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# COMPARISON OF HIGH PLATELET COUNT WITH CONCOMITANT HYPERKALEMIA IN PATIENTS OF CARDIAC DYSFUNCTION IN A CARDIAC SUPER-SPECIALITY HOSPITAL OF EASTERN INDIA

Biochemistry

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## ABSTRACT

**Introduction:** Hyperkalemia is a frequent complication in cardiac disorders. We aimed to establish an association between high serum potassium (> 5.0 mEq/L) and high platelet count ≥ 4.5 X 105/cu mm) in patients of cardiac dysfunction and demonstrate association of normal serum levels of potassium (< 5.0 mEq/L) with normal platelet count (< 4.5 X 105/cu mm) in patients with cardiac diseases as well as in selected controls with normal platelet count and normal renal function and no cardiac disease. **Methods:** We conducted a retrospective audit. Routinely requisitioned platelet counts and serum potassium values fulfilling our inclusion criteria were screened. From the total screened, 159 patient reports showed high and 168 showed normal platelet counts [designated as cases and controls respectively]. Serum creatinine of both groups was also noted and only those with normal renal function were included in the study. The data was analyzed by GraphPad Prism (v.8.4.3) and MS Excel 2013, considering a p value of ≤ 0.05 to be statistically significant. **Results:** Among the 159 patient reports singled out on basis of high platelet count, 61 had hyperkalemia and on comparing both parameters in this subset, a significant association was found between platelet counts and serum potassium [p value = 0.0002; unpaired t-test]. 152 out of the 168 normal platelet counts with normal serum potassium showed significant association between both parameters [p value <0.0001; unpaired t-test]. A trend analysis of serum electrolytes [sodium and potassium] across entire spectrum of platelet count [normal to high], reflected serum sodium exhibiting a steady trend across platelet counts, while in contrast, serum potassium showed a sharp rise in mean levels from 4.27 mEq/L to 4.86 mEq/L, on corresponding increase of platelet count from 3.5 x 105 - 4.5 X 105 /cu mm to 4.5 X 105 - 5.5 X 105 /cu mm, respectively. **Conclusions:** Thrombocytosis and hyperkalemia thus exist in individuals with cardiac dysfunction as well as in those without and needs cautious interpretation so that neither true hyperkalemia gets overlooked nor thrombocytosis associated hyperkalemia gets over-corrected.

## KEYWORDS

Thrombocytosis, Hyperkalemia, Cardiac, Creatinine

## INTRODUCTION

Hyperkalemia, defined as K+ levels greater than 5.0 mEq/L,[1] [2] is a frequent complication in cardiac dysfunction and a major concern to treating physicians owning to the potential fatality of this phenomenon.[3] On the other hand, pseudo-hyperkalemia results from leakage of potassium from cellular elements most commonly due to hemolysis but also in individuals with essential thrombocytosis, polycythemia vera and chronic lymphocytic leukemia (CLL) to name a few.[4] It is estimated that serum potassium rises by essential thrombocytosis is estimated to be 0.07-0.15 mmol/L for every increase in platelets by 100,000, beyond 450,000/cu mm.[5] The phenomenon of pseudo-hyperkalemia, often an in-vitro one, is evidenced by leaking of K+ from cells, after blood collection, characterized by severe hyperkalemia yet accompanied by paucity of signs and symptoms, along with no evidence of renal dysfunction (adequate urine output, normal urea/creatinine/eGFR) and no forthcoming history of usage of drugs likely to elevate serum potassium levels.[3]

Apart from CLL that predisposes to reverse pseudo-hyperkalemia; characterized by higher plasma potassium than in serum, thrombocytosis remains a forerunner of in-vitro rocketing of serum potassium levels, chiefly released from the activated platelets during the process of coagulation.[2][6] The current study setting being a cardiac super-speciality hospital, hyperkalemia constitutes a definite emergent condition necessitating prompt intervention, when considered from the cardiac perspective. The present study was thus undertaken to differentiate the true hyperkalemia from pseudo-hyperkalemia; in order to avoid inappropriate interventions in case of the latter while ensuring prompt intervention in case of the former. Our chief objectives were to establish an association between high serum potassium (> 5.0 mEq/L) and high platelet count ≥ 4.5 X $10^5$/cu mm) in patients of cardiac dysfunction while simultaneously demonstrating an association of normal serum levels of potassium (< 5.0 mEq/L) with normal platelet count (< 4.5 X $10^5$/cu mm) in patients with cardiac diseases but with normal renal function.

