

# Therapeutic Thrombocytapheresis as an Important Tool in the Management of Symptomatic Hyperthrombocytosis: A Single-Institution Experience from India

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## ABSTRACT

**Background & Objectives:** Hyperthrombocytosis may cause acquired thrombosis-related symptoms and fatal vascular complications. Currently, therapeutic platelet reduction (TPR) with medical therapy remains the mainstay of hyperthrombocytosis management. We encounter patients with high platelet counts with requests for TPR. Here, we share our experience of TPR procedures in patients with symptomatic hyperthrombocytosis due to various underlying etiologies. **Methods:** The study from January 2013 to October 2020 included 36 patients of hyperthrombocytosis who underwent 82 TPR procedures by apheresis technology. Patient details were obtained from the treatment file and all procedures were performed following recommended instructions and protocol. Statistical analysis was done using the SPSS statistical package. **Results:** The median age of patients was 53 years with mean hemoglobin, platelet count, plateletcrit, and platelet distribution width of 9.9 g/dL,  $1711.3 \times 10^6/\text{mL}$ , 0.57%, and 43.4%, respectively. A total of 26 patients had primary thrombocytosis. The mean TPR procedure time, whole blood volume processed, and anticoagulant used were 162 min, 5070 mL, and 430.3 mL, respectively. The mean reduction of platelets in patients who underwent two and three procedures was 72.4% and 82.7%, respectively ( $P = 0.003$ ). **Conclusion:** We conclude that TPR is a useful method in reducing platelet count rapidly in hyperthrombocytosis. It relieves patients of acute symptoms and prevents thrombotic events. The decision to perform TPR should be individualized and based on the clinical scenario, degree of thrombocytosis, and risk factors associated with TPR procedures.

**KEYWORDS:** Apheresis, essential thrombocythemia, hyperthrombocytosis, therapeutic platelet reduction, thrombocytapheresis

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## INTRODUCTION

Hyperthrombocytosis is defined as platelet counts  $>800-1000 \times 10^9/\text{L}$ .<sup>[1-4]</sup> and may be an incidental finding in patients or may be present with thrombocytosis-related symptoms and complications. Conditions such as benign myeloproliferative neoplasm (MPN) such as essential thrombocythemia (ET), chronic myeloproliferative diseases (CMPD) such as chronic myeloid leukemia (CML), malignancy, chronic inflammatory diseases, bone marrow recovery following myelosuppressive therapy, splenectomy, infections, trauma, hemorrhage, or burns may cause hyperthrombocytosis.<sup>[1,5,6]</sup> While hyperthrombocytosis is reported in up to 50% of MPN patients, its incidence is

lower in CML.<sup>[7,8]</sup> Symptoms are predominantly vasomotor and may include headaches, dizziness, blurring of vision, syncope, and erythromelalgia. In addition, patients with hyperthrombocytosis are at increased risk for major thrombotic and hemorrhagic complications.<sup>[9,10]</sup> Approximately 90% of patients with ET show a mutually exclusive JAK2, CALR, or myeloproliferative leukemia (MPL) mutation.<sup>[11]</sup> Patients with hyperthrombocytosis who have active ongoing complications

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or have additional cardiovascular and/or thrombotic risk factors need treatment.<sup>[12]</sup> While long term management includes drugs like hydroxyurea, anagrelide or interferon-alfa; therapeutic thrombocytapheresis or cytoreduction or therapeutic platelet reduction (TPR) is reserved for acute events. However treatment of uncomplicated hyperthrombocytosis is still a subject of debate.<sup>[13]</sup> The choice and intensity of cytoreduction depends on the severity of thrombocytosis and impending risk for ischemic/hemorrhagic events.<sup>[14]</sup>

TPR is currently a Category II (second-line therapy) American Society for Apheresis (ASFA) recommendation in symptomatic primary thrombocytosis and Category III (optimum role not established, decision individualized) in the prophylactic high-risk ET or secondary thrombocytosis setting.<sup>[15]</sup> The role of TPR as a prophylactic measure to prevent untoward consequences in patients at high risk for occlusive or hemorrhagic events has also been described.<sup>[16,17]</sup> Ours being a tertiary care hospital with a dedicated blood center with apheresis facilities, we encounter patients with high platelet counts with requests for TPR.

