Original Article

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Education Section

Role of Oral versus Intravenous Calcium Supplementation in Plateletpheresis Donors: A Prospective Observational Study

V NAVEEN KUMAR[1], D UMESH[2], A SIVARAMAKRISHNAN[3], ARUMUGAM POTHIPILLAI[4]

ABSTRACT

Introduction: Single Donor Platelets (SDP) are in high demand and are the preferred choice for patients requiring recurrent platelet transfusions. Citrate, being the anticoagulant of choice, may result in symptoms of citrate toxicity due to repeated frequent donations or increased procedure time.

Aim: The present study aimed to evaluate the role of prophylactic calcium supplementation (oral vs intravenous) on plateletpheresis donors and correlate their effects with adverse donor reactions (citrate toxicity).

Materials and Methods: This prospective observational study on plateletpheresis donors was conducted for a period of one year in the Department of Transfusion Medicine at Government Royapettah Hospital, The Tamil Nadu Dr. MGR Medical University, Chennai, India. It included 63 plateletpheresis donors divided into two groups based on random allocation-the Oral calcium supplementation group (n=32 donors) and the intravenous calcium supplementation group (n=31 donors). For both groups, their biochemical parameters (serum calcium, serum ionised calcium, serum magnesium) were measured before and within 30 minutes after the plateletpheresis procedure. The parameters were analysed for symptoms of citrate toxicity. Analysis was carried out using Statistical Package for Social Sciences (SPSS) Software version 20.0, and paired t-test was used for analysing biochemical parameters.

Results: A statistically significant decline in serum ionised calcium levels (1.17±0.09 vs 1.10±0.11) (preprocedure level vs postprocedure level) was observed in the oral calcium supplementation group compared to the intravenous calcium supplementation group (1.07±0.25 vs 1.11±0.14). The authors observed a decline in the mean levels of serum calcium in both the oral calcium group (10.33±1.62 vs 9.88±1.00) and the intravenous calcium group (10.31±1.33 vs 10.21±0.88). Furthermore, the authors observed a decline in mean serum magnesium levels in the oral calcium group (2.13±0.30 vs 2.07±0.24) with no difference observed in the intravenous calcium group (2.14±0.22 vs 2.14±0.14). Mild citrate toxicity symptoms in the form of tingling sensation and perioral paraesthesia were observed in 26 out of 32 donors in the oral calcium group, whereas no symptoms were recorded in the intravenous calcium group.

Conclusion: Prophylactic intravenous calcium supplementation resulted in better bioavailability of serum ionised calcium levels with no citrate toxicity symptoms compared to oral calcium supplementation. This results in better retention of plateletpheresis donors, enabling smooth and comfortable collection of a high concentration of platelets from a single donor. However, it is imperative to conduct more studies with a larger number of plateletpheresis donors to observe donor adverse reactions specific to the population.

Keywords: Citrate toxicity, Serum ionised calcium, Single donor platelets

INTRODUCTION

Apheresis is a procedure in which whole blood removed from the body is passed through an apparatus that separates one (or more) particular blood constituents and returns the remaining constituents to the individual's circulation [1]. In the plateletpheresis procedure, a portion of the donor's platelets and some plasma are removed, with the donor's Red Blood Cells (RBCs), White Blood Cells (WBCs), and remaining plasma returned to the circulation [2]. The plateletpheresis procedure allows for the collection of a larger volume of platelets, increasing the ability to produce optimal components for the patient and preventing wastage [1].

The SDPs are in high demand and are the preferred choice for patients requiring recurrent platelet transfusions, especially in treating severe hyperproliferative thrombocytopaenia due to haematological malignancies {Acute Myeloid Leukaemia (AML), Acute Lymphocytic Leukaemia (ALL)}, cytotoxic chemotherapy, haematopoietic cell transplant, congenital platelet function defects, and the use of HLA-matched or human platelet antigen-matched platelets to treat platelet refractoriness [3-5]. The use of SDPs leads to a reduced risk of alloimmunisation and Transfusion Transmissible Infections (TTI). High-quality, leukoreduced platelets with a full and effective transfusion dose are obtained during SDP procedures [2].

Citrate is used as an anticoagulant in SDP procedures to prevent clotting of extracorporeal blood in the apheresis circuit and is generally safe. However, certain biochemical changes occur following plateletpheresis procedures, such as a reduction in serum divalent cations, especially calcium and magnesium, due to the infusion of citrate anticoagulation, resulting in hypocalcaemic symptoms. The rapidity of the plateletpheresis procedure is limited by citrate toxicity [6,7]. Furthermore, repeated platelet donations or prolonged procedure time may result in symptoms of citrate toxicity, causing significant donor discomfort.

