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Comparison of efficacy of low and high dose prophylactic platelet transfusion therapy in thrombocytopenic haemato-oncology patients

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ABSTRACT

Introduction: To determine an optimal platelet dose in thrombocytopenic patients is important for their judicious use. Transfusing platelets in different doses and comparing their post transfusion response can achieve this.
Aim: To compare the efficacy of low and high dose single donor apheresis platelets (SDAP) with standard dose transfusions in terms of Corrected Count Increment (CCI), Percent Platelet Recovery (PPR) and transfusion free interval.
Method: It was a prospective case control study done from January 2016 to April 2017. Twenty-eight hemato-oncology patients with CCI ≥ 5000 at 20–24 hours after standard dose (3×10^{11}/unit), received low dose (1.5×10^{11} platelets/unit) and high dose ($> 4 \times 10^{11}$ platelets/unit) SDAP. CCI and PPR were calculated after 20 to 24 hours of transfusion. Transfusion free interval and bleeding episodes were also noted. Grading was done according to WHO bleeding scale.
Result: There was no statistical difference in CCI and PPR when standard dose was compared with low dose (CCI: p = 0.92, PPR: p = 0.89). When standard and high dose was compared, standard dose gave better results than the high dose in terms of CCI (p = 0.006) and PPR (p = 0.008) although the post transfusion increments were comparable (p = 0.938). High dose gave better (p = 0.005) platelet count increments than low dose but CCI (p = 0.04) and PPR (p = 0.05) was significantly less than the low dose. The difference in transfusion free intervals after three doses was not significant. Donor exposure to the patients was significantly (p = 0.000) reduced to 17.5%.
Conclusion: Possibility of low dose as an alternative to standard dose can be considered in view of comparable platelet response indicators and significantly reduced donor exposure.

1. Introduction

Determining an optimal platelet dose for transfusion in thrombocytopenic patients is essential. There is always an increase in demand with increasing awareness, stringent storage requirement for obtaining them, a short shelf life to benefit more patients and to maintain the inventory further demands judicial use of this scarce resource. As per American Association of Blood Banks [1] the recommended dose of single donor apheresis platelets is 3×10^{11} per unit for a 75 kg adult with BSA 2.0m [2].There are only a handful of western studies on platelet doses and have shown different aspects. According to Slichter et al [2], low dose of platelets led to a lesser number of platelets transfused per patient, but an increased number of transfusion events and platelet dosing had no significant effect on the incidence of bleeding in hypo proliferative thrombocytopenia patients. Heddle et al. [3] indicated that a transfusion of low dose resulted in significantly more platelet transfusion episodes but the donor exposures from platelet transfusions were not significantly different in the standard and low dose. Hence, this study was planned to compare the efficacy of low and high dose with the standard dose of single donor apheresis platelet (SDAP) transfusions in terms of platelet transfusion response indicators-Corrected Count Increment (CCI), Percent Platelet Recovery (PPR), their transfusion free interval and bleeding episodes in thrombocytopenic hemato-oncology patients, so as to optimize the use of one of the most precious resource of our blood component inventory.

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2. Materials and methods

This was a prospective case control study conducted at a tertiary care centre in North India from January 2016 to April 2017.Hemato-oncology patients requiring frequent blood and blood components were included in the study. The study was done after getting approval from the Institute Ethics Committee and obtaining a written informed consent from the patients after explaining the nature of the study.

Study population included adult patients who had an adequate platelet response and were unlikely to be refractory to platelet transfusion at the time of enrollment and would require multiple platelet transfusions.

2.1. Inclusion criteria

- Patients with age > 18 years.
- Patients without any active bleeding at the time of enrolment.
- Thrombocytopenic hemato-oncology hospitalised patients with the diagnosis of AML, aplastic anaemia, patients on chemotherapy for hematological malignancies which are non refractory to platelet transfusion.

