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Original Research Article

HYPONATREMIA: A PROGNOSTIC INDICATOR IN PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

BACKGROUND-
Coronary artery disease is the leading cause of mortality globallyaccounting for roughly 7 million deaths.(1) The 30 day outcome in STEMI were 9% death, 23% reinfarct, 0.8%shock. In non ST-segment elevation myocardial infarction 30 day outcome was 3.7% mortality, 1.2% reinfarct, 0.3% shock.(2) Hyponaetremia is common after myocardialinfarction(MI), and clinical improvement is accompanied by a rise in plasma sodiumconcentration. However, prognostic value of Hyponaetremia in chronic heart failure is well established , but on the prevalence and prognostic importance of hyponatremia in the setting of acute myocardial infarction are lacking.

AIM-To study the prevalence of hyponaetremia in patients with Acute coronary syndromes and also analyse prognostic values of hyponaetremia in patients with Acute Coronary Syndromes.

METHODS-Cross sectional prospective study of 75 patients with Acute Coronary Syndromes (ACS) ,admitted in ICU of a super specialty hospital in central India, over a period of 1 year between June 2022to May2023. Study design is single centered, prospective, follow up study.

RESULTS-Age ≥ 65 Years, EF < 40%, hyponatremia at admission, Hyponaetremia at 48hours, hyponatremia at discharge, elevated troponin 'T' and Killip classification ≥ 2 aresignificantandstrongindependentriskfactorsforpredictingdeathinpatientsdiagnosedacutecoronarysyndrome.

So we find out that patients diagnosed of acute coronary syndrome have 3-5 times morechancesof death ifone oftheaboveindependentpredictorvariablealsooccurs.

CONCLUSION-Thus hyponatremiaat admission or early development is a independent marker for predicting short term mortality in ACS.

Keywords- hyponatremia, ACS, short-term mortality, prognostic factor

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1. INTRODUCTION

Coronary artery disease is the leading cause of mortality globally accounting for roughly 7 million annually. India has the greatest burden of Acute Coronary syndromes in the world.(1) Indian patients with ACS usually have higher incidence of ST-segment elevation myocardial infarction (61%) than patients in high income countries(20%).(2)
The 30 day outcome in STEMI were 9% death, 23% reinfarct, 0.8% shock. In non ST-segment elevation myocardial infarction 30 day outcome was 3.7% mortality, 1.2% reinfarct, 0.3% shock.(2) Hyponatremia has been shown to be a predictor of cardiovascular mortality among patients with heart failure.(3)(4) In fact, the neurohumoral activation that accompanies acute myocardial infarction is similar to that which accompanies heart failure.(5)

Hyponatremia is common after myocardial infarction (MI), and clinical improvement is accompanied by a rise in plasma sodium concentration . However, while the prognostic value of hyponatremia in chronic heart failure is well established, but data on the prevalence and prognostic importance of hyponatremia in the setting of acute myocardial infarction are lacking.(6) Hence we done a study to determine the prognostic significance of hyponatremia in the setting of Acute coronary syndrome and to determine its usefulness in predicting short term mortality (30 day outcome).(7)

Coronary artery disease is the leading cause of mortality and morbidity in the world and Acute coronary syndromes (ACS), which encompass Unstable Angina(UA), Non-ST segment elevation myocardial infarction, ST-segment elevation myocardial infarction, are the commonest causes of mortality in Coronary artery disease. ACS in Indians occurs 5-10 years earlier than in other populations around the world and the major effect is on the productive workforce of the country aged 35-65 years. India has the highest burden of ACS in the world.
The rising incidence of ACS in Indians (12)(15) may be because of lifestyle modifications, western food practices, increasing incidence of Diabetes mellitus and probably genetic factors too. Asian Indians, usually have higher incidence of coronary artery disease in comparison to other ethnic groups. Coronary artery disease in Asian Indians tends to be more severe and is associated with serious complications and also increased mortality at a much younger age.

