is out of 1047 cases 339 had developed hyponatraemia during their study.[24]

With incidence rate 32% and allowable error 30%, sample size i.e.

n= 94 ($n= 4pq/L^2$), where p= incidence rate

q= 1-p

L= Allowable error

Method of Collection of Data

The study was carried out on patients presenting with acute ST-elevation myocardial infarction.

Inclusion Criteria

All acute myocardial infarction patients having

a) Chest pain lasting more than 20 minutes.

b) Diagnostic ECG changes with characteristic ECG alterations consisting of new pathological Q-waves or ST segment and T-wave changes.

Qualifying patients underwent detailed history and clinical examination. Patients of acute myocardial infarction received thrombolytic therapy (tissue-type plasminogen activator or streptokinase). Plasma sodium concentrations were obtained on admission and at 24, 48 and 72 hours thereafter.

Study End Points and Definitions

The primary end point was all-cause mortality within 30 days following myocardial infarction. Mortality data after discharge but within 30 days of myocardial infarction were obtained by personal attendance or by phone or postcard returned by patients or their families. When no postcard was received, follow-up status was determined over telephone or visit to their house whichever possible.

Plasma sodium concentrations were determined by using an ion selective electrode autoanalyzer (Roche Omni C).

Hyponatraemia was defined as sodium level less than 135mmol/L (< 135 mEq/L).

Statistical Method

1. Odd ratio.
2. Confidence interval.
3. Mean + standard deviation.
4. Suitable parametric and non-parametric tests (Chi-square test for non-continuous variables, Analysis of variance for continuous variables, Z test etc.).
5. Univariate and multivariate logistic regression tests to determine the association between hyponatraemia and 30-day mortality.

RESULTS

Age Distribution

- The youngest age was 30 years.
- The eldest age was 85 years.

The maximum number of patients were in the age group of 51 – 60, which is 35% of the cases and next highest numbers of patients were found in the age group of 61 - 70 (27%). Mean age of presentation was 59.77 ± 12.23 years.

Sex Distribution

Among 100 patients studied, 80% were Males and 20% were Females. In this study, ratio is M: F= 4: 1

Risk Factors	Normal Sodium Levels	Hyponatraemia on Admission	Hyponatraemia within 72 Hours
Diabetes	9(12.6%)	3(27.5%)	8(44.45%)
Smoking	50(70%)	9(81%)	11(61%)
Hypertension	14(5.6%)	2(18.18%)	4(22.22%)

Table 1. Showing prevalence of Risk Factors among Patients with Normal and Decreased Sodium Levels

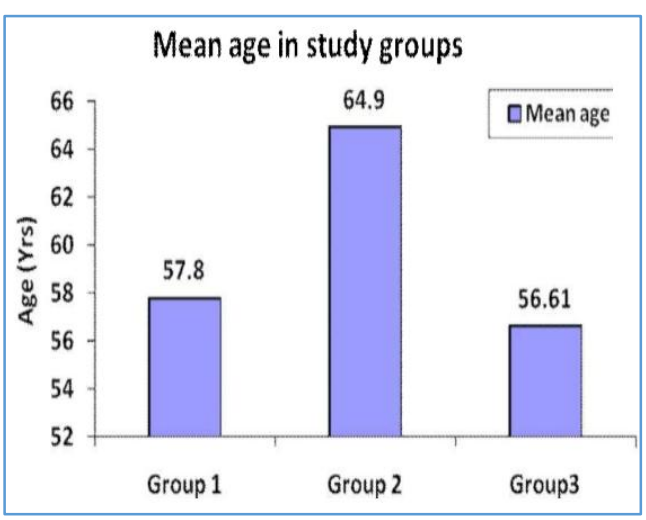
Patients who presented with or developed hyponatraemia more often were smokers (81%), had diabetes (44%) and were known hypertensives (22.22%) when compared to patients with normal sodium levels.