2.2. Exclusion criteria

- Bleeding during study period.
- Patients with inadequate response (CCI < 5000) to platelet transfusion as revealed after receiving a standard dose (3×10^{11} /unit) of apheresis platelets.
- Use of drugs affecting platelet number or function (eg Amphotericin B, vancomycin)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic Uremic Syndrome (HUS)
- Fever or sepsis
- Patients with splenomegaly

2.3. Study methodology

Patients fulfilling the inclusion criteria and requiring prophylactic platelet transfusion therapy were first given a standard platelet dose to screen the response to platelet transfusion. CCI < 5000 at 20–24 h of transfusions determined by the laboratory criteria was considered inadequate, as there was a risk of refractoriness. If CCI ≥ 5000 then they were given a low dose platelet transfusion followed by a high dose platelet transfusion for their second and third platelet transfusion episodes respectively. Thus, the same patient acted as a case (low/high dose) as well as a control (standard dose) at different time points during their stay in the hospital based on the type of platelet dose they received as shown in Fig. 1.

2.4. Platelet product preparation

ABO identical SDAPs were prepared by using automated cell separator (TRIMA accel, Terumo BCT, Lakewood, Colorado, USA) or (AMICUS, Fresenius Kabi, Germany) obtained either from replacement or voluntary donors who qualified the criteria for apheresis platelet donation as per DGHS [4] technical manual and after obtaining an informed consent for the procedure from the donors. For Standard dose, platelet yield of 3×10^{11} /unit was harvested. For low dose, standard dose apheresis product was split, using sterile connecting device (Terumo Sterile Tubing Welder) into two low dose products (i.e. 1.5×10^{11} platelets/unit) or a double yield (6×10^{11} platelets/unit) SDAP product was divided into one low dose (1.5×10^{11} platelets/unit) and one high dose ($\geq 4.5 \times 10^{11}$ platelets/unit). The platelet yield depended on the pre-procedure platelet count of the donors, which was done on a hematology analyzer (ORION 60) after drawing 2 ml of EDTA sample. SDAP was harvested according to the requisition received from

the clinician as per the patient's platelet counts and their clinical profile. These SDAP products were then divided into required doses by observing the actual count in the harvest by the hematological analyzer (ORION 60). According to dose they were further divided into volumes after weighing the bags.

$$\text{Volume of product} = \frac{\text{Weight of the product}}{\text{Specific gravity}}$$

This product was then released for transfusion as and when required. Thus, the same patient acted as the control as well as the case in the study at different point of time.

Patients received apheresis platelets as low dose (1.5×10^{11} platelets /unit), medium dose (3×10^{11} platelets/unit) and high dose ($> 4.5 \times 10^{11}$ platelets/unit) after splitting of SDAP products when a request was received based on the pre transfusion platelet count of the patient. Pre transfusion threshold was as per our institutions protocol (Fig. 2).

The post transfusion counts were assessed after 20–24 h of transfusion and corrected count increment (CCI), percent platelet recovery (PPR) was calculated.

Inter transfusion interval was also recorded as the number of days between two platelet transfusions of different doses.

Bleeding episodes were also noted during the study period in each patient after every dose and graded according to WHO bleeding scale [3].

2.5. Statistical analysis

In this study the measurable data was presented as mean and standard deviation. The numeric data was tested for its normality using Kolmogorov Smirnov Test (K-S test).

As each patient received all three doses of platelets, we compared the post transfusion platelet increment, post transfusion platelet count, CCI, percent platelet recovery and the transfusion free interval. Comparison was done between these dose groups as standard dose vs low dose, standard dose vs. high dose and low dose vs. high dose by using Paired-T test. The difference was considered significant if $p < 0.05$. Statistical analysis was performed using SPSS statistical Software.

3. Results and observation

A total of 81 adult in-patients suffering from hemato-oncological disorders received standard dose and were screened for an adequate response to the first transfusion. They were not eligible to participate in the study if CCI was < 5000 after 20 to 24 h to platelet transfusion therapy to avoid inclusion of possible refractory patients. Finally 28 stable patients with adequate platelet response of CCI ≥ 5000 and fulfilling the inclusion criteria were enrolled in the study. Out of these 28 patients, 17 were males and 11 were females with Male: Female ratio of 1.5:1 and their age ranged from 18 years to 70 years with a mean age of 36.71 ± 15.13 years. Mean weight (kg) and height (cm) was 63.75 ± 12.05 and 166.09 ± 10.30 respectively. Mean body surface area (m²) and blood volume (ml) was 1.68 ± 0.22 and 4781.2 ± 903.8 respectively.

