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Original Research Articlw

Study of cardiac biomarkers in severe hypokalemia

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ABSTRACT

Background: Potassium haemostasis is critical in cellular functioning, cardiac rhythm and neuromuscular wellbeing. Hypokalemia is associated with adverse cardiac, neuromuscular, gastrointestinal outcomes. Cardiovascular mortality owing to arrhythmia is more common with altered potassium levels. Correlating hypokalemia with cardiac biomarkers is still not conclusively documented although many AMI cases report significant hypokalemia. So present study tries to make a point on impact of severe hypokalemia on cardiac biomarkers.

AIM & Objectives: To determine the effect of severe hypokalemia on levels of cardiac biomarkers.

Materials and Methods: A longitudinal observational study included in patients with clinically suspected and confirmed biochemically as hypokalemia. 102 patients enrolled after consent and ethical clearance. Severe hypokalemia patients were grouped into 2 with serum K+ level <2 meq/l and in between 2-2.5 meq/l. Results were interpreted in terms of demographic variables and in terms of Serum cardiac biomarkers- Trop I, Total Creatinine Phosphokinase and CPK-MB. ECG changes of ACS (ST changes) were analysed statistically in both groups.

Result and conclusion: 81 patients had serum Potassium level < 2 meq/l and 21 patients had between 2-2.5 meq/l (Mean 1.781± 0.35). There was significant difference of CPK-MB and Trop-I values between these two groups having χ^2 value 6.11 and 8.35 respectively with p value <0.05. Total CPK level was not significantly different in both groups. In terms of ECG changes suggestive of ACS, sensitivity of 100% was observed in patients with serum K^+<2 meq/l, whereas specificity of 32% was observed in the other group. Results document severe hypokalemia induced acute myocardial injury with evidence of significant elevation of cardiac Biomarkers with ECG changes suggestive of ACS/Acute MI mostly seen in the group with serum potassium value <2 meq/l.

1. Introduction

Potassium is the major intracellular cation and is important for regulating cellular functions and allows conductivity between intracellular and extracellular space. Different ion channels and exchange pumps are important to maintain Potassium homeostasis.[1,2] In cardiac cells, potassium plays a critical role in maintaining cardiac muscle function and rhythm. Derangement in serum K+ level are associated with rhythm abnormalities, neuromuscular and gastrointestinal manifestations.[1]

Hypokalemia is defined as serum K+ concentration <3.5mmol/L and is observed in about 20% of hospitalized patient.[3] A 10 fold increase in in-hospital mortality occurs due to adverse effects of hypokalemia on cardiac rhythm, blood pressure and heart failure.[3] Severe hypokalemia is defined as plasma serum K^+ less than 2.5mmol/L. About 7 to 17% of patients with cardiovascular disease have got

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documented hypokalemia.[3,4] Significant Q-T prolongation, risks of Torsade's De Pointes, Ventricular fibrillations and sudden cardiac deaths can be attributed to severe hypokalaemia.[1,3]

The pathogenesis of severe hypokalemia causing elevation of cardiac biomarkers is multifactorial.In the state of severe hypokalemia, the decreased regional blood flow causes relative ischemia in active muscle as hypokalemia causes impaired vasodilation during muscle activity, consequently leading to muscle cramp and in severely depleted state may cause muscle necrosis and rhabdomyolysis.[5] Hypokalemia induced impairment in muscle metabolism also contribute muscle dysfunction.[5] Creatinine Kinase may be elevated mostly with associated hyperaldosteronism with hypokalemia. In other patients of hypokalemia 10% may have increased CPK due to other disease processes including cardiac ailments.[6]

Evidence suggests that hypokalemia may be associated with patients with myocardial infarction and also guidelines suggest to avoid hypokalemia in these patients.[7–9] As there is lack of study regarding the correlation of severe hypokalaemia and elevation of cardiac biomarkers it required a detailed study. In the present study the relationship of severe hypokalaemia and the level of cardiac biomarkers was studied. Also we have tried to find out whether diagnosing hypokalemia early has any predictive value in prognosis of acute coronary syndromes.