## MATERIALS AND METHODS:

### Study variables:

The study was a retrospective, analytical, comparative audit with appropriate age and sex matched controls, undertaken in the Department of Laboratory Medicine of CK-Birla Hospitals, CMRI & BM Birla Heart Research Centre, Kolkata, from 1st January 2023 to 30th April 2023, following set inclusion & exclusion criteria.

### Screening and selection of cases and controls:

Briefly, all routinely requisitioned platelet counts and serum potassium & creatinine values fulfilling study inclusion criteria were screened. Reports of all patients having platelet count ≥ 4.5 X $10^5$/cu mm with normal renal function were included as cases while controls were constituted by patients with normal platelet count (1.5 X $10^5$- 4.5 X $10^5$/cu mm) and normal renal function.

Reports of patients with established or suspected chronic kidney disease with serum creatinine ≥ 1.5 mg/dL, known hemolytic disorders and those taking any medication with established effect on serum potassium levels, were excluded from the study.

In summation, a total of 159 patient reports were designated as “cases” while 168 patient reports constituted “controls”.

### Ethical considerations:

Since the entire study was conducted as a retrospective audit on reports of patient samples coming to lab for routine investigations, hence ethical clearance was not required separately for the same.

### Study parameter estimations:

Platelets were counted by electrical impedence in automated analyzer Horiba Pentra XL80 [biological reference interval 1.5 X $10^5$/cu mm - 4.5 X $10^5$/cu mm]. Serum sodium & potassium [biological reference interval 136-146 mEq/L & 3.5 -5.0 mEq/L, respectively] were estimated by direct potentiometry using HDC Lyte electrolyte analyzer. Serum creatinine [biological reference interval 0.70 -1.30 mg/dL (males); 0.55 -1.02 mg/dL (females)] was estimated by modified kinetic Jaffe method using auto-analyzer Roche Cobas 6000.

**Statistical analyses:**
The data generated was analysed by Graph-Pad Prism v.8.4.3, using appropriate statistical tools. The data were expressed as Mean ±S.D. and the normality of the sample distribution was tested by D'Agostino & Pearson omnibus normality test. Trend analysis of serum potassium and sodium vis-vis platelet count was performed on MS Excel 2013. For analyzing association between platelet counts and potassium levels, unpaired t-test was used. In all statistical analysis P value ≤0.05, was considered as statistically significant.

## RESULTS:

**1. Association between high platelet count and serum potassium levels:**
Out of the 159 patient reports showing high platelet count [≥ 4.5 X $10^5$/cu mm], 61 had concomitant hyperkalemia [> 5.0 mEq/L]. **Table 1** summarizes the range alongwith mean values of both parameters in this subset.

Furthermore, a significant association was found between platelet count platelet count [≥ 4.5 X $10^5$/cu mm] and serum potassium [> 5.0 mEq/L] by unpaired t test [p value = 0.0002; **Fig 1**]

**2. Association between normal platelet count and serum potassium levels:**
Out of the 168 patient reports showing normal platelet count [< 4.5 X $10^5$/cu mm], 152 had concomitant normokalemia [< 5.0 mEq/L]. **Table 2** summarizes the range alongwith mean values of both parameters in this subset.

Furthermore, a significant association was found between platelet count platelet count [< 4.5 X $10^5$/cu mm] and serum potassium [<5.0 mEq/L] by unpaired t test [p value < 0.0001; **Fig 2**]

**3. Trend analysis of serum electrolyte levels with platelet counts:**
Furthermore, we performed a trend analysis of serum electrolytes across the entire spectrum of platelet count of our selected reports i.e. in both normal count group [1.5 x $10^5$ - 4.5 X $10^5$/cu mm] as well as high count group [> 4.5 X $10^5$/cu mm]. **Fig 3A** & **3B** represent the trends exhibited by serum potassium and serum sodium respectively, over entire spectrum of platelet count, from normal to abnormally high. While serum sodium showed a steady trend across platelet counts, serum potassium showed a sharp rise in mean levels from 4.27 mEq/L to 4.86 mEq/L, on corresponding increase of platelet count from 3.5 x $10^5$ - 4.5 X $10^5$/cu mm to 4.5 X $10^5$ - 5.5 X $10^5$/cu mm, respectively.