The efficacy of low and high dose with respect to the standard dose was assessed in terms of their transfusion response indicators and patient's clinical profile.

Twenty-four out of these 28 patients receiving the standard dose were followed up for the low dose as three of them were discharged due to the spontaneous recovery in their platelet counts and one of them had grade III bleed. Twenty-two of these twenty four patients were followed up for the high dose as two out of these twenty four patients were discharged due to adequate rise in their platelet counts after low dose. Thus, we followed 28 transfusion episodes after standard dose, 24
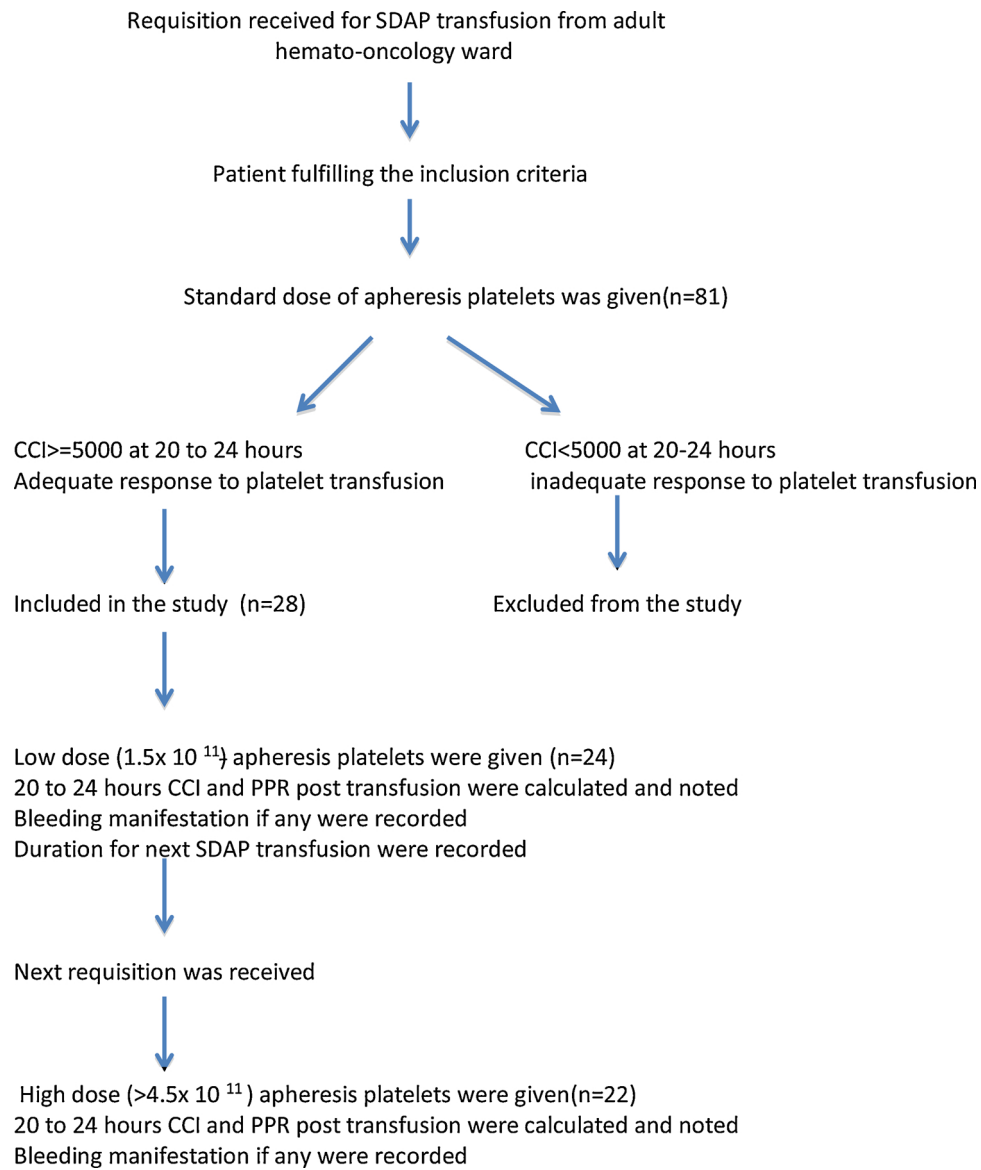
Requisition received for SDAP transfusion from adult
hemato-oncology ward