2. Aims and Objectives

1. To observe the effect of Severe Hypokalemia on levels of cardiac biomarkers.
2. To study the changes in levels of cardiac biomarkers in severe hypokalemia in comparison with patients of Acute Coronary Syndrome.

3. Materials and Methods

This is a longitudinal, observational study conducted between December 2018 to November 2020 in the Dept. of General Medicine, VIMSAR, Burla, Sambalpur, Odisha. Clinically suspected and biochemically confirmed cases of hypokalemia were taken in this study after institutional ethical permission and proper consent.

Sample size was estimated as 100 and convenience sampling was done. 102 patients were finally enrolled for the final analysis.

3.1. Inclusion criteria

1. Diagnosed cases of severe hypokalaemia (serum K^+<2.5 meq/l) admitted to medicine wards
2. Age >14yrs of both sexes.

3.2. Exclusion criteria

1. Drugs and Trauma induced hypokalemia and Inflammatory myopathy.
2. Patients unwilling for consent.
3. Pregnancy and other vulnerable groups.

Each case was studied as per medical history, detailed general and systemic examination, laboratory workups at baseline. Severe hypokalemia patients were grouped into two groups. The first group with serum K+ level <2 meq/l and the second group with seum K+ level between 2-2.5 meq/l. Results were interpreted in terms of demographic variables like age and sex distributions and in terms of Serum cardiac biomarkers- Trop I, Total Creatinine Phosphokinase and CPK-MB. ECG changes of ACS (ST changes) were analysed in both groups.

3.3. Statistical analysis

Data were analysed by SPSS software (version 17.0) and appropriate statistical methods.To measure the strength of association between two continuous variables we used Pearson's 2 tailed correlation. Chi square test was done to find out difference between the two groups. Level of statistical significance was taken as P value<0.05.

3.4. Ethical approval

Institutional ethical committee clearance was taken prior to study.

4. Results

Out of 102 patients with severe hypokalaemia (serum K^+<2.5 meq/l), 59% were male and remaining 41% were females. Most patients (26%) were of the age group 36-45 years and least were from age group 76-85 years. Males were found to be more commonly affected than female with ratio of approximately 3:2. Fig 1 and 2 depicts age and sex distribution of study participants.

81 patients had serum Potassium levels < 2 mEq/l and 21 patients had between 2-2.5 meq/l. 40 patients had Serum Trop- I value < 100 ng/l out of whom 26 patients had serum K^+< 2 meq/l and the rest 14 patients had serum K+ > 2 meq/l. 62 patients had Trop- I value >100 ng/l out of whom 55 patients had serum K^+< 2 meq/l and 7 patients had > 2 meq/l. 35 patients had CPK-MB value < 16 IU/L out of whom 23 patients had serum K^+<2 meq/l and 12 patients had >2 meq/l. 67 patients had CPK-MB value >16 IU/L out of whom 58 patients had serum K^+<2 meq/l and 9 had >2 meq/l. 16 patients had Total CPK <130 IU/L out of whom 10 had serum K^+<2meq/l and 6 had >2 meq/l.

Table 1 shows the distribution of cardiac biomarkers and ECG changes across the cases of severe hypokalaemia.86 patients had Total CPK >130IU/L out of whom 71 had serum Potassium <2 meq/l and 15 had >2 meq/l. 38 patients

Table 1: Distribution of patients with Cardiac Biomarkers and ECG changes in both groups of Severe Hypokalaemia

serum K^+ meq/l)	No of patients	Trop I <100 ng/L	Trop I>100 ng/L	CPK-MB<16	CPK-MB>16	Total CPK <130	Total CPK >130	ECG changes with ACS	No ECG changes of ACS
<2	81	26	55	23	58	10	71	38	43
2-2.5	21	14	7	12	9	6	15	0	21
total	102	40	62	35	67	16	86	38	64