## DISCUSSION:

Pseudohyperkalemia first described by Hartmann and Melinkoff in 1955 is an in vitro occurrence characterized by the paucity of signs and symptoms of true hyperkalemia such as ECG changes, along with no response to common treatments of hyperkalemia.[7] It is a commonly encountered problem in the setting of thrombocytosis and leukocytosis. Unlike other commonly encountered interferences, this phenomenon cannot be absolved merely by repeat sampling.[8] The phenomenon of thrombocytosis is fairly common in cardiac dysfunction, and in consequence spuriously raised potassium levels are frequently encountered as a result of release in-vitro into serum, from this high number of activated platelets during the process of coagulation. The problem can be circumvented by using heparinized plasma in lieu of serum, which can avoid the potentially unnecessary and undesired further diagnostic testing and potentially detrimental over-correction.[9]

Our current study, conducted in a cardiac super-speciality hospital of Eastern India, highlighted the existence of the phenomenon of pseudo-hyperkalemia in the cardiac patients who while exhibiting thrombocytosis concomitantly, showed none of the clinical perturbations associated with actual hyperkalemia, as the potassium elevation in such cases was almost entirely in-vitro from activated platelets, during blood clotting. Monitoring the mean potassium levels across an entire spectrum of platelet counts, from our recruited patient reports [inclusive of both cases i.e. those having platelet count ≥ 4.5 X $10^5$/cu mm and controls i.e. those having platelet count between 1.5 X $10^5$ - 4.5 X $10^5$/cu mm] showed a marked rise in mean serum levels from 4.27 mEq/L to 4.86 mEq/L, on corresponding increase of platelet count from 3.5 x $10^5$ - 4.5 X $10^5$/cu mm to 4.5 X $10^5$ - 5.5 X $10^5$/cu mm, respectively. Serum sodium on the other hand showed no such tectonic shift. Furthermore, a significant association was found between raised platelet count [≥ 4.5 X $10^5$/cu mm] and raised serum potassium [> 5.0 mEq/L] as well as between normal platelet count [<4.5 X $10^5$/cu mm] and normal serum potassium [< 5.0 mEq/L].

It also remains prudent to keep in mind other potential causes of pseudohyperkalemia which can be commonly encountered in laboratory. Notable among them include, pseudohyperkalemia consequent to is in vitro hemolysis, often with a prevalence of up to 3.3%. and commonly occurring after blood collection following a difficult venous accessibility.[10] The other cause is florid leukocytosis, characterized by increased leukocte fragility that results in release of intracellular potassium to blood circulation.[11] Less common occurrences include familial pseudohyperkalemia characterized by mutation in the gene encoding for the ABCB6 transporter and RBC defects, such as hereditary spherocytosis, that also lead to spuriously elevated serum potassium levels.[12]

However in cardiac set-ups thrombocytosis still remains as one of the chief triggers of pseudohyperkalemia and one that until its confirmation, can ensue inappropriate hospitalizations and unnecessary investigations such as repetitions of laboratory tests, ECGs and inappropriate treatments, in addition to diet modifications.[13] Distinguishing from true hyperkalemia also is extremely crucial, since the true potassium excess has serious adverse effects particularly on the heart, which in patients of already compromised cardiac status can well prove life-threatening. Since true hyperkalemia is commonly seen in individuals with chronic kidney disease we excluded from our study patient reports where serum creatinine was ≥ 1.50 mg/dL. In cardiac setups, where thrombocytosis is rampant, it might be well advised to thus opt for heparinized plasma as the sample of choice for potassium estimations, particularly if concomittant renal dysfunction is present.[14]

## CONCLUSIONS:

Thrombocytosis and hyperkalemia thus exist in individuals with cardiac dysfunction as well as in those without. Hence this condition reeds cautious interpretation and close monitoring. Meticulous monitoring is hence vital so that that neither true hyperkalemia gets overlooked nor thrombocytosis associated (pseudo) hyperkalemia gets over-corrected. In addition, usage of heparinized plasma as an alternative sample of choice for potassium estimations may also be advocated in such scenarios.