↓

Patient fulfilling the inclusion criteria

↓

Standard dose of apheresis platelets was given(n=81)

↙   ↘

CCI>=5000 at 20 to 24 hours   CCI<5000 at 20-24 hours
Adequate response to platelet transfusion   inadequate response to platelet transfusion

↓   ↓

Included in the study (n=28)   Excluded from the study

↓

Low dose (1.5x 10^{11}) apheresis platelets were given (n=24)
20 to 24 hours CCI and PPR post transfusion were calculated and noted
Bleeding manifestation if any were recorded
Duration for next SDAP transfusion were recorded

↓

Next requisition was received

↓

High dose (>4.5x 10^{11}) apheresis platelets were given(n=22)
20 to 24 hours CCI and PPR post transfusion were calculated and noted
Bleeding manifestation if any were recorded

Fig. 1. Flow diagram of study showing patient enrollment and platelet transfusion.

• Platelet count $\leq 10 \times 10^9$/L in a patient without bleed
• Platelet count $\leq 20 \times 10^9$/L in a patient with fever/sepsis /chemotherapy and other drugs.
• Platelet count $\leq 50 \times 10^9$/L for an invasive procedure (liver biopsy) /central line insertion.
• Platelet count $\leq 100 \times 10^9$/L for major surgical procedure.

Fig. 2. Prophylactic platelet transfusion trigger.

transfusion episodes after low dose and 22 after high dose platelets.

Majority of our patients were AML (n = 13, 46.42%) followed by APML (n = 7, 25%), Aplastic anemia (n = 4, 14.2%), multiple myeloma (n = 2, 7.14%) and others like CLL (n = 2), MDS (n = 2), DLBL (n = 2) and Hodgkin's Lymphoma (n = 2) together as 7.14%.

Post transfusion response indicators (CCI and PPR) along with platelet increments and transfusion free intervals and bleeding episodes have been summarized in Table 1. Figs. 3 and 4 shows a trend of CCI

and PPR with all the three doses of platelet transfusion.

The comparison of response indicators (CCI and PPR) of the standard versus low dose group, did not yield statistically significant (CCI = 12,553 ± 7598, PPR = 36.11 ± 24 vs. CCI = 12,279 ± 10,842, PPR = 35.00 ± 31.7, (p = 0.922, p = 0.89) results. On comparison of standard with high dose platelet transfusions, significantly better CCI and PPR were observed with the standard dose (CCI = 12267.04 ± 7790.5, PPR = 35.27 ± 24.64 vs. CCI = 6979.8 ± 4182.8, PPR = 19.99 ± 12.68), (p = 0.006, p = 0.008) at 20–24 h. Whereas, the comparison of low and high dose platelet transfusion episodes, significantly better CCI and PPR were observed with the low dose (CCI = 11,583 ± 10205.5, PPR = 32.88 ± 29.65 vs. CCI = 6979.7 ± 4182.8, PPR = 19.99 ± 12.68, (p = 0.04,p = 0.05) platelet transfusions.

No significant difference was observed in transfusion free intervals with standard and low dose (p = 0.85), with standard and high dose (p = 0.20) and with low and high dose (p = 0.21).

Donor Exposure to the patient due to splitting of SDAP to form different dose

A total of 61 SDAP products were harvested for 28 enrolled patients during study period, but 74 SDAP platelet transfusions were given. This was possible due to the splitting of 61 apheresis units to form 74

Table 1
Post transfusion platelet increments and response indicators (CCI and PPR) with different doses of platelet products.