According to the literature, about 16%-50% of SDP donors develop citrate-related reactions. Hypocalcaemia and hypomagnesemia increase nerve membrane excitability and cause peri-oral and acral paraesthesia. Other symptoms of citrate toxicity include shivering, nausea, vomiting, fever, chills, lightheadedness, tremors, and muscle cramps [8].

In severe hypocalcaemia, frank tetany with life-threatening laryngospasm, QT prolongation, and fatal arrhythmias can also occur [8]. To enhance operational efficiency and the level of donor comfort, calcium supplementation is required, either in the form of oral calcium supplements or intravenous calcium administration [6,7]. Additionally, the effects of intravenous citrate administration

are more predictable and effectively counteracted with intravenous calcium infusions than with oral supplements [9].

This study mainly aimed to attain a safe donor profile and a robust quality assurance system for the smooth and comfortable collection of high concentrations of SDPs by studying the effects of prophylactic calcium supplementation (oral vs. intravenous) in plateletpheresis donors and analysing the adverse events (citrate toxicity) with changes in serum ionised calcium.

MATERIALS AND METHODS

This prospective observational study was conducted on plateletpheresis donors from July 2016 to August 2017 at the Department of Transfusion Medicine, Government Royapettah Hospital, The Tamil Nadu Dr. MGR Medical University, Chennai. The study received approval from the Institutional Ethical Committee (IEC) (R.No: ECMGR0309052).

Inclusion and Exclusion criteria: The inclusion and exclusion criteria were in accordance with the guidelines of the Directorate General of Health Services (DGHS) for plateletpheresis donation. The plateletpheresis donors were between 18-50 years of age, weighed 60 kg and above, and met all the criteria specified by the DGHS for plateletpheresis donation [2]. Blood donors who did not meet the DGHS selection criteria and those who were unwilling to participate in the study were excluded.

Study Procedure

Donor-informed consent was obtained for participation in the study. All procedures were performed using an intermittent flow-based apheresis machine, and the citrate-to-blood ratio was fixed at 1:9. The plateletpheresis procedure followed departmental Standard Operating Procedures (SOPs) in accordance with the manufacturer's instructions.

Baseline biochemical parameters (serum calcium, ionised calcium, and magnesium levels) were recorded for each plateletpheresis donor. The donors were informed about the symptoms of citrate toxicity during plateletpheresis, such as peri-oral numbness and tingling sensation. A total of 63 plateletpheresis donors were enrolled and further divided into two groups based on random allocation (odd and even number method)-Group A donors (n=32) were given prophylactic oral calcium supplementation (1 tablet containing 0.323 g Total Ca^{2+}/125 mg elemental Ca^{2+}), and Group B donors (n=31) were given prophylactic slow calcium infusion drip (1 ampoule = 0.931% calcium) with normal saline. The symptoms of citrate toxicity were documented during the procedure, and based on the subjective symptoms, calcium supplementation was titrated accordingly [10]. Post-procedure biochemical parameters (serum calcium, ionised calcium, and magnesium levels) were collected and recorded within 30 minutes of completing each plateletpheresis procedure. The biochemical parameters were analysed using a biochemical analyser, and the results were recorded in the proforma sheet.

STATISTICAL ANALYSIS

The analysis was carried out using SPSS software version 20.0. Demographic details were expressed using descriptive statistics. Pre- and post-procedure biochemical parameters were analysed using a paired t-test. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic profile: Donors in both groups were comparable with respect to age, gender, Body Mass Index (BMI) [11], and haematological parameters, with no significant difference [Table/Fig-1]. The majority of the donors belonged to the younger age group (21-30 years, 40 (63.5%). Among the remaining donors 23 (22.22%) belonged to the age group 31-40 years 14 (11.11%) belonged to the age group 41-50 years, 7 (3.17%) belonged to the age group 18-20 years (n=2).

Parameters	Group-A (Oral calcium group)	Group-B (i.v. Calcium group)
No. of donors (all males)	32	31
Mean age (in years)	29.25	29.77
BMI	26.39	27.07
Hb- Pre procedure (g/dL)	15.1	14.5
Platelet count- pre procedure ($\times 10^9$/L)	267.31	260.19

[Table/Fig-1]: Demographic and common haematological profiles of donors in each group.
BMI: Body mass index

Effect of plateletpheresis on calcium levels: In the present study, a statistically significant decline in S. ionised calcium levels was observed in the oral calcium supplementation group compared to the intravenous calcium supplementation group (1.17±0.09 vs. 1.10±0.11 vs. 1.07±0.25 vs. 1.11±0.14). However, these levels remained within the critical limit for the development of hypercalcaemic symptoms [Table/Fig-2].