HYPONATREMIA

Hyponatremia, which is defined as a plasma sodium concentration of less than 135 mmol per liter, is the most common electrolyte abnormality in hospitalized patients; it affects approximately 15 to 30% of children and adults who are hospitalized.(8)(9)(16)

PSEUDO HYPONATREMIA

Gross elevation in plasma lipids or proteins increase the plasma volume and can cause reduction in the measured plasma sodium concentration. The hyponatremia in this situation does not present a decrease in extra cellular sodium relative to extra cellular water.(10)(11)(12)(17)(18)

Hyponatremia with normal plasma osmolality is seen in

Hyperlipidemia
Hyperproteinaemia
Post TURP
Increased plasma osmolality

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Hyperglycemia
Mannitol

Hyponatremia is sub divided as:
1. Hypovolemic
2. Euvolemic
3. Hypervolemic

1. HYPOVOLEMIC HYPONATREMIA:
It can be divided as
(A) Urinary sodium > 20mmol/l -renal loss
(B) Urinary sodium<20mmol/l-extra renal loss

(A) Renal loss: Causes:
Diuretic excess
Salt losing nephropathy
Mineralo-corticoid deficiency
Osmotic diuresis
Cerebral salt wasting
Bicarbonate urea with Renal tubular acidosis and metabolic alkalosis

(B) Extra renal loss: Causes:
Vomiting
Diarrhea

2. EUVOLEMIC HYPONATREMIA:
Euvolemic hyonatremia is associated with increased total body water but total body sodium is normal and no edema.

Causes:
Gluco corticoid deficiency
Hypothroidism
Psychosis
Post operativehyponatremia
Exercise induced hyponatremia
Drugs- Thiazide diuretics, Selective Serotonin Reuptake Inhibitors (SSRI`s), Desmopressin, IV Ig.
Syndrome of inappropriate ADH secretion (SIADH)

3. HYPERVOLEMIC HYPONATREMIA.
(A)Urinary sodium < 20mmol/l occurs in,
CHF, Liver cirrhosis, NS

(B)Urinary sodium > 20mmol/l ,
AKI or CRF.

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CLINICAL FEATURES

Most patients with serum sodium concentration > 125mmol/l are asymptomatic.
When sodium concentration is < 125 mmol/l there is, Headache, Yawning, Lethargy, Nausea, Reversible ataxia, Psychosis, Seizures, Coma

AIMS OF THE STUDY

To study the prevalence of hyponaetremia in patients with Acute coronary syndromes.
To analyse prognostic significance of hyponaetremia in patients with Acute Coronary Syndromes.
To access usefulness of hyponaetremia in predicting short term mortality.

2. MATERIALS AND METHODS

Cross sectional prospective study of 75 patients with Acute Coronary Syndromes (ACS), admitted in ICU of a super speciality hospital in central india, over a period of 1 year between June 2022to May2023. Studydesign is single centered , prospective , follow up study .

DIAGNOSIS OF STEMI:

Chest pain more than 20 minutes duration

ST segment elevation > 1mm in 2 standard limb leads (or) >2mm in 2 contiguous precordial leads (or) new onset LBBB (and/or) elevated serum cardiac biomarkers.

Inclusion criteria:

Patients presented within 12 hours of symptoms with ECG evidence of STEMI, end STEMI or UA were included in our study.

Exclusion criteria:

People with previous history of CAD, Arrythmias, Cardiomyopathy or heart failure
People with previous diuretic use
People with Cirrhosis of liver, Hypothyroidism, Renal disease
Patients with creatinine >2mg/dl, urea>60mg/dl
Patients who were not willing to participate were voluntarily excluded

Definition of the location of infarct:

Antro septal MI: When ST elevation is seen in V1-V4.

Antro lateral MI: When ST elevation is seen in L1, avL, V4-V6. Extensive anterior wall MI: When ST elevation is seen in I, aVL, V1-V6.

Inferior wall MI: When ST elevation is seen in LII, III, aVF.

Right ventricular wall MI: When ST elevation is seen V3R, V4R.

Posterior wall MI: when there is tall and wide R wave, depressed and concave upwards ST, widened and upright T wave in V2.

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Participating patient's baseline data like age, gender, risk factors were recorded. Pulse, Blood pressure, JVP of the patient were recorded. Twelve lead ECG for all patients was taken. Leads V3R, V4R, V7, V8, V9 were taken if the patient had inferior wall MI.

Cardiovascular and Respiratory system findings were recorded.(13) Lab investigations - blood sugar, renal function test and electrolytes were done for all participating patients at admission. Lipid profile and chest X-ray were done for the participating patients before discharge. Plasma sodium concentration of the participating patients were obtained during admission at 48 hours and at discharge.

All patients were treated in accordance to AHA/ACC guidelines as required. Hemodynamic status of the patients were monitored at regular intervals clinically. Ejection fraction and regional wall motion abnormalities were analysed with echocardiogram. After discharge the participating patients were followed up weekly for 30 days. Morbidity data and mortality data were recorded.

The primary end point of the study was mortality within 30 days of acute coronary syndrome.