Parameters	Standard dose (3.1 $\pm$ 0.14 $\times$ 10^{11} platelets per unit) (n = 28)	Low dose (1.49 $\pm$ 0.30 $\times$ 10^{11} platelets per unit) (n = 24)	High dose (4.9 $\pm$ 1.0 $\times$ 10^{11} platelets per unit) (n = 22)
Pre-transfusion platelet count(X10^9/L) (Mean $\pm$ SD)	13.071 $\pm$ 5.96	12.416 $\pm$ 6.39	13.318 $\pm$ 7.133
Post-transfusion platelet Count after 20–24 h of transfusion(X10^9/L) (Mean $\pm$ SD)	36.071 $\pm$ 13.64	24.125 $\pm$ 12.45	35.954 $\pm$ 21.03
Post-transfusion increment(X10^{9}platelets/L) (Mean $\pm$ SD)	23.000 $\pm$ 11.89	11.708 $\pm$ 10.28	22.636 $\pm$ 18.06
CCI (Mean $\pm$ SD))	12511.50 $\pm$ 7384.5	12279.92 $\pm$ 10842.72	6979.77 $\pm$ 4182.8
PPR (%) (Mean $\pm$ SD)	35.81 $\pm$ 23.23	35 $\pm$ 31.7	19.9 $\pm$ 12.6
Bleeding episode	Grade III bleed in one patient	Nil	Grade I bleed in one patient
Interval to next transfusion (Mean $\pm$ SD)	3.71 $\pm$ 3.4 days	3.36 $\pm$ 4.4 days	7.24 $\pm$ 7.9 days

customized units of low or high dose for a particular patient. Thus, there was a 17.5% reduction in donor exposure and was statistically significant (p = 0.000).

3.1. Bleeding episodes

Grade I bleed was seen in one patient after high dose and Grade III bleed was seen in another patient after standard dose of platelet transfusion. Whereas, no bleeding episode was observed after the administration of low dose.

3.2. Adverse events with different doses

Out of total 74 transfusion events, a single adverse event was observed in the form of petechiae after receiving high dose platelet transfusion. This was grade I bleed according to WHO bleeding scale and was recorded as a bleeding episode for assessment of clinical efficacy. There were no other adverse events seen in the study population during the study period.
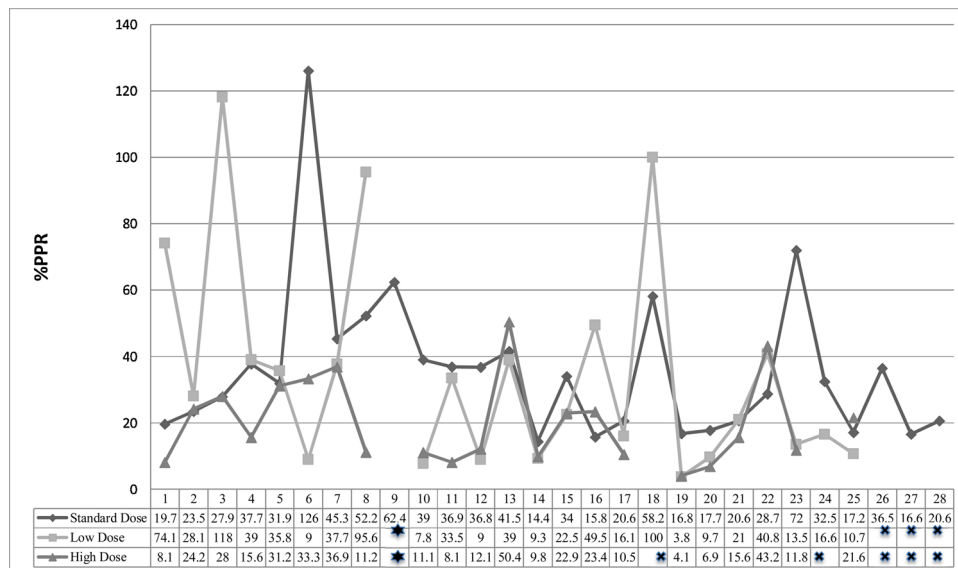
3.3. Gender based comparison

In males and females with a low dose, we observed that increments (males = 8000 $\pm$ 6653 vs. females = 19,125 $\pm$ 12,574) and platelet

recovery (males = 26.09 $\pm$ 22.25 vs. females = 52.82 $\pm$ 41.22) were significantly higher (p = 0.009) in females suggesting the efficacy of low dose. These post transfusion recovery parameters were not statistically significantly different for standard and high dose.