S. No.	Biochemical parameters	Mode (groups)	Preprocedure	Postprocedure*	Diff.	p-value
1.	S. Calcium (mg/dL)	Oral Ca^{2+}	10.33±1.62	9.88±1.00	0.45±1.35	0.067
		i.v. Ca^{2+}	10.31±1.33	10.21±0.88	0.10±1.22	0.661
2.	S.i.Ca^{2+} (mmol/L)	Oral Ca^{2+}	1.17±0.09	1.10±0.11	0.08±0.14	0.003 (<0.05)
		i.v. Ca^{2+}	1.07±0.25	1.11±0.14	(-) 0.04±0.27	0.472
3.	S. Magnesium (mg/dL)	Oral Ca^{2+}	2.13±0.30	2.07±0.24	0.05±0.28	0.285
		i.v. Ca^{2+}	2.14±0.22	2.14±0.14	0.00±0.26	0.995

[Table/Fig-2]: Biochemical parameters before and after plateletpheresis (n=63)- Oral Ca^{2+} group (n=32) and i.v. Ca^{2+} group (n=31).

Adverse reactions and citrate toxicity: Out of the 63 plateletpheresis donors, mild citrate toxicity in the form of perioral numbness and tingling sensation was reported in 26 out of the 32 donors in Group A (oral calcium group), while none were reported in Group B (intravenous calcium group). Relationship of oral calcium and intravenous calcium supplementation group with serum ionised calcium levels: Analysing the number of calcium tablets with serum ionised calcium levels among the oral calcium group, six of the donors maintained serum ionised calcium levels within the normal range with a pre-procedural prophylactic dose of one tablet (125 mg elemental calcium) [Table/Fig-3].

No. of calcium tablets given to donors (prophylactic +therapeutic)	No. of donors	Predonation S.i Ca^{2+} (mmol/L)	Postdonation S.i Ca^{2+} (mmol/L)
1 (1+0)	6	1.17±0.60	1.20±0.10
2 (1+1)	7	1.24±0.11	1.11±0.11
3 (1+2)	15	1.15±0.93	1.03±0.08
4 (1+3)	3	1.17±0.09	1.14±0.60
6 (1+5)	1	1.10	1.23

[Table/Fig-3]: Relationship of calcium tablets in the Oral Ca^{2+} supplementation group (n=32) with serum ionised Calcium levels.

Furthermore, analysing the biochemical parameters of all 63 donors with mild citrate toxicity [Table/Fig-4], there was a statistically significant difference in serum ionised calcium levels. The group of donors who manifested mild citrate toxicity (n=26) showed a post-procedure drop in serum ionised calcium levels, while the group of donors who did not manifest mild citrate toxicity (n=37) showed a post-procedure rise (p-value=0.003). However, these changes remained within the critical limits for the development of hypocalcaemia (0.5 mmol/L) and hypercalcaemic symptoms (1.75 mmol/L), respectively.

Parameters	No. of donors manifested with mild citrate toxicity (26)			No. of donors not manifested with mild citrate toxicity (37)			p-value bet. (a) and (b)
	Pre-proc.	Post-proc.*	Diff. (a)	Pre-proc.	Post-proc.*	Diff. (b)	
S.Ca^{2+} (mg/dL)	10.08±1.04	9.70±0.92	0.38±0.83	10.49±1.71	10.28±0.90	0.21±1.54	0.612
S.i.Ca^{2+} (mmol/L)	1.18±0.10	1.07±0.10	0.11±0.12	1.09±0.23	1.12±0.14	(-) 0.04±0.26	0.013 (<0.05)
S.Mg^{2+} (mg/dL)	2.10±0.23	2.05±0.22	0.06±0.26	2.15±0.27	2.15±0.17	0.01±0.28	0.483

[Table/Fig-4]: Comparison of Biochemical profile with mild citrate toxicity among all plateletpheresis procedures.
*values after intervention with calcium supplements (both oral and intravenous calcium infusion drip with normal saline)

DISCUSSION

In the present study, the mean age of all plateletpheresis donors in both groups was observed to be 29.51±7.02 years, with the majority of the donors belonging to the younger age group (21-30 years, n=40; 63.5%). This finding is similar to a study conducted by Suresh B et al., [4], where the majority of the donors (n=55; 61.1%) also belonged to the 21-30 years age group. Furthermore, in the present study, 57.14% of donors (n=36) with a mean BMI of 26.73±3.39 belonged to the pre-obese category based on World Health Organisation (WHO) classification [11]. This finding is comparable to a study conducted by Mangwana S et al., [12], where the mean BMI was 26.80±8.32 kg/m^2.