### Aims and objectives

Here, we share our experience of TPR procedures in patients with symptomatic hyperthrombocytosis due to various underlying etiologies.

## MATERIALS AND METHODS

The observational prospective study from January 2013 to October 2020 included 36 patients of hyperthrombocytosis who underwent 82 TPR procedures. All procedures were performed by the same apheresis team following the manufacturer's instructions and departmental standard operating procedure (SOP).

### Ethical committee clearance

Due ethical clearance was obtained from the hospital ethics committee to conduct the study. Procedures were done using recommended apheresis equipment (Amicus version 3.21, Fresenius Kabi AG, Bad Homburg, Germany), closed system disposable kits, and anticoagulants (acid-citrate-dextrose-A [ACD-A]) after obtaining prescription from the treating physician. Before starting TPR, detailed demographic, laboratory, and clinical details were obtained from each patient and documented accordingly. For patients with poor antecubital venous access, indwelling central or peripheral venous catheters were used for the procedure. The of each procedure was based on the maximum volume or number of platelets that could be removed based on patient weight, height, hematological values, and total blood volume. As per SOP, a maximum of 1.5 times blood volume was processed over any range of platelet counts.

Procedure details such as total blood volume processed, ACD-A volume infused, procedure time, and blood flow rate were recorded for each procedure in the procedure register. All patients were administered prophylactic oral or intravenous calcium (1000 mg) 30–45 min before procedure

to prevent citrate-related toxicities. All were explained the details of procedure before starting it. They were advised to report discomfort, if any, to the apheresis team during or after the procedure and were asked to take adequate rest after the procedure. Adverse reactions, if any, were managed appropriately and documented following departmental SOP.

### Statistical analysis

Statistical analysis was done using the SPSS statistical package (IBM, 2015, Armonk, New York, USA). Demographic, laboratory, and clinical details of patients' were obtained from hospital computer software, captured in the MS office excel sheet, and statistically analyzed. Quantitative variables were calculated as mean  $\pm$  standard deviation or N (%) and analyzed using the paired Student's *t*-test. "*P*" value of  $< 0.05$  was considered statistically significant.

## RESULTS

The observational prospective study included 36 patients with hyperthrombocytosis who underwent therapeutic thrombocytapheresis for platelet reduction. The median age of patients was 53 years with a male preponderance. Table 1 describes the demographic, laboratory, and clinical features of these patients. The mean hemoglobin, platelet count, plateletcrit, and platelet distribution width were observed to be 9.9 g/dL,  $1711.3 \times 10^6/\text{mL}$ , 0.57%, and 43.4% respectively. A total of 26 patients (72.2%) had primary thrombocytosis mainly caused by ET and CML. Out of 10 cases of secondary thrombocytosis, 5 (50%) had hyperthrombocytosis following surgery. Thirty-one (86.1%) patients complained of constant lightheadedness or dizziness, followed by 29 (80.6%) with persistent headache. Tingling sensation in extremities was observed in 21 (58.3%) patients. A total of 82 therapeutic thrombocytapheresis procedures were performed in 36 patients using the Amicus apheresis equipment [Table 2]. Forty-nine (60.5%) procedures were done using central or peripheral catheters under aseptic and antiseptic measures. Mean procedure time, whole blood volume processed, and anticoagulant used were 162 min, 5070 mL, and 430.3 mL, respectively. Mean platelet collection efficiency of the equipment was normal and calculated to be 64.7%. The mean postprocedure platelet count in the patients was observed to be  $383.4 \times 10^6/\text{mL}$ .