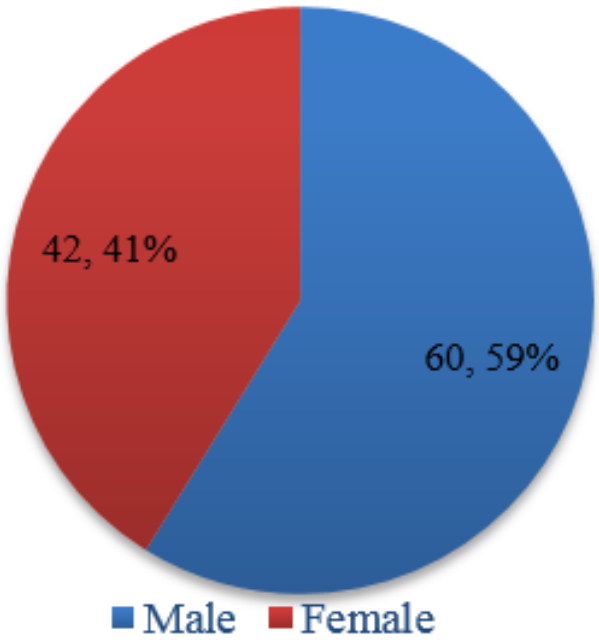

Fig. 1: Sex distribution of severe hypokalaemia cases

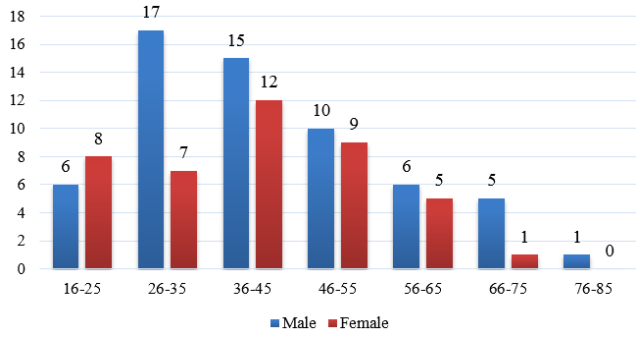

Fig. 2: Age distribution of Severe Hypokalemia (k+ <2.5meq/L)

had ECG changes of ACS with serum Potassium <2 meq/l and none of the patients having serum potassium > 2 meq/l had ECG changes of ACS. 64 patients had no ECG changes of ACS out of whom 43 had serum K^+<2 meq/l and 21 had >2 meq/l.

A total of 102 severe hypokalemic patients were taken for study and there was a significant relationship existing between serum potassium, serum Trop-I and CPK-MB with P value <0.05. Mean value of serum potassium was 1.781± 0.35 meq/l. Mean values of serum Trop-I, Total CPK and CPK-MB were 1157.595 ng/l, 1433.11IU/l, and 414.944 IU/l respectively which were above the normal range. Raised serum Trop-I, Total CPK and CPK-MB levels suggest myocardial injury.

Significant elevation of serum CPK-MB levels suggestive of myocardial injury (>16 IU/l) was seen in 58 patients with serum potassium <2 meq/l but only 9

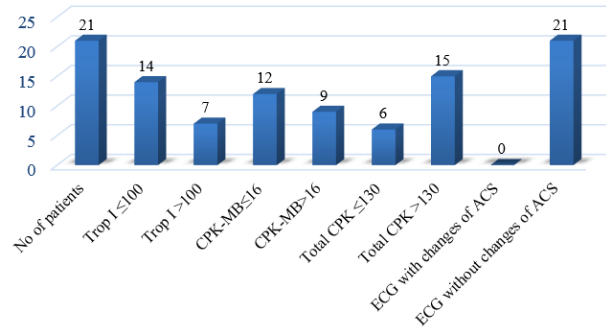

Fig. 3: Distribution of patients with Cardiac Biomarkers and ECG changes with Severe Hypokalemia 2-2.5 meq/L