MEASUREMENT OF SERUM SODIUM:
Plasma sodium concentration was measured by using an ISE (Ion Selective Electrode). Hyponatremia was considered as sodium < 135mmol/l.(14)

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$.

3. RESULT

Table 1: distribution of patients according to sodium concentration

Groups	Definition of subjects	Number
Hyponatremia	Blood sodium < 135mEq/L	9
Normonatremia	Blood sodium >135mEq/L	66

Table 2: Age Distribution

Age	Hyponatremia	Normonatremia	Combined	Hyponatremia %	Normonatremia %	Combined %
≤ 40 years	1	19	20	11.11	28.79	26.67

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41-50 years	3	21	24	33.33	31.82	32.00
51-60 years	3	12	15	33.33	18.18	20.00
61-70 years	2	11	13	22.22	16.67	17.33
71-80 years	0	3	3	0.00	4.55	4.00
Total	9	66	75	100	100	100

Table 3: statistical analysis of age distribution

Age Distribution	Hyponatremia	Normonatremia	Combined
Mean	54.44	48.95	49.61
SD	10.04	11.77	11.63
P value Unpaired t Test		0.1853	

Among the study patients, there was no statistically significant difference in relation to age distribution between Hyponatremia group (mean=54.44, SD=10.04) and Normonatremia group (mean=48.95, SD=11.77) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in age distribution between the study groups. The mean age in our study is 49.61+/- 11.63, while in study of Goldberg et. al.(27) it was 61+/-12. Hence Indians are prone to get MI at an younger age.

Table 4: Gender Distribution

Gender	Hyponatremia	Normonatremia	Combined	Hyponatremia%	Normonatremia%	Combined%
Male	4	44	48	44.44	66.67	64.00

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Female	5	22	27	55.56	33.33	36.00
Total	9	66	75	100	100	100
P value Fishers Exact test			0.1935			

Among the study patients, there was no statistically significant difference in relation to gender status between Hyponatremia group (majority are females – 55.56%) and Normonatremia group (majority are males – 66.67%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in gender status between the study groups.

Table 5: Sodium concentration at different time period of hospitalisation

Blood Sodium Levels		Na^+ at Admission (mg/dl)	Na^+ at 48 hours (mg/dl)	Na^+ at Discharge (mg/dl)
Hyponatremia	Mean	131.11	132.67	131.78
	SD	2.80	2.87	3.56
Normonatremia	Mean	137.71	138.03	138.68
	SD	1.48	2.64	2.68
P value Unpaired t Test		<0.0001	<0.0001	<0.0001

SODIUM CONCENTRATION AT ADMISSION

Among the study patients, there was a statistically significant difference in relation to Na^+ at Admission distribution between Hyponatremia group (mean=131.11, SD=2.80) and Normonatremia group (mean=137.71, SD=1.48) with a p value of <0.05 as per unpaired t test. Therefore we reject the null hypothesis that there is no difference in Na^+ at Admission distribution between the study groups. The mean Na^+ at Admission was significantly less in Hyponatremia group compared to Normonatremia group by a mean difference of 6.60 mg/dl (5% lower). This difference is significant with a p-value of <0.0001 as per unpaired t test.

In this study we can safely conclude that a significantly decreased Na^+ at Admission is associated with Hyponatremia compared to increased Na^+ at Admission found in Normonatremia in patients with acute coronary syndrome.

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SODIUM CONCENTRATION AT 48 Hrs

Among the study patients, there was a statistically significant difference in relation to Na^+ at 48 hours distribution between Hyponatremia group (mean=132.67, SD=2.87) and Normonatremia group (mean=138.03, SD=2.64) with a p value of <0.05 as per unpaired t test. Therefore we reject the null hypothesis that there is no difference in Na^+ at 48 hours distribution between the study groups.

The mean Na^+ at 48 hours was significantly less in Hyponatremia group compared to Normonatremia group by a mean difference of 5.36 mg/dl (4% lower). This difference is significant with a p-value of <0.0001 as per unpaired t test.

In this study we can safely conclude that a significantly decreased Na^+ at 48 hours is associated with Hyponatremia compared to increased Na^+ at 48 hours found in Normonatremia in patients with acute coronary syndrome.

SODIUM CONCENTRATION AT DISCHARGE

Among the study patients, there was a statistically significant difference in relation to Na^+ at discharge distribution between Hyponatremia group (mean=131.78, SD=3.56) and Normonatremia group (mean=138.68, SD=2.68) with a p value of <0.05 as per unpaired t test. Therefore we reject the null hypothesis that there is no difference in Na^+ at discharge distribution between the study groups.