Figure 1 shows the gradual decrement of platelet counts in patients who underwent 2 or 3 procedures of therapeutic thrombocytapheresis consecutively. The mean preprocedure platelet counts were observed to be  $2200.1 \times 10^6/\text{mL}$  (range: 1661.3–2921.3) and  $1401.9 \times 10^6/\text{mL}$  (range: 1120.2–1648.4) in patients undergoing three and two procedures, respectively ( $P = 0.039$ ). In patients who underwent three procedures, the mean platelet count reduced from  $2200.1 \times 10^6/\text{mL}$  to  $379.6 \times 10^6/\text{mL}$  (82.7%) after the third procedure. The mean reduction of platelets in patients who underwent two procedures was 72.4% ( $P = 0.003$ ). We observed that the mean reduction of platelets after the first procedure was significantly high when the mean preprocedure platelet count was more ( $2200.1 \times 10^6/\text{mL}$  vs.  $1401.9 \times 10^6/\text{mL}$ ). The mean reduction of platelet count was 51.3% after the first procedure in patients undergoing three procedures; the reduction was



**Table 1: Demographic, laboratory, and clinical features of patients undergoing therapeutic platelet reduction (n=36)**

Donor parameters	Statistical values
Demography	
Age (years), median (range)	53 (16-78)
Gender (female: male)	1:2.5
Weight (kg), mean±SD	61.9±9.6
Height (m), mean±SD	1.62±0.1
BSA (m <sup>2</sup> ), mean±SD	1.64±2.7
TBV (mL), mean±SD	Male: 4717±411, Female: 3379±369
Laboratory	
Hb (g/dL), mean±SD	9.9±2.4
Hct (%), mean±SD	30.7±7.4
WBC count (×10 <sup>6</sup> /mL), mean±SD	10.6±4.1
Platelet count (×10 <sup>6</sup> /mL), mean±SD	1711.3±514.3
Pct (%), mean±SD	0.57±0.19
MPV (fL), mean±SD	10.1±2.31
PDW (%), mean±SD	43.4±5.82
FVIII (IU/mL), mean±SD	1.08±0.24
Fibrinogen (mg/dL), mean±SD	325.3±71.7
Clinical details n (%)	
Diagnosis	
Primary thrombocytosis (n=26)	
Essential thrombocythemia	11 (42.3)
Chronic myeloid leukemia	13 (50)
Chronic myelomonocytic leukemia	2 (7.7)
Secondary thrombocytosis (n=10)	
Postoperative	5 (50)
Malignancy	2 (20)
Chronic inflammation	2 (20)
Infection	1 (10)
Symptoms, n (%)	
Headache	29 (80.6)
Lightheadedness or dizziness	31 (86.1)
Weakness	27 (75)
Fainting	7 (19.4)
Tingling sensation in extremities	21 (58.3)
Heaviness in chest	8 (22.2)

BSA: Body surface area, TBV: Total blood volume, Hb: Hemoglobin, WBC: White blood cells, Pct: Plateletcrit, MPV: Mean platelet volume, PDW: Platelet distribution width, SD: Standard deviation, FVIII: Factor VIII, Hct: Hematocrit

42.6% in those who underwent two procedures ( $P = 0.032$ ). Reduction of platelets in subsequent procedures was comparable in both categories of patients.

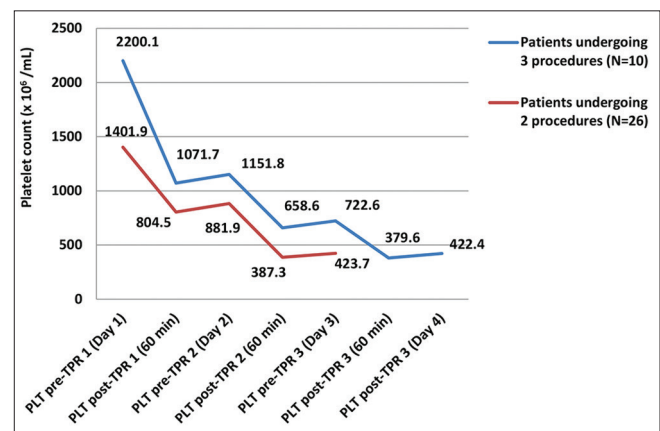
## DISCUSSION

All patients of hyperthrombocytosis need evaluation to differentiate a primary proliferative process or a reactive response to an inciting condition as the cause of elevated platelet counts.<sup>[18]</sup> The present study observed 26 patients of primary thrombocytosis and 10 patients of secondary thrombocytosis. While CML was the major cause of primary thrombocytosis, the main inciting condition leading to

