

Original Research Article

Effectiveness of platelet transfusion in acute leukemic pediatric patients: a prospective study

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ABSTRACT

Background: In India, leukemia account for 25-35% of hematologic malignancies affecting children. Pediatric patients with acute leukemia have to undergo chemotherapy, which may cause protracted thrombocytopenia due to the cytotoxic effects of the drugs prescribed and due to the primary disease. The aim of the present study was to evaluate the need for platelet transfusion in leukemic children and to assess the effectiveness of platelet transfusion among them.

Methods: A prospective observational study was conducted in the Department of transfusion medicine and hematology at a tertiary care teaching hospital for a period of one year. The study population included children diagnosed as acute leukemia in the age group 1-12 years. The transfusion was given depending upon the clinical sign of bleeding and the platelet count. The pre and post transfusion platelet count (24 hours after the transfusion) were estimated using hematology analyzer. Statistical analysis was performed using SPSS software.

Results: 198 episodes of platelet transfusion were given to 30 children with acute leukemia. It was found for 95% CI of the mean between the pre and post-transfusion platelet count for single, double units and more than two units platelet transfusion, the rise in platelet count was significant ($p < 0.0001$) and there was no refractoriness. All children were negative for transfusion transmissible infections at the end of the study.

Conclusions: In the present study, the clinical management of children with acute leukemia has significantly improved with use of platelet transfusions and thereby, the mortality rate due to bleeding complications has dropped rapidly with remarkable clinical improvement in clinical outcomes.

Keywords: Leukemia, Platelet transfusion, Refractoriness

INTRODUCTION

In India, leukemia account for 25-35% of hematologic malignancies affecting children.¹ The incidence of different types of leukemia varies with age throughout the world.² The majority of them are ALL and most were in age groups 0-3 yrs, 4-6 yrs and 7-9 yrs.² Pediatric patients with acute leukemia have to undergo chemotherapy, which may cause protracted thrombocytopenia due to the

cytotoxic effects of the drugs prescribed and due to the primary disease. Life threatening complication such as bleeding is a common problem even after prophylactic or therapeutic platelet transfusion.³ Maintenance of hemoglobin concentration of a patient with thrombocytopenia at higher levels may contribute to improve hemostasis.⁴ In tertiary care centre, the number of platelet transfusions has increased in thrombocytopenic leukemic patients due to aggressive

chemotherapies producing more acute and prolonged thrombocytopenia.^{5,6} In leukemic children, skin bleeding (Petechiae) is a sufficient clinical sign to transfuse platelets.⁷ The other common clinical indicators for therapeutic platelet transfusion are gastrointestinal, genitourinary (Hematuria) and retinal hemorrhages. Significant bleeding included all bleeding except petechiae formation in dependant areas, ecchymoses not larger than 1 cm in diameter and/or more than 5 in number or oozing of blood from the periodontal groove.⁸ Prophylactic transfusion may or may not improve platelet survival when compared to transfusion in response to active bleeding.³ The life span of platelets is dependent on a patient's platelet count. Although a platelet survives approximately nine days in a normal individual, platelets have a reduced survival in thrombocytopenic patients. The residual mean life span corresponds to the maximal expected life span of a donated platelet product after infusion into the patient.

The explanation offered for these observed differences is that the platelets are removed from the circulation by two mechanisms. First is simply platelet senescence which accounts for majority of platelet loss in normal individual and the second is a constant loss due to the routine maintenance of vascular integrity (an endothelial supportive role). The number of platelets required for this endothelial supportive role has been estimated to be $7.1 \times 10^3/\mu\text{L/day}$.⁹

Hospitals have tried to reduce platelet use and the cost of platelet transfusion by transfusing platelets at lower platelet counts more frequently. There are studies determining the optimal transfusion trigger for prophylactic platelet transfusions in patients who have chemotherapy induced thrombocytopenia.⁶ Earlier studies of spontaneous bleeding demonstrated that bleeding risk increased dramatically only at platelet counts below 5×10^9 litre.¹⁰

Recent studies suggest that the threshold for prophylactic platelet transfusion may be safely lowered to $10 \times 10^9/\text{L}$ from previous standards of $20 \times 10^9/\text{L}$.¹¹ However, increase in platelet transfusions may lead to alloimmunisation. Alloimmunisation represents the major complication of platelet transfusion therapy for patients with acute leukemia.¹²

Patients who become alloimmunized following induction will continue to require HLA matched platelets. However, patients who do not become immunized during induction can easily and repeatedly be transfused with random donor platelets and can therefore be given subsequent prophylactic transfusions liberally without concern for the induction of alloimmunisation.¹² Pooled platelet products and single donor apheresis platelet concentrates are considered to be equally effective and safe.¹³ A standard dose of 0.5×10^{11} platelets per 10 kg for platelet transfusion is generally accepted.^{11,13} Acute Leukemic children during therapy receive on an average

80-110 units of platelets.¹⁴ Frequent and multiple platelet transfusion can lead to platelet refractoriness. Therefore, the present study was undertaken to study the need for platelet transfusion in leukemic children and to evaluate the effectiveness of platelet transfusion among them.