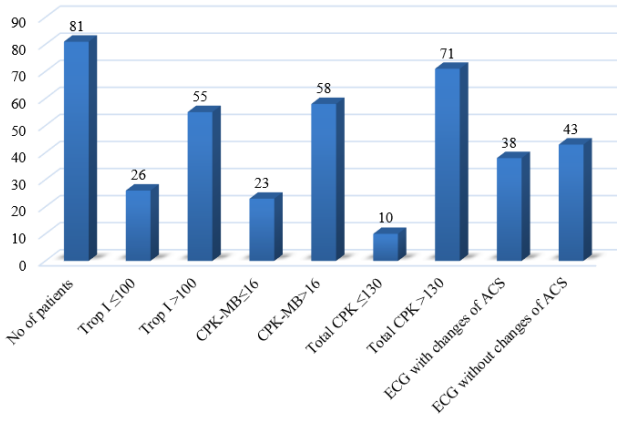

Fig. 4: istribution of patients with Cardiac Biomarkers and ECG changes with Severe Hypokalaemia < 2meq/L

patients had elevated serum CPK-MB levels with serum levels of potassium between 2-2.5 mEq/l. Overall 65.6% of patients have got elevated levels of serum CPK-MB >16 IU/l.Chi-square test was done to find out the difference between two groups having serum potassium value <2 meq/l & between 2-2.5 meq/l and total serum CPK-MB.There was a significant difference of CPK-MB values between these two groups having chi square value 6.11, p =0.0134 .

Elevation of serum total Creatine Phosphokinase levels suggestive of myocardial injury (>130IU/l) was seen in 71 patients with serum potassium <2 meq/l but when serum levels of potassium is between 2- 2.5 meq/l only 15 patients had elevated serum total creatine phosphokinase levels. Overall 86 patients out of 102 have got significant elevation of serum Total CPK.Chi-square test was done to find out the difference between two groups having serum potassium value < 2 meq/l & 2-2.5 meq/l and serum Total CPK.There was no significant difference of total CPK values between these two groups having chi square value 3.31, p value= 0.0684 .

Chi-square test was done to find out the difference between the two groups having serum potassium value < 2 meq/l & 2-2.5 mEq/l and serum Trop I.There was a significant difference between these two groups in Trop –I level, chi square value 8.35, p value =0.0038 .62 patients had Trop I >100ng/L, out of which 55 patients had potassium level <2 meq/l with sensitivity of 88.7% and 14 patients have got Trop- I<100ng/l when serum potassium is >2 meq/l with specificity of 35% out of 40 patients. Over all 60.7% of severe hypokalemic patients got significant elevated Trop I levels >100ng/l.

Table 2 shows that 38 patientshave got significant ECG changes suggestive of ACS in the group with serum K^+<2meq/l with sensitivity of 100%, remaining 21 patients have got no ECG changes suggestive of ACS with serum potassium levels between 2-2.5 mEq/l(specificity32%). Overall 38 people out of 102 severe hypokalaemia patients got significant ECG changes suggestive of ACS.

5. Discussion

Severe hypokalemia is a medical emergency as it causes life threatening cardiac conduction disturbances, cardiac arrest, hypotension, respiratory arrest and neuromuscular dysfunction.

As there is paucity of studies regarding the effect of severe hypokalaemia causing elevation of cardiac biomarkers it required a detail study. In the present study the relationship of severe hypokalaemia and levels of cardiac biomarkers was analysed.

Males (59%) were more in number than females (41%) in the present study with a ratio of 3:2 with maximum participants (26%) of the age group 36-45 years. Mean serum K+ value was 1.781± 0.35 meq/l. Values of CPK, CPK-MB and Trop- I were assessed in two groups having serum K+ values <2 meq/l and with 2-2.5 meq/l.Chi square test was used for assessment of level of significance.

In the present study, 60.78% patients had Trop I elevation. In the group with patients having potassium levels <2 meq/l 67.87% have got significantly elevated Trop- I levels. In the second group with serum potassium levels 2-2.5 meq/L, only 33.33% had elevated Trop- I levels. Raised levels of Trop I(>100ng/dl) signify cardiac myocyte injury in severe hypokalemia as evidenced by significant correlation between severe hypokalaemia and serum Trop I with P value (<0.05).

In the group of patients with potassium levels <2meq/l significant elevated serum CPK-MB levels (>16 IU/L)observed in 72% while in the other group only 43% have elevated serum CPK-MB when serum potassium level is 2-2.5 meq/l. Overall 65.69% of patients have got elevated levels of serum CPK-MB. We observed a significant correlation between severe hypokalemia and serum CPK-MB with P value (<0.05).