**Table 2: Details of therapeutic platelet reduction procedures (n=82)**

Parameters	Statistical values
Venous access, n (%)	
Antecubital venous access	33 (40.2)
Central or peripheral catheters	49 (59.8)
Anticoagulant (ACD) (mL), mean±SD	430.3±80.3
Draw rate (mL/min), mean±SD	52.8±10.7
Return rate (mL/min), mean±SD	66.4±8.9
Mean procedure time (min), mean±SD	162±32.4
Whole blood processed (mL), mean±SD	5070±977.2
Mean collection efficiency (%), mean±SD	64.7±5.3
Procedure with adverse events, n (%)	4 (4.9)
Postprocedure platelet count (×10 <sup>6</sup> /mL), mean±SD	383.4±52.4
Postprocedure Hb (g/dL), mean±SD	9.2±2.1
Postprocedure Hct (%), mean±SD	28.9±8.1
Postprocedure FVIII (IU/mL), mean±SD	1.02±0.31
Postprocedure fibrinogen (mg/dL), mean±SD	298.7±68.8

ACD: Acid-citrate-dextrose, SD: Standard deviation, Hb: Hemoglobin, FVIII: Factor VIII, Hct: Hematocrit

**Figure 1: Decrement of platelet counts in patients undergoing therapeutic platelet reduction (N=36)**

secondary thrombocytosis was postsurgical events. It was interesting to note that all 10 patients requiring three TPR procedures for cytoreduction belonged to the category of primary thrombocytosis. Considering all patients of primary thrombocytosis, the mean preprocedure platelet count was observed to be  $1507.9 \times 10^6/\text{mL}$ . A total of 18 of these patients (69.2%) revealed JAK2 mutations and one showed MPL mutations (exons 10 and 11) who was otherwise negative for JAK2 mutations. In an Indian study by Sazawal *et al.*, JAK2 V617F mutation was found in 68% of CMPD, 82% of polycythemia vera (PV), and 70% of ET.<sup>[19]</sup> The median age at diagnosis of ET is in the sixth decade of life, with <20% of patients being diagnosed below 40 years.<sup>[20]</sup> The median age of patients under the present study was 53 years and that with ET only was 59 years. As high as 25 (69.4%) patients were males with an M: F ratio of 2.3:1. Ten patients who underwent three consecutive TPR procedures had a mean preprocedure platelet count of  $2200.1 \times 10^6/\text{mL}$ , which



was significantly higher than those who underwent two TPR procedures ( $P = 0.039$ ).

The risk of thrombotic complications with reactive thrombocytosis is low, and 1.6% of patients with reactive thrombocytosis had thrombotic complications in one large case series.<sup>[21]</sup> In clonal thrombocytosis, especially in ET and PV, thrombotic complications are a major cause of morbidity and mortality and the primary factor in determining treatment strategy.<sup>[22]</sup> We observed thrombotic complications in 7 (63.6%) patients of ET in the form of stroke or transient ischemic attack.

Previous authors have suggested that aged patients (>60 years) with prior thrombohemorrhagic event and platelet counts  $>1500 \times 10^6/\text{mL}$  confer a high risk for thrombohemorrhagic events in primary thrombocytosis and respond well to cytoreductive treatment.<sup>[23]</sup> Selected patients of hyperthrombocytosis may need rapid platelet reduction during the first critical days. Such intervention provides symptomatic relief and prevents new or worsening major vascular complications.<sup>[24]</sup> Cases illustrating the role of TPR to prevent untoward consequences in patients at high risk for occlusive or hemorrhagic events have also been described.<sup>[16,17]</sup> We performed 82 procedures of TPR in 36 patients and successfully reduced the platelet burden in all patients.