METHODS

A prospective observational study was conducted in the Department of transfusion medicine and hematology at a tertiary care teaching hospital for a period of one year. The study population included children diagnosed as acute leukemia in the age group 1-12 years.

Inclusion criteria

- All acute leukemic Children aged from 1-12 years both male and female.
- Children diagnosed as acute lymphoblastic leukemia and acute myeloid leukemia requiring transfusion support both under treatment and on follow up study.

Exclusion criteria

- Leukemic children below 1 year and above 12 years.
- Lymphoma evolving to leukemic phase.
- Juvenile myelomonocytic leukemia.
- Not willing to participate in this study.

All individuals above the age of 18 years were included in to the study. Informed consent was taken prior to conduct of the study.

Variables Studied

- Pre-transfusion platelet count
- No of platelet units transfused
- Post platelet count after 24 hrs of transfusion
- Clinical features of the patients

The platelet concentrate was prepared by platelet rich plasma method and were stored at 20-24°C (shelf life 5 days) under constant gentle agitation. The platelets were neither leuko reduced nor irradiated. No apheresis platelets were used. The bleeding event were categorized based on WHO grading of symptoms as no bleeding, non-clinically significant bleeding and clinically significant bleeding.^{4,9} The transfusion was given depending upon the clinical sign of bleeding and the platelet count. The pre and post transfusion platelet count were estimated 24 hours after the transfusion using hematology analyzer. All the platelets transfused were abo group identical between platelet product and the recipient.

Statistical analysis

Information was collected in a structured proforma. Data was entered in ms office excel format and statistical analysis was performed using spss software (version 20).

Univariate and multivariate analysis was done. Paired t-test and chi-square test was employed to detect any significant correlation between different variables. P value less than 0.05 was considered statistically significant.

RESULTS

198 episodes of platelet transfusion given to 30 children with acute leukemia were analyzed. Table 1 shows that out the study population, there were 76.67% males & 23.33% females and 73.33% were acute lymphoblastic leukemia & 26.67% were acute myeloid leukemia.

Table 1: Age and Gender distribution.

Age (in years)	ALL		AML	
	Male	Female	Male	Female
1-3	5	2	1	0
4-6	5	1	3	0
7-9	2	1	2	0
10-12	3	3	2	0
Total	15	7	8	0

Table 2 shows that the hepatomegaly and splenomegaly were among the clinical features and 22% of the patients presented with bleeding.

Table 2: Clinical features.

Clinical features (n=30)	ALL (n=22)		AML (n=8)	
	n	%	n	%
Fever	2	9.1	0	0
Hepatomegaly	16	72.7	5	62.5
Splenomegaly	11	50	3	37.5
Lymphadenopathy	6	27.8	6	75
Bleeding	4	18.2	4	50

Table 3 shows the relation between bleeding and platelet count and bleeding was definitely associated with thrombocytopenia [Odds ratio = 21(p < 0.05)].

Table 3: Correlation of Bleeding and Platelet count.

Bleeding	Platelet Count < 5000/ μ l	Platelet Count > 5000/ μ l
Present	4	4
Absent	1	21

Table 4 shows the relation between splenomegaly and platelet count and splenomegaly was definitely associated with thrombocytopenia [Odds ratio = 2.5 (p<0.05)]. Table 5 shows the relation between fever & platelet count and presence of fever also contributes to thrombocytopenia [Odds ratio = 6 (p<0.05)].

Table 4: Correlation of Splenomegaly and Platelet Count.

Splenomegaly	Platelet Count < 5000 / μ l	Platelet Count > 5000 / μ l
Present	2	12
Absent	1	15

Table 5: Correlation of Fever and Platelet Count.

Fever	Platelet Count < 5000 / μ l	Platelet Count > 5000 / μ l
Present	1	1
Absent	4	24

Analysis of Platelet Transfusions:

Table 6 shows analysis of the Pre and Post-transfusion platelet count for single unit, double unit and for 3 & 4 units platelet transfusion. In the above analysis, it was found for 95% CI of the mean between the pre and post-transfusion platelet count for single, double units and more than two units platelet transfusion, the rise in platelet count was significant (p<0.0001). Platelet count increment was present in all transfusion episodes and there was no refractoriness. 6.67% experienced febrile non-hemolytic transfusion reaction. All children were negative for transfusion transmissible infections at the end of the study.

Table 6: Analysis of platelet transfusions.