The mean Na^+ at discharge was significantly less in Hyponatremia group compared to Normonatremia group by a mean difference of 6.90 mg/dl (5% lower). This difference is significant with a p-value of <0.0001 as per unpaired t test.

In this study we can safely conclude that a significantly decreased Na^+ at discharge is associated with Hyponatremia compared to increased Na^+ at discharge found in Normonatremia in patients with acute coronary syndrome.

Table 6: Killip Classification

KillipClassification	Hyponatremia	Normonatremia	Combined	Hypo-natremia %	Normo natremia %	Combined %
Class 1	5	50	55	55.56	75.76	73.33
Class 2	3	16	19	33.33	24.24	25.33
Class 3	1	0	1	11.11	0.00	1.33
Total	9	66	75	100	100	100
P value (Fishers Exact test)			0.0461			

Among the study patients, there was a statistically significant difference in relation to Killip classification status between Hyponatremia group (majority had class 1 – 55.56%) and Normonatremia group (majority had class 1 – 75.76%) with a p value of <0.05 as per unpaired t test. Therefore we reject the null hypothesis that there is no difference in Killip classification status between the study groups.

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The Killip classification class 1 incidence was significantly less in Hyponatremia group compared to Normonatremia group by a percentage difference of 20.20 points (27% lower). The Killip classification class 2 & 3 incidence was significantly more in Hyponatremia group compared to Normonatremia group by a percentage difference of 20.20 points (45% higher). This difference is significant with a p-value of 0.0461 as per unpaired t test.

In this study we can safely conclude that a significantly elevated Killip classification is associated with Hyponatremia compared to decreased killip classification found in Normonatremia in patients with acute coronary syndrome. In other words elevated Killip classification (class 2&3) were 1.83 times more common in Hyponatremia compared Normonatremia in patients with acute coronary syndrome.

4. DISCUSSION

NEURO-HORMONAL MECHANISM FOR HYPONATREMIA FOLLOWING ACUTE CORONARY SYNDROMES

In an acute myocardial infarction AVP is released in a non osmotic fashion due to left ventricular dysfunction which ensues , in response to pain, stress or in response to diuretic administration.(19)(20)

In this setting AVP levels are found to increase along with renin and nor epinephrine.(21) However levels of AVP do not correlate with the serum osmolarity which suggest that non osmotic mechanisms are involved.(22)

As in congestive cardiac failure activation of carotid and aortic baroreceptors due to arterial underfilling (22) has been implicated as one of the reasons for non osmotic release of AVP. Moreover the renal effect of AVP is enhanced primarily in the collecting duct.(23)

In myocardial infarction renin-angiotensin axis and catecholamines decrease the Glomerular filtration rate, contributing to decreased renal water excretion and hyponatremia.(24)(25)

Flear CT et al in their study in patients who were admitted in a coronary care unit, concluded that the presence of hyponaetremia, hypochloraemia, and also uraemia were common in patients who were confirmed to have myocardial infarction. The degree of the infarct correlated with all the above indices. In hospital mortality rates of patients with hyponaetremia was higher in their study.(6)

Szatalowicz VL et al have shown that the presence of AVP is essential for development of hyponatremia and also that AVP levels were detectable in 30 of 37 patients with CHF.(26)

Sigurdsson A. et al in their study conducted on 55 patients with acute MI have concluded that the sustained neurohormonal activation that follows MI usually occurs in patients in whom there is clinical heart failure and is also related to the magnitude of the myocardium that is damaged , even in patients without heart failure.(4)

Goldberg et al. in their study of 978 patients have concluded that the presence of early hyponatremia is a simple marker of the neurohormonal activation that occurs during acute phase of MI and is a predictor of the long-term development of failure and death.(27)

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Rouleau JL et al. in their study of 534 patients have concluded that the presence of neurohormonal activation even at the time of discharge from the hospital in post infarction patient is by itself a sign of poor prognosis.(28)

Bogdan et al reported that a high prevalence of hyponatremia was seen within first 72 hours of transmural MI.(29)

5. CONCLUSION

Asians are more prone to develop ACS at a younger age when compared to Western population. Age ≥ 65 Years, EF < 40%, hyponatremia at admission, hyponatremia at 48 hours, hyponatremia at discharge, elevated troponin T and Killip classification ≥ 2 are significant and strong independent risk factors for predicting death in patients diagnosed acute coronary syndrome.

In other words patients diagnosed of acute coronary syndrome have 3-5 times more chances of death if one of the above independent predictor variable also occurs. Hence hyponatremia on admission or early development appears to be a significant independent risk factor in predicing short term mortality in ACS.

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