A mean whole blood volume of 5070 mL was processed in a mean time of 162 min using 430.3 mL of mean anticoagulant volume. A total of 49 (59.8%) patients required central or peripheral catheterization due to poor peripheral venous access. Methods involving TPR in patients and plateletpheresis in normal donors are almost identical. TPR is performed on sick individuals and involves the processing of maximum allowable whole blood volume to reduce platelets optimally and control the state of hyperthrombocytosis. As procedure time directly concerns the donor/patient in apheresis, it is an important parameter to evaluate their safety and comfort. While Burgstaler *et al.* and Das *et al.* observed mean procedure time of 78 min and 79.6 min by Amicus during normal plateletpheresis, other studies on TPR estimated procedure time between 103 min and 218 min using various apheresis equipments.<sup>[25-28]</sup>

Apheresis is a safe procedure without significant complications, but at times, symptoms due to citrate toxicity and other adverse events may cause discomfort to the donors.<sup>[29]</sup> Adverse events such as citrate toxicity and vasovagal reactions were observed in four patients (4.9%). Despite administering prophylactic calcium (1000 mg) as suggested by previous authors, citrate toxicity was found in two female patients of primary thrombocytosis.<sup>[26,30]</sup> Various reasons of citrate toxicity despite prophylactic calcium administration have been observed and discussed by previous authors.<sup>[29,30]</sup>

Plateletpheresis has effects on coagulation parameters. Decrease in prothrombotic FVIII, fibrinogen, antithrombin, protein C, and protein S levels has been observed by previous authors.<sup>[31,32]</sup> Due to limited resources, only FVIII and fibrinogen were measured in patients under study. Although

FVIII and fibrinogen values reduced from 1.08 IU/mL and 325.3 mg/dL to 1.02 IU/mL and 298.7 mg/dL, respectively, at every instance, the values were found to be within recommended ranges.

The usefulness of rapid plateletpheresis in preventing additional morbidity in patients with thrombocytosis by removing large numbers of circulating platelets has already been documented.<sup>[33,34]</sup> While Taft *et al.* were able to collect  $16\text{--}26 \times 10^{11}$  platelets, and up to  $98 \times 10^{11}$  when processing volumes of more than 10 L by using the Haemonetics model 10 and the Aminco Celltrifuge, McCarthy *et al.* found a reduction between  $1580$  and  $2665 \times 10^3/\mu\text{L}$  of peripheral platelets by apheresis when using the CS-3000 Fenwal separator.<sup>[34,35]</sup> Das *et al.* found the Haemonetics MCS + to be highly efficient in the acute management of ET, and consecutive three procedures could reduce the platelet count significantly and prepare the patient for cardiac surgery.<sup>[16]</sup> After successful completion of cytoreduction therapy using apheresis technology, the mean postprocedure platelet count in the current study was observed to be  $383.4 \times 10^6/\text{mL}$  with a significant mean decrement of 76.4% ( $P = 0.027$ ).

Mean platelet count reduced by 82.7% and 72.4%, respectively, in patients who underwent three and two procedures. We also observed that the mean reduction of platelets after the first procedure was statistically significant ( $P = 0.032$ ) when the mean preprocedure platelet count was higher. Such a result may be expected because, with a higher number of platelets in the patient/donor, a greater platelet yield is obtained in the end product, thereby causing a greater fall in the person's platelets after TPR/plateletpheresis.<sup>[36,37]</sup>

Data on the clinical utility of TPR are largely based on anecdotal experience, and the current AFSA guidelines are not supported by randomized controlled trials.<sup>[38]</sup> TPR should be considered with relative urgency in patients with platelet counts above  $1500 \times 10^6/\text{mL}$  and an increased risk of major hemorrhage, especially in settings where cytoreductive agents are contraindicated or less desirable due to their relatively slow onset of action.<sup>[15]</sup>

## CONCLUSION

TPR is a useful method in reducing platelet count rapidly in hyperthrombocytosis and relieving patients of acute symptoms and preventing them from thrombotic events. Such procedures should always be performed very meticulously to maintain patient safety. Moreover, decision to perform TPR should be individualized and based on the clinical scenario, degree of thrombocytosis, and risk factors associated with TPR procedures.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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