Original Research Article

Platelet Refractory Cases after Transfusion of Fresh and Stored Platelet in ALL Children

Dr. Alamgir Ahmed[*1], Dr. Mafruha Akhter[2], Dr. Mohammad Mizanur Rahman[3], Dr. Mohammad Ali[4], Dr. Md. Kamrul Hossain[5], Dr. Lokesh Chakraborty[6], Dr. S. M. Masud[7], Dr. Salma Sadiya[8], Dr. Rawshan Ara[9], Dr. Delara Sultana[10]

[1]Assistant Professor, Department of Clinical Pathology, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh
[2]Assistant Professor, Department of Haematology & BMT, Dhaka Medical College Hospital, Dhaka, Bangladesh
[3]Associate Professor, Department of Pathology, Chandpur Medical College Hospital, Chandpur, Bangladesh
[4]Associate Professor & Head, Department of Haematology, National Institute of Cancer Research & Hospital, Dhaka, Bangladesh
[5]Assistant Professor, Department of Anaesthesiology, Cumilla Medical College Hospital, Cumilla, Bangladesh
[6]Assistant Professor, Department of Clinical Pathology. National Institute of ENT, Tejgoan, Dhaka, Bangladesh
[7]Associate Professor, Department of Laboratory Medicine, National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka, Bangladesh
[8]Assistant Professor, Department of Biochemistry and Molecular Biology, Bangladesh Shishu Hospital & institute, Dhaka, Bangladesh
[9]Assistant consultant, Department of Pediatrics and Neonatology, BSH, Dhaka, Bangladesh
[10]Resident Medical Officer, Department of Clinical Pathology, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh

*Corresponding author: Dr. Alamgir Ahmed
Assistant Professor, Department of Clinical Pathology, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh

Abstract

Introduction: Acute leukemia is the most common form of cancer in children, platelet transfusion is needed for the chemotherapy of acute lymphoblastic leukaemia children. Platelets are transfused for therapeutic and prophylactic purposes. Transfusion of stored platelet concentrates (up to 5 days) has been demonstrated to be as effective as transfusion of fresh platelet concentrates (upto 24 hours). Platelet refractory cases were also observed in this study that was detected by Corrected Count Increment (CCI) and Percent Platelet Recovery (PPI) at 1hour and 24 hours. *Aim of the study:* The aim of this study was to observe the platelet refractory cases after transfusion of fresh and stored platelet in acute lymphoblastic leukemia (ALL) in a tertiary care hospital, Dhaka. *Methods*: A cross-sectional study was conducted in the Department of Clinical Pathology, Paediatric Haematolo- Oncology and transfusion Medicine BSMMU, Department of Haematology and Paediatric Haemato-Oncology in Dhaka Medical College Hospital from March 2010 to February 2011 where 81 children diagnosed with acute lymphoblastic leukaemia were taken as the study population. Non probability purposive sampling was used by fulfilling the inclusion criteria. Ethical consideration was taken by the BSMMU ethical review committee. A data sheet with two parts (Part A and Part B) was designed with a view to collect data from the patients to be enrolled in the study. Data were analyzed using the SPSS version 25.0. *Results:* Out of 81 in 47 children with acute lymphoblastic leukemia (ALL), fresh platelet concentrates (FPC) (upto 24 hours) or day-0 platelets were transfused. In 34 children, stored platelet concentrates (SPC) (days 1–5) were transfused. In 27 cases, platelet concentrates were transfused both fresh and stored. In FPC and SPC, the corrected count increment at one hour (CCI 1h) was 20.5×10^9/L and 18.9×10^9/L respectively. FPC and SPC values for the mean corrected count increment at 24 hours (CCI 24h) were 15.5×10^9/L and 13.8×10^9/L respectively. Platelet refractory cases were 15(18.5%) out of 81 cases transfused. Platelet refractory cases were 7(15%) out of 47 cases transfused with FPC and 8(23%) out of 34 cases transfused with stored platelet concentrate (SPC). There were no significant differences (P<0.05) between FPC and SPC according to platelet refractoriness. *Conclusion*: In vivo quality of freshly generated platelet (upto 24 hours) versus stored platelet concentrates (up to 5 days) were determined after 1 hour and 24 hours. 1-5 day's stored PRP-PCs are as effective as fresh PRP-PCs for sufficient platelet increment.
Keywords: Acute lymphoblastic leukemia; Platelet refractory; Children; Transfusion; Corrected Count Increment.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development (Williams, 2010). In ALL, platelets are transfused to stop bleeding. Bizzozero characterized platelets and their role in haemostasis for the first time in 1881-1882 [1]. Duke originally demonstrated the value of platelet transfusion in 1910, when he described three patients with hemorrhage related to thrombocytopenia who had improvement with whole blood transfusion [2]. According to the annual report of the Department of Transfusion Medicine at Bangabandhu Sheikh Mujib Medical University Hospital (BSMMU), 2071 platelet concentrates were distributed in the year 2010. Two hundred forty platelet concentrates were distributed to leukemic patients in a day care center [3]. For children with acute lymphoblastic leukemia (ALL), platelet transfusion is required because ALL is five times more prevalent than acute myeloid leukemia (AML) [4]. Stored platelet concentrates are as efficient as fresh platelet concentrates (upto 24 hours) when transfused for up to five days [5]. One platelet concentrate containing 60×10^9/L platelets in 30-50 mL autologous plasma should be transfused to small children weighing up to 15 kg [6]. 2 PCs is the recommended dose for 15-30 kg and 4 PCs is the recommended dose for >30 kg. Unacceptable recovery of transfused platelets on two or more occasions is referred to as refractoriness.