Regarding the effect of calcium supplementation, a statistically significant decline in serum ionised calcium levels was observed in the oral calcium supplementation group compared to the intravenous calcium supplementation group. However, these changes remained within the critical limit for the development of hypocalcaemia symptoms. The decrease in post-procedure serum ionised calcium levels in the oral calcium group and the corresponding increase in the intravenous calcium group may be attributed to the level and mode of calcium supplementation, with better bioavailability of intravenous calcium infusion drip with normal saline compared to oral calcium supplements [9,13].

In terms of adverse events, the most common adverse event observed in the present study was mild citrate toxicity (41.30%) in the form of tingling, numbness, and perioral paraesthesia. This incidence was higher compared to other studies conducted by Patidar GK et al., (9%) [14], Barbosa MH et al., (2.2%), Khajuria K et al., (3.03%), and lower compared to a study conducted by Dogra K et al., (46.1%) [15-17]. All adverse reactions were observed in the oral calcium group, while the intravenous calcium supplementation group had no adverse reactions, likely due to better bioavailability of calcium supplementation and maintenance of serum ionised calcium levels within the normal range. Additionally, no symptoms of severe citrate toxicity, such as tetany or seizures, were observed in either of the supplementation groups. Despotis GJ et al., reported a severe citrate toxicity rate requiring hospitalisation of only 0.04%, and McLeod BC et al., reported a severe citrate toxicity rate of 0.09% [18,19].

Analysing the number of calcium tablets with serum ionised calcium levels among the oral calcium group, the findings in the present study were similar to the study conducted by Bolan CD et al., [9]. In their study, ingestion of 1 of oral calcium resulted in minimal adverse effects, while ingestion of 2 g of oral calcium resulted in a significant reduction in the severity of paraesthesia's and a modest increase in serum ionised calcium levels. Based on these findings, for Indian population, it may be considered to provide atleast three times the minimal dose of oral calcium tablets (each tablet containing 125 mg elemental calcium) prophylactically to mitigate the symptoms of mild citrate toxicity and enhance donor comfort.

Similarly, on analysing the intravenous calcium group (n=31) with serum ionised calcium levels, there was a modest increase in post-procedure levels (not significant, p-value=0.472), but no manifestations of mild citrate toxicity were observed. This can be attributed to the slow infusion of intravenous calcium along with normal saline, which provides better bioavailability, improved donor comfort, and maintenance of serum ionised calcium levels within the normal range.

These findings are similar to a study conducted by Bolan CD et al., on leukapheresis procedures, where prophylactic calcium infusions reduced clinically significant paraesthesia's by 96%, safely attenuating the marked metabolic effects of citrate administration and resulting in faster and more comfortable procedures [20]. However, it is important to note that cardiac monitoring is required when placing donors on prophylactic intravenous calcium infusion with normal saline due to the inherent risk of developing cardiac arrhythmias and precipitating cardiac arrest [21].

Limitation(s)

Long-term studies on magnesium levels and magnesium supplements following the plateletpheresis procedure need to be conducted to assess the safety profile of donors in relation to hypomagnesaemia.

CONCLUSION(S)

Prophylactic intravenous calcium supplementation showed better bioavailability of serum ionised calcium levels compared to oral calcium supplementation, as evidenced by the absence of symptoms of citrate toxicity. However, if oral prophylactic calcium supplementation is preferred, administering 2-3 tablets of calcium (0.969 g of total calcium/375 mg of elemental calcium) often prevents mild citrate toxicity in Indian population. This results in better retention of plateletpheresis donors, enabling a smooth and comfortable collection of high concentrations of platelets from a single donor. However, it is imperative to conduct more studies with a large number of plateletpheresis donors to observe any donor adverse reactions specific to Indian population.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Transfusion Medicine, RSRM Lying in Hospital, Government Stanley Medical College, Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Transfusion Medicine, Government Stanley Medical College, Affiliated to the Tamil Nadu Dr. MGR Medical University, Chennai, Tamil Nadu, India.
3. Assistant Professor, Department of Transfusion Medicine, ESIC Medical College and PGIMSR, KK Nagar, Chennai, Tamil Nadu, India.
4. Professor and Head, Department of Transfusion Medicine, The Tamil Nadu Dr. MGR Medical University, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. V Naveen Kumar,
Assistant Professor, Department of Transfusion Medicine and Blood Centre,
Government RSRM Lying in Hospital, Government Stanley Medical College,
Chennai-600013, Tamil Nadu, India.
E-mail: naveenkumarv1000@gmail.com

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