**Tables**

**Table 1:** Descriptive statistics of subset of high platelet count [≥ 4.5 x 105 /cu mm] with concomitant hyperkalemia [> 5.0 mEq/L]. Subset n=61; Platelet count range: 4.52 x 105 – 12 x 105 /cu mm; Serum potassium range: 5.01 – 6.01 mEq/L

| Variables | Platelet count (≥ 4.5 X 105/cu mm) | Serum Potassium ( > 5.0 mEq/L) |
|---|---|---|
| Number of values | 61 | 61 |
| Minimum | 4.520 | 5.010 |
| 25% Percentile | 5.215 | 5.185 |
| Median | 5.830 | 5.320 |
| 75% Percentile | 6.445 | 5.645 |
| Maximum | 12.00 | 6.010 |
| Mean | 6.101 | 5.417 |
| Std. Deviation | 1.376 | 0.2838 |

**Table 2:** Descriptive statistics of subset of normal platelet count [< 4.5 x 105 /cu mm] with normal serum potassium level [< 5.0 mEq/L]. Subset n=152; Platelet count range: 1.50 x 105 – 3.89 x 105 /cu mm; Serum potassium range: 2.60 – 4.98 mEq/L

| Variables | Platelet count (≥ 4.5 X 105/cu mm) | Serum Potassium ( > 5.0 mEq/L) |
|---|---|---|
| Number of values | 152 | 152 |
| Minimum | 1.500 | 2.600 |
| 25% Percentile | 1.700 | 3.900 |

| | | |
|---|---|---|
| Median | 1.995 | 4.220 |
| 75% Percentile | 2.588 | 4.448 |
| Maximum | 3.890 | 4.980 |
| Mean | 2.189 | 4.175 |
| Std. Deviation | 0.6303 | 0.4081 |

**Figures:**

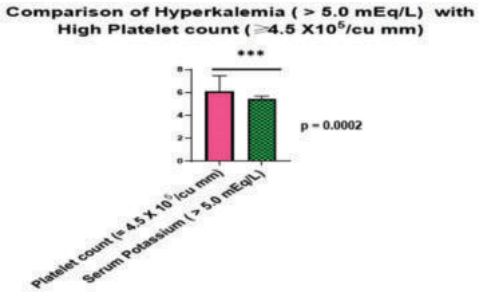


**Fig 1:** Comparison of hyperkalemia (> 5.0 mEq/L) with high platelet count (≥ 4.5 x 105 /cu mm). 61 out of 159 had concomitant platelet count ≥ 4.5 X 105/cu mm & serum potassium > 5.0 mEq/L; Significant association was found b/w platelet counts and serum potassium by unpaired t test [p value = 0.0002].

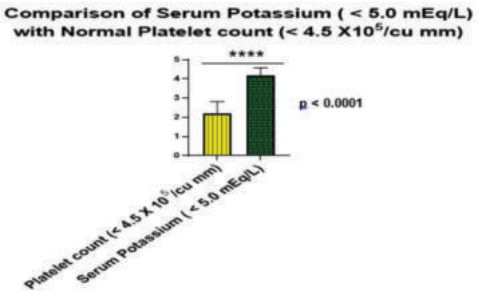


**Fig 2:** Comparison of serum potassium (< 5.0 mEq/L) with normal platelet count (< 4.5 x 105 /cu mm). 152 out of 168 had concomitant platelet count < 4.5 X 105/cu mm & serum potassium < 5.0 mEq/L; Significant association was found b/w platelet counts and serum potassium by unpaired t test [p value < 0.0001]

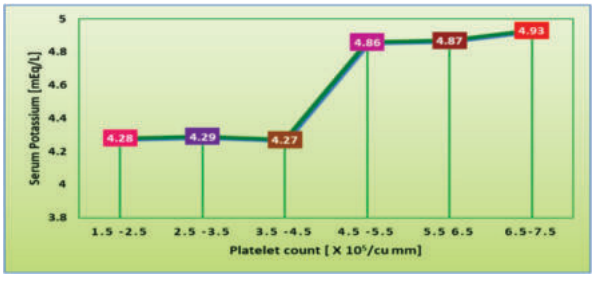


**Fig 3A:** Trend analysis of average potassium levels [mEq/L] in different ranges of platelet count [x 105 /cu mm]

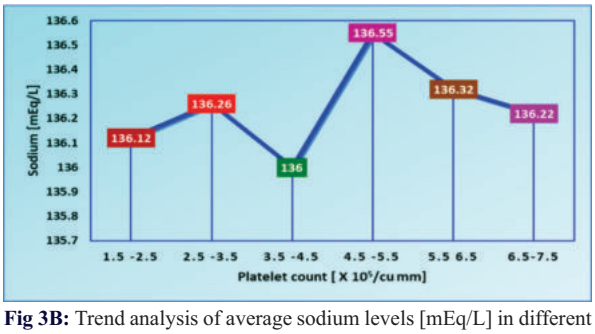


**Fig 3B:** Trend analysis of average sodium levels [mEq/L] in different ranges of platelet count [x 105 /cu mm]

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