Characteristics	Normal Sodium Level (n= 71)	Hyponatraemia on Admission (n= 11)	Hyponatraemia within 72 hrs. (n= 18)	P value
	Mean ± SD, Number (%) or Median			
Age (yrs.)	57.8 ± 11.7	64.9 ± 13.1	56.61 ± 11.54	F=1.97 P=0.145
Male Sex	57 (71)	9 (81)	14 (77)	X^2=0.082 p=0.962
Diabetes	9 (12.6)	3 (27.5)	8 (44.45)	X^2=9.466 p=0.009
Smoking	50 (70)	9 (81)	11 (61)	X^2=4.938 p=0.0085
Hyper tension	14 (5.6)	2 (18.18)	4 (22.22)	X^2=0.082 p=0.960
Anterior Infarction	45 (63)	8 (72)	15 (83)	X^2=2.754 p=0.252
Killip Class	1.06 ± 0.23	1.18 ± 0.40	1.06 ± 0.24	F=1.18 p=0.312
Ejection Fraction (%)	44.63 ± 11.19	40.36 ± 6.14	50.11 ± 13.26	F=2.86 p=0.06

Table 2. Showing Baseline Characteristics of 100 Patients

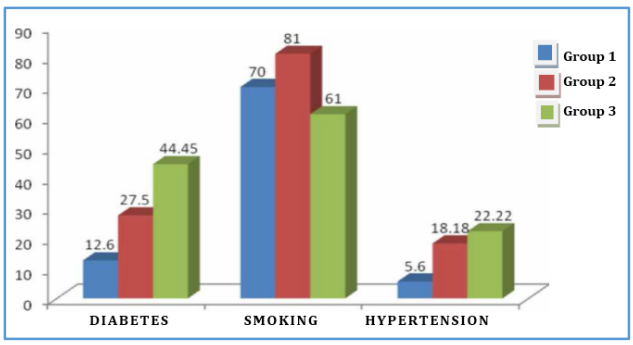
Patients presented with hyponatraemia on admission were older than patients with normal sodium levels. Males made up 81% of patients who presented with hyponatraemia on admission and 77% of patients who developed hyponatraemia within 72 hours.

Patients who presented with hyponatraemia also had higher incidence of anterior infarction (72 and 83%), higher Killip class, lower ejection fraction (40.36 ± 6.14) compared to patients with normal sodium levels.



Graph 1

Group 1= Patients with normal sodium levels; Group 2= Hyponatraemia on admission; Group 3= Hyponatraemia within 72 hours.



Graph 2. Distribution of Patients with Normal Sodium Levels, Hyponatraemia on admission and Hyponatraemia within 72 hrs. among Diabetics, Hypertensives and Smokers

Group 1= Patients with normal sodium levels.
Group 2= Hyponatraemia on admission.
Group 3= Hyponatraemia within 72 hours.

	Normal Sodium Levels	Decreased Sodium Levels	Total
No. of Patients	71	29	100
Mortality in each group at the end of 30 days	2	6	8
Percentage of Patients	2.817	20.69	8

Table 3. Showing Mortality at the end of 30 days among Patients with Normal and Decreased Sodium Levels

Among the patients who presented with normal sodium levels, mortality at the end of 30 days was 2 when compared to 6 in patients with decreased sodium levels and 8 as a total.

But in terms of percentage of deaths in each group at the end of 30 days, patients in the group of decreased sodium levels had a significantly high percentage (20.69) of deaths when compared to patients with normal sodium levels (2.817) and total (8).

	Decreased Sodium Levels	Hypo natraemia On Admission	Hypo natraemia within 72 Hours
No. of Patients	29	11	18
Mortality in each group at the end of 30 days	6	3	3
Percentage of Patients	20.69	27.273	16.667

Table 4. Showing Patients with Hyponatraemia on admission and at 72 hours and outcome in Terms of Mortality

Patients who presented with decreased sodium levels had 6 deaths among 29 patients (20.69%), patients with hyponatraemia on admission had lightly higher percentage (27.273%) with 3 deaths among 11 patients and patients with hyponatraemia within 72 hours had 3 deaths among 18 patients (16.667%).

	Normal Sodium Levels	Hypo natraemia On Admission	Hypo natraemia within 72 Hours	Total
No. of Patients	71	11	18	100
Mortality in each group at the end of 30 days	2	3	3	8
Percentage of Patients	2.817	27.273	16.667	8

Table 5. Showing comparison between Patients with Normal Sodium Levels, Hyponatraemia on admission and at 72 hours and outcome in Terms of Mortality

Patients presenting with hyponatraemia on admission had high percentage of deaths (27.273) when compared to patients presenting with hyponatraemia after 72 hours (16.667) and patients presenting with normal sodium levels (2.817).