4. Discussion

This study was conducted to assess the efficacy of three different apheresis platelet dose products (standard, low and high) in hemato-oncology patient in our institute with carefully designed exclusion criteria to avoid the bias due to immune and non-immune causes. Many factors both immune and non-immune can influence the post transfusion platelet recovery in multi-transfused hemato-oncology patients such as; alloimmunization to Human platelet antigen (HPA) system and Human Leucocyte antigen (HLA) system. Patients showing an adequate post transfusion response as CCI $\geq$ 5000 at 20–24 h were included in the study thereby excluding potentially refractory patients. Dose response relationship between the number of platelets transfused and the incidence of alloimmunization has not been established so far to the best of our knowledge. In our study, efficacy of different doses of apheresis platelet products was evaluated in terms of post transfusion platelet increment, CCI and PPR.As per our institute transfusion policy, these patients were transfused only ABO identical SDAP to prevent the interference of naturally occurring ABO isoagglutinins which can lead

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Standard Dose	19.7	23.5	27.9	37.7	31.9	126	45.3	52.2	62.4	39	36.9	36.8	41.5	14.4	34	15.8	20.6	58.2	16.8	17.7	20.6	28.7	72	32.5	17.2	36.5	16.6	20.6
Low Dose	74.1	28.1	118	39	35.8	9	37.7	95.6	✹	7.8	33.5	9	39	9.3	22.5	49.5	16.1	100	3.8	9.7	21	40.8	13.5	16.6	10.7	✹	✹	✹
High Dose	8.1	24.2	28	15.6	31.2	33.3	36.9	11.2	✹	11.1	8.1	12.1	50.4	9.8	22.9	23.4	10.5	✹	4.1	6.9	15.6	43.2	11.8	✹	21.6	✹	✹	✹

✹	Gap in continuity of line diagram signifies unavailability of patient due to discharge
✷	Grade III bleed

Fig. 3. % PPR in Standard, low and high dose in 28, 24 and 22 patients respectively.
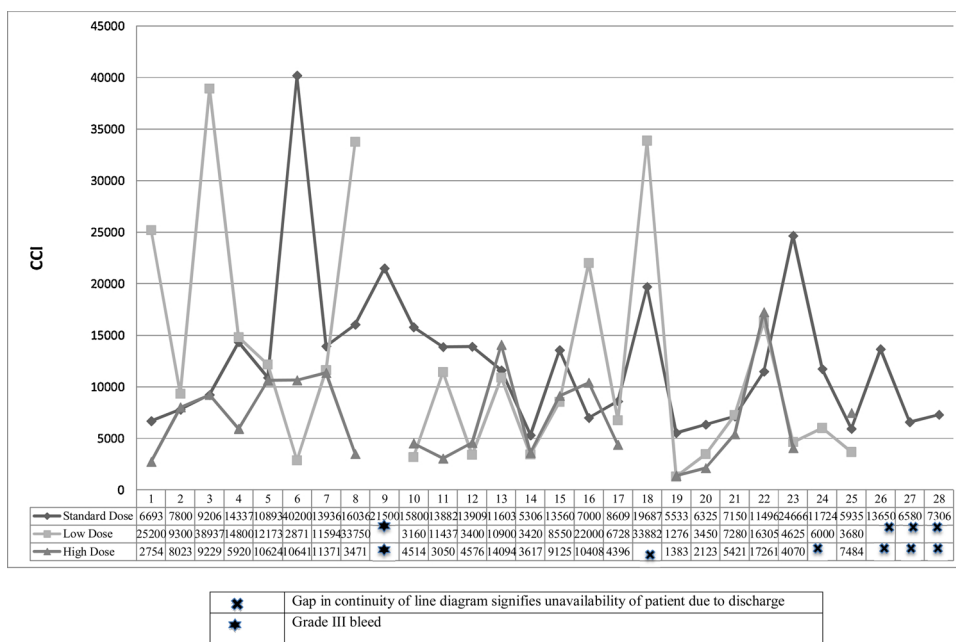
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Standard Dose	6693	7800	9206	14337	10893	40200	13936	16036	21500	15800	13882	13909	11603	5306	13560	7000	8609	19687	5533	6325	7150	11496	24666	11724	5935	13650	6580	7306
Low Dose	25200	9300	38937	14800	12173	2871	11594	33750	✖	3160	11437	3400	10900	3420	8550	22000	6728	33882	1276	3450	7280	16305	4625	6000	3680	✖	✖	✖
High Dose	2754	8023	9229	5920	10624	10641	11371	3471	✳	4514	3050	4576	14094	3617	9125	10408	4396	✖	1383	2123	5421	17261	4070	✳	7484	✳	✳	✳