Analysis of platelet transfusion	Single unit platelets transfusion	Double unit platelets transfusion	More than 2 units platelets transfusion
No. of patients receiving transfusion	47	51	15
Mean of the pre-transfusion platelet count in $10^3 \mu$ l/l	39.3745	35.5843	27.7133
Mean of the post-transfusion platelet count in $10^3 \mu$ l/l	44.3553	45.3784	38.9600
Mean difference platelet count in $10^3 \mu$ l/l (i.e., platelet increment)	4.9809	9.7941	11.2467
p-value	P < 0.0001	P < 0.0001	P < 0.0001
Paired t test analysis	17.572	19.448	4.880

DISCUSSION

Hemato-oncology services require many transfusions for a prolonged period. Normal platelet survival is approximately nine days. Hanson SR et al, suggested that patients undergoing induction chemotherapy for leukemia often require platelet transfusion at least every three days.¹⁵ Pattern E et al, published that acute leukemic patients receive on average 80-110 units of platelets.^{14,16}

In the present study, 198 random donor platelet transfusions were given to 30 leukemic children (mean 2.3). Out of the 30 leukemic children, 17 of them received less than 5 units, 8 of them received 5 to 10 units and 5 of them received more than 20 units. A prophylactic platelet transfusion approach can prevent bleeding, as opposed to therapeutic approach, in which platelet transfusions are given after a certain degree of hemorrhage has occurred. Guidelines for the use of prophylactic platelet transfusion are primarily based on clinical experience. In pediatric oncology patients, there are two contrasting points of view. One group tells that the patients should be transfused whenever platelet count falls below 20000/ μ L, whereas the other groups believes that patient should be transfused only when frank bleeding occurs.

Bayer wL et al, found that patients with platelet counts less than 6000/ μ L received prophylactic transfusion, where as those with counts greater than 20000/ μ L were transfused only for major bleeding. They concluded that prophylactic level of 5000/ μ L was safe in the absence of fever or bleeding.¹⁷

Gmur et al, Heckman et al, Rebullia et al, have compared the bleeding risk and platelet transfusion needs of groups of thrombocytopenic patients' who received platelets either at the 10000/ μ L or 20000/ μ L threshold.^{9,18,19} They found that there is no difference in hemorrhagic morbidity and mortality rates when the lower platelet transfusion trigger values are used. One major reason for variable practice is based on the need to modify threshold numbers when thrombocytopenia is combined with other complications that increase the risk of bleeding. In the present study no transfusion trigger was followed. Platelets were transfused to 30 Leukemic children based on the platelet count the presence of bleeding.

In concordance with other studies, the present study documented 2 (6.3%) patients with fever and one among the above two patients had bleeding event with pre-transfusion platelet count of <5000/ μ L.^{20,21,22}

Janice P Dutcher et al, studied in 114 patients with acute lymphoblastic leukemia who received multiple course of chemotherapy and several platelet transfusions and found that 92% of the patients never become alloimmunized and responded to random donor platelets. Those who remain alloimmunized tended to remain alloimmunized for their entire clinical course. There was no difference in

age or sex between groups and prognostic factors predicting alloimmunization.²³ Dutcher in his previous studies also found that there is no dose response relationship between the development of alloimmunization and the number of units of platelets given during induction. In the present study there was platelet increment in all the transfusion episodes and there was no refractoriness. The mean increment for single unit transfusion (2.6) is 4900/ μ L and for double unit transfusion (2.6) is 9700/ μ L and for more than 2 units (1.36) is 11200/ μ L and the standard deviation is \pm 1943, 3596 and 8925 respectively.²³

McCullough J documented in 2000 that the use of platelet transfusion is associated with increased risk of viral and bacterial infection and alloimmunisation. In the present study of thirty leukemic children, all were negative for transfusion transmissible infections. He also found that transfusion reaction occurs after 5% to 30% of platelet transfusion and the most common adverse reaction is febrile non hemolytic transfusion reaction which is caused by the patients leukocyte antibodies reacting with leucocytes in the transfused components. In the present study out of 30 children who received platelet transfusion, two of them experienced febrile non-hemolytic transfusion reaction.⁶

CONCLUSION

The clinical management of patients with acute leukemia has significantly improved with use of platelet transfusions and thereby, the mortality rate due to bleeding complications has dropped rapidly with good improvement in clinical outcomes. In the present study, there was remarkable clinical improvement in all acute leukemic children after platelet transfusion. Even though, platelet transfusions are lifesaving, they can cause immune mediated and non-immune mediated complications such as transfusion transmitted viral & bacterial infections, hemolytic & non-hemolytic transfusion reactions, non-responding hemorrhage due to platelet refractoriness and acute lung injury. Therefore, the clinician has to weigh the benefits and risks before prophylactic platelet transfusions. Further, more studies have to be done with bigger sample size to evaluate prophylactic platelet transfusions and rationalize the indications, dose and complications of platelet transfusions in hemato-oncology patients.

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