88% of patients had elevated serum Total CPK levels (>130IU/L) in the group with serum K+ <2meq/l and 71% of patients had elevated serum Total CPK levels (>130IU/L)

Table 2: Sensitivity & Specificity of Severe Hypokalaemia vs ECG Changes suggesting Acute Coronary Syndrome

	ECG Changes Present	ECG Changes Absent	Total	
Serum K^+<2 meq/l	**38**	43	81	Sensitivity 100%
Serum K^+ 2-2.5 meq/l	0	**21**	21	Specificity 32%
Total	38	64	102	

in the group with serum potassium levels 2-2.5meq/L. Overall 84.31% of patients with severe hypokalemia have got elevated serum Total CPK levels. But this result was not significant statistically.

In our study only 32% of patients have shown significant ECG changes suggestive of ACS when serum potassium is <2meq/L.

Patil S. et al[8] in a prospective case control study showed average value of serum potassium to be 3.81±0.48 meq/L in AMI patients. Around 24% of AMI patients were found to be hypokalemic with a p value of 0.0402 for hypokalaemia.

Mudaraddi R. et al[9] documented results of a case control study with 120 subjects where serum K^+ levels were significantly lower in AMI patients than controls (4.43 ± 0.44 vs 3.88 ± 0.57, p<0.001) .

Rathore V. et al in 2018[10] conducted a study in 100 subjects with 50 patients of AMI and 50 normal healthy individuals as controls. There was a significant decrease in the levels of serum potassium in AMI patients (3.57±0.81 meq/L vs. 4.36±0.45 meq/L, p<0.001).

Meghwal P. et al. 2019[11] in their study analysed 76 subjects with 38 AMI cases and 38 healthy individuals as controls demonstrated that mean serum potassium levels among the AMI group was found to be 85.6 mmol/L,significantly lower than that of the control group, which was found to be 93.4 mmol/L.[11]

Studies have shown that hypokalemia can also produce ST Segment elevation like that of Acute MI. Relative hyperkalemia due to change in the intracellular/extracellular K+ ratio resulted in hypokalemia related ST segment elevation. Profound hypokalemia can mimic acute MI and pseudo-ischemic ECG changes.[12] K+ may serve as an adjuvant diagnostic marker for ACS. Sudden cardiac death is due to alteration at the level of myocyte and Purkinje fibres that are mainly regulated by electrolyte imbalance and autonomic nervous system activity.[13]

There is a strong association between K+ levels, cardiac arrhythmias and cardiovascular deaths in patients with non ST segment elevation MI or Unstable angina.[14] Hypokalemia is associated with Non obstructive coronary artery myocardial infarction with positive cardiac biomarkers and Non ST elevation myocardial infarction due to inflammatory mechanisms, endothelial injury or dysfunction causing coronary slow flow. Acute MI is accompanied by the catecholamine surge that stimulates Na+ K+ ATPase pump shifting K+ intracellularly causing re-distributional hypokalaemia and as a result, non-ischemic myocardium is hyperpolarized and electrical in-homogeneity occurs leading to ventricular arrythmias.[14]

6. Conclusion

This is an indirect study of severe hypokalemia induced acute myocardial injury evidenced by elevated cardiac biomarkers with ECG changes suggestive of ACS. Acute

conditions of severe hypokalemia can cause intrinsic cardiac myocyte injury which is mostly seen with serum potassium level <2 meq/l. Apart from causing cardiac arrythmias severe hypokalemia can cause myocardial injury/infarction and can play an important role as a diagnostic marker in Acute coronary syndrome. As this study was done only on the basis of biochemical reports and ECG changes in emergency basis, further evaluation of the study is required with serial ECG and cardiac biomarkers monitoring with 2D Echo for regional wall motion abnormalities and finally coronary Angiography studies to confirm severe hypokalemia induced myocardial injury.

7. Sources of Funding

No financial support was received for the work within this manuscript.

8. Conflicts of Interest

No conflicts of interest.

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