✖	Gap in continuity of line diagram signifies unavailability of patient due to discharge
✳	Grade III bleed

Fig. 4. CCI in Standard, low and high dose in 2824 and 22 patients respectively.

to low CCI post transfusion. In this study, we also excluded patients with sepsis as hematophagocytosis is commonly observed in these patients and can lead to sepsis-induced thrombocytopenia. In addition, sepsis produces a pro inflammatory response leading to thrombocytopenia due to their sequestration in lungs liver and intestine. All this leads to a drop in CCI due to more consumption of platelets in a septic state. Fever is an important cause of refractoriness in hemato-oncological patients therefore we tried to exclude patients with high fever or other confounding factors. Another important reason for decreased recovery of transfused platelets in these patients is a large spleen leading to early sequestration of platelets. All the patients in our study had a normal spleen as per their clinical records. The use of various chemotherapeutic agents in these patients can be associated with decreased platelet recovery and survival due to formation of drug dependent platelet antibodies. Majority of our patients were of AML who were mostly in induction phase or consolidation phase receiving cytarabine and doxorubicin. APML patients were on Arsenic trioxide (ATO) and All-trans retinoic acid (ATRA). Aplastic anemia patients were usually on no drugs other than multivitamins and transfusion support. Patients on antibiotics for active infections were also excluded. So, in our study we tried to reduce the chance of drugs interfering in post transfusion outcomes to as minimum as possible.

We even compared all the possible parameters after giving different doses unlike the other studies where they compared only pinpoint parameters like either the increment or the CCI or only the adverse events associated with different doses or transfusion free intervals. Table 2(Annexure 1) compare other studies with our study with respect to all these parameters. We also tried to analyze our data on the basis of gender and attempted to compare the findings in male and female patients. We observed that post transfusion platelet count increment and %PPR after the low dose was found to be significantly high in females than the male patients with the p value of 0.009 and 0.049 respectively. Whereas, CCI and transfusion free interval were comparable in males and females after transfusion of low dose. These findings are concordant to our knowledge that in females due to less blood volume and BSA the post transfusion increments are better than males. The better post transfusion recovery in female patients in our study with the low dose further supports the efficacy of low dose.