Range of Sodium Levels in Hyponatraemia Patients (mmol/L)	No. of Patients	Mortality
<130	3	3 (100%)
131-134	26	3 (11.11%)

Table 6. Showing Severity of Hyponatraemia and outcome in terms of Mortality

Severity of hyponatraemia correlated well with the mortality, total of three patients had sodium levels less than 130 mmol/L and all the three died when compared to 3 deaths among 26 patients with sodium levels between 131 - 134 mmol/L.

Odds Ratio for 30-Day Mortality
Group 1 versus Other Groups

	Survivors	Non-Survivors	Odds Ratio	P value
Group 1	69	2		
Group 2	8	3	5.03	0.01
Group 3	15	3	6.9	0.02

Table 7

Group 1= patients with normal sodium levels; Group 2= Hyponatraemia on admission; Group 3= Hyponatraemia within 72 hours.

Odds ratio for 30-day mortality was found to be high in hyponatraemic groups (Group 2= 5.03, Group 3= 6.9).

	Survivors	Non-Survivors	T or ^{x}	P value
n	92	8		
Age (yrs.) (mean ± SD)	57.7 ±12.1	65.5 ± 7.58	2.63	0.025
Sex M/ F	76 (82%) 16 (18%)	4 (50%) 4 (50%)	4.89	0.027
Hyponatraemia (mean ± SD)	136.96 ± 1.92	134.09 ± 3.53	2.27	0.057
Smoking	66 (72%)	4 (50%)	1.65	0.198
Diabetes	16 (17%)	4 (50%)	4.891	0.027
Hypertension	16 (17%)	4 (50%)	4.891	0.027
Infarct Site Anterior Inferior	63 (68%) 29 (32%)	5 (63%) 3 (37%)	0.002	>0.05

Killip Class I II	88 (95%) 4 (5%)	5 (63%) 3 (37%)	12.426	0.001
EF (%) (Mean±SD)	47.7 ± 12.7	38.6 ± 10.9	2.24	0.05

Table 8. Survivors and Non-Survivors were also compared for Various Factors

It was seen that serum sodium levels were statistically significant in determining mortality. Mean serum sodium level was 136.96 ± 1.92 in the survivors and 134.09 ± 3.53 in non-survivors.

Other factors such as Killip class, hypertension, diabetes, age and sex were found to be statistically significant in determining mortality.

Multivariate analysis is the best way to summarise a data tables with many variables by creating a few new variables containing most of the information. These new variables are then used for problem solving and display that is classification, relationships, control charts and more.

Logistic regression analysis (LRA) extends the techniques of multiple regression analysis to research situations, in which the outcome variable is categorical. In practice, situations involving categorical outcomes are quite common. In the setting of evaluating an educational program, for example, predictions may be made for the dichotomous outcome of success/ failure or improved/ not improved. Similarly, in a medical setting, an outcome might be presence/ absence of disease. The focus of this document is on situations in which the outcome variable is dichotomous, although extension of the techniques of LRA to outcomes with three or more categories (e.g. improved, same or worse) is also possible.

Multivariate analysis using logistic regression analysis was performed including variables that had 'p' value < 0.2 in the univariate analysis to identify the variables that were independently associated with 30-day mortality.

Variable	P value
Age	0.025
Sex	0.027
Smoking	0.198
Hypertension	0.027
Diabetes	0.027
Killip Class	0.001
Hyponatraemia	0.057
Ejection Fraction	0.05

Table 9

So multivariate analysis showed that along with other risk factors, hyponatraemia was the significant independent predictor of 30-day mortality.

DISCUSSION

Our study suggests that patients presenting with acute myocardial infarction who had hyponatraemia on admission or developed hyponatraemia after admission represent high-risk population.

In our study, substantial proportion of patients who presented with acute ST-elevation myocardial infarction were hyponatraemic on admission or developed hyponatraemia shortly after admission. In our study, hyponatraemia was present on admission in 11 patients (11%). Hyponatraemia developed in 18 patients (18%) during the first 72 hours of hospitalisation. In a similar study conducted by Goldberg[24] et al, hyponatraemia was present in 131 patients (12.5%) and hyponatraemia developed in 208 (19.9%) during the first 72 hours of hospitalisation.

Patients who presented or developed hyponatraemia more often had diabetes, anterior infarction and higher Killip class and lower ejection fraction. This is in accordance to the study conducted by Goldberg[24] et al.

In our study, a total of 8 deaths (8%) occurred within 30 days of admission. 2.8% (2/71) of patients without hyponatraemia, 27.5% (3/11) of patients with hyponatraemia on admission, 16.67% (3/18) of patients who developed hyponatraemia after admission.

In study done by Goldberg[24] et al, a total of 105 deaths (10%) occurred within 30 days of admission. 6.2% (44/708) of patients without hyponatraemia, 19.8% (26/131) of patients with hyponatraemia on admission and 16.8% (35/208) of patients who developed hyponatraemia after admission.

In comparison with the above study our study had higher mortality in patients with hyponatraemia on admission, whereas mortality was almost equal in patients who developed hyponatraemia after admission.

In our study, odd's ratio for 30-day mortality in patients with hyponatraemia on admission and patients who developed hyponatraemia was high (5.03 and 6.9). This was in concordance with study done by Golderg[24] et al.

In our study, we found a trend of increasing mortality with the severity of hyponatraemia. We stratified patients into two groups depending on the mean sodium level. The group with sodium level < 130 mmol/L had 100% mortality and those with serum sodium in the range of 131 - 134 mmol/L suffered 12% deaths. This was in concordance with the study conducted by Goldberg[24] et al, who showed increasing mortality with severity of hyponatraemia.

When we compared the various risk factors and outcomes among the survivors and the non-survivors, we found apart from age, sex, diabetes, hypertension, Killip class on admission, ejection fraction hyponatraemia was the significant risk factor in determining mortality. All the variables among the survivors and non-survivors that were significantly associated with mortality were included in the multivariate logistic regression analysis. Hyponatraemia remained a significant independent predictor of mortality. This is in concordance to similar study conducted by Goldberg[24] et al. They found that hyponatraemia was independently associated with 30-day mortality.

In a similar study of 235 patients admitted to a coronary care unit, Flear[9] et al found higher in-hospital mortality rates among patients with minimal plasma sodium levels < 130 mmol/L.

Thus, Goldberg[24] et al concluded in their study that the development of hyponatraemia is a marker that most likely incorporates different prognostic entities including the severity of the left ventricular dysfunction, haemodynamic alterations and the extent of neurohumoral activation.

Hence, in our study we concluded that hyponatraemia on admission or early development of hyponatraemia in patients with acute ST-elevation MI is an independent predictor of 30-day mortality.

Summary

Hyponatraemia is one of the predictor of cardiovascular mortality in patients with heart failure. In fact, the neurohormonal activation that accompanies acute myocardial infarction is similar to that which accompanies heart failure. Hence, we aimed to investigate the prognostic importance of hyponatraemia in the setting of acute ST-elevation MI and to determine its usefulness in predicting short-term survival.

In our study, substantial proportion of patients who presented with acute ST-elevation myocardial infarction were hyponatraemic on admission or developed hyponatraemia shortly after admission. The odd's ratio for 30-day mortality was found to be high in the hyponatraemic groups compared to normal group. We also found a significant linear relationship between severity of hyponatraemia and mortality.

Univariate analysis of the several variables among survivors and non-survivors identified hyponatraemia as significant risk factor in determining mortality. Other factors like Killip class on admission, age, sex, diabetes, hypertension, ejection fraction were also found to play a significant role in mortality.

Multivariate analysis was performed which identified hyponatraemia on admission or early development of hyponatraemia as a significant independent predictor of 30-day mortality.

CONCLUSION

In our study, we concluded that hyponatraemia on admission or early development of hyponatraemia in patients with acute ST-elevation myocardial infarction is an independent predictor of 30-day mortality. Plasma sodium levels may serve as a simple marker to identify patients at risk.

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