Our response to platelet transfusion was more consistent and similar

to other studies with standard and low dose however as we increased the dose the post transfusion increments were less than the expected increments. Similar observations has been recorded previously in the studies on mathematical model on platelet survival by JK Hersh et al. [5], where authors observed that survival would be decreased at very high platelet concentrations relative to survival at normal concentrations. In the STOP study by Heddle et al. [3] grade 4 bleed was seen in 5.2% of patients receiving the low dose which lead to discontinuation of the study. We did not have any episodes of grade 4 bleed in our study. There was one episode of grade 1 bleed with high dose. In the probe study [6] CCI's after the administration single and double high doses were $10.6 \pm 5.4 \times 10^9$ and $12.5 \pm 5.8 \times 10^9$ respectively without any statistically significant difference whereas in our study CCI after high dose was less as compared to standard dose (p = 0.006). This could be due to the fact that patients receiving the high dose were generally in their mid phase of highly intensive induction therapy or consolidation phase which lead to a lot of micro vascular endothelial damage and the platelets transfused during this phase were utilized for immediate repair of the micro vascular system hence didn't reflect as an actual rise in platelet response indicators. However number of patients enrolled in our study was less as compared to other platelet dose studies. This was because our study was time bound and enrolled only stable hemato-oncology patients which was in itself a very difficult task because by the time hemato-oncology patients reach a tertiary care hospital they already have some associated comorbid conditions. This paves a way to further studies with larger number of patients and with longer follow up to further add to the knowledge in this important area in management of hemato-oncology patients.

5. Conclusion

The possibility of low dose as an alternative to standard dose can be considered in stable thrombocytopenic patients owing to the comparable post transfusion response indicators (CCI and %PPR) and a significant reduction in donor exposure without any associated risk of bleeding. Nevertheless standard dose as the first choice for hemato-oncology patients cannot still be ruled out.'

Table 2
Comparative assessment of post transfusion parameters with other dose study.

Study	Francois Norol [7]	Klumpp [8]	PROBE Study [6]	Stop Study [9]	Slichter et al. [2]	Plado [10]	Timmouth A et al. [11]	Present study
No. of Patients	69 adults 13 child	46	101	119	1272	1102	111	28
Platelet dose (platelets /unit)	Medium (4.6 ± 0.6 × 10^{11}) High(6.5 ± 0.5 × 10^{11}) Very high (8.9 ± 0.7 × 10^{11})	Low (3.1 × 10^{11}) High (5 × 10^{11})	High (0.5 × 10^{11}/10 kg) Double of high (1 × 10^{11}/10 kg)	Low(1.53 × 10^{11}) Standard (3 × 10^{11})	Low (1.1 × 10^{11}) Standard (2.2 × 10^{11}) High (4.4 × 10^{11})	Low (1.1 × 10^{11}) Standard (2.2 × 10^{11}) High (4.4 × 10^{11})	Low (3RDP units) High (5RDP units)	Standard(3.1 ± 0.14 × 10^{11}) Low (1.49 ± 0.30 × 10^{11}) High (4.9 ± 1.0 × 10^{11})
CCI	NA	NA	10.6 ± 5.4 12.5 ± 5.8	NA	NA	NA	NA	12511.50 ± 7384.5 12279.92 ± 10842.7 6979.777 ± 4182.8
%PPR	28 ± 13 30 ± 15 29 ± 13	NA	NA	NA	NA	NA	NA	35 ± 23 35 ± 31 19 ± 12
Platelet Increment (X10^{9}platelets /L)	33 ± 22 × 10^9/L 51 ± 29 × 10^9/L 62 ± 34 × 10^9 /L	17.01 × 10^9/L 37.01 × 10^9/L	20.8 ± 13.5 × 10^9 /L 44.5 ± 23.5 × 10^9/L	NA	10.00 × 10^9/L 19.00 × 10^9/L 38.00 × 10^9 /L	NA	7 × 10^9 /L 14 × 10^9/L	23.000 ± 11.89 × 10^9 /L 11.708 ± 10.28 × 10^9 /L 22.636 ± 18.06 × 10^9 /L
Haemorrhage	NA	NA	5 patients 9 patients	All grade IV bleed) In low dose group (study stopped	Grade II or higher) 71% 69% 70%	NA	25% decrease in utilization with low dose	Grade III Nil Grade I
Inter transfusion	2.6 ± 0.7	2.16	2.6	NA	1.1	More adverse effects with high dose	NA	3.71 ± 3.4
Interval (days)	3.3 ± 1.2 4.1 ± 1.4	3.03	3.9	NA	1.9 2.9			3.36 ± 4.4 7.24 ± 7.9

(NA-Not Assessed).

6

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