Alloantibodies and autoantibodies are connected with refractoriness. Non-immune variables including splenomegaly, fever, infection, immune complexes, bone marrow transplantation and amphotericin [7]. Refractoriness to platelet transfusion is a clinical state that can be defined as an unacceptable recovery of transfused platelets on two or more occasions [8]. Patients with a CCI $<7.5 \times 10^9$/L and $<4.5 \times 10^9$/L after 1 hour and 24 hours of transfusion on at least two consecutive occasions are considered refractory to platelet transfusion [9]. Causes of platelet refractoriness can be subdivided into immune mechanisms most importantly HLA alloimmunization and non-immune platelet consumption. The latter is the most frequent mechanism of platelet refractoriness, usually associated with sepsis. Alloimmunization to HLA antigens was recognized as the main cause of platelet refractoriness. HLA antibodies mediate a rapid clearance, because even 10 min after transfusion only a minor fraction of the transfused platelets is in the circulation [10]. Fever is produced by the action of circulating cytokines, such as IL-I and TNF, on the hypothalamus resulting in the secretion of PG- E_2 which mediates the elevation of body temperature. Besides other biological actions they promote endothelial cells activation with expression of adhesion molecule and procoagulant activity. The endothelial activation could be responsible for rapid clearance of transfused platelet and would explain the association of fever with platelet transfusion refractoriness [9].

Immune	Non-immune
Platelet antibodies	Infection
HLA	Splenomegaly
HPA	Disseminated intravascular coagulation
Other antibodies	Bleeding
Platelet autoantibodies	BMT
Drug- dependent platelet antibodies	
ABO antibodies	
Immune complexes	

The table shows the causes of platelet refractoriness [11]. Despite its clinical relevance, platelet refractoriness is not routinely diagnosed in services that provide hemotherapeutic support because of the labor-intensive process involved and the need for qualified professionals from various sectors. The aim of the present study was to observe the platelet refractory cases after transfusion of fresh and stored platelet in acute lymphoblastic leukemia (ALL) in a tertiary care hospital, Dhaka.

OBJECTIVE

The objective of this observative cross-sectional study was to observe the platelet refractory cases after transfusion of fresh and stored platelet in acute lymphoblastic leukemia (ALL) in a tertiary care hospital, Dhaka.

METHODOLOGY

This observative cross-sectional study was conducted in the Department of Clinical Pathology, Paediatric Haemato-Oncology and Transfusion Medicine BSMMU, Department of Hematology and Paediatric Haemato-Oncology in Dhaka Medical College Hospital from March 2010 to February 2011. Children diagnosed as acute lymphoblastic leukaemia in the Department of Paediatric Haemato-Oncology in BSMMU, Department of Paediatric Haemato-Oncology and Department of Haematology in Dhaka Medical College Hospital who has fulfilled the inclusion criteria, has been enrolled in this study. The research protocol was approved by the ethical review committee, Bangabandhu Sheik Mujib Medical University and the formal permission was obtained from the respective authorities of BSMMU for data collection. Actual

sample size was 81. Non probability purposive sampling was used to conduct the study. Patients who were transfused with fresh platelet concentrates, platelet

count was done before transfusion, at 1 hour and after 24 hours of transfusion. Platelet count increment was calculated from the formula:

Corrected Count Increment at 1 hour

$$CCI_{1hr}=\frac{(post\ transfution\ platelet\ count\times10^9/L)-(pre\ transfution\ platelet\ count\times10^9/L)}{Number\ of\ Platelet\ transfused\times10^9/L}\times BSA\ (body\ surface\ area\ in\ m^2)$$

Corrected Count Increment at 24 hours

$$CCI_{24hr}=\frac{(post\ transfution\ platelet\ count\times10^9)-(pre\ transfution\ platelet\ count\times10^9)}{Number\ of\ Platelet\ transfused\times10^9/L}\times BSA$$

Percent Platelet Recovery at 1 hour

$$PPR_{1hr}=\frac{(post\ transfution\ platelet\ count-pre\ transfution\ platelet\ count)\times10^9/L\times Blood\ volume\ (BV)/L}{Platelet\ dose\ transfused\ x\ 10^9/L}\times 100$$

Percent Platelet Recovery at 1 hour

$$PPR_{24hr}=\frac{(post\ transfution\ platelet\ count-pre\ transfution\ platelet\ count)\times10^9\times Blood\ volume\ (BV)/L}{Platelet\ dose\ transfused\ x\ 10^9/L}\times 100$$

Blood sample (2 ml) had been collected in an EDTA tube with full aseptic condition. The skin was cleaned with alcohol. A rubber tourniquet was applied round the arm. 2ml blood was collected with a sterile dry syringe. When the needle was in the vein, the tourniquet was loosened to avoid hemoconcentration. Blood was drawn slowly and transferred into a sterile EDTA tube. Platelet count had been done preferably within 2 hours of collection. If delayed, blood sample was kept at 4^0 C before test. Same procedure was done in patients who were transfused with stored platelet concentrates (1 day's, 2 day's 3 days, 4 day's or 5 day's). In fully automated hematology analyzer Sysmex xt-2000i platelet count was done, where electrical impedance or light scattering property was used. Platelet count was rechecked manually using Neubauer counting chamber in light microscope and phase contrast microscope. All necessary and relevant data of the patients were recorded methodically in the data sheet. All the cases were numbered chronologically. Haematological analyses were performed with pre-transfusion and post-transfusion data. Data were stored in a personal computer and results were expressed as mean standard deviation. Mean values were calculated in pre-transfusion and post-transfusion platelet count. The student t-tests were employed to estimate the differences between groups. Differences were considered to be significant when the probability p<0.05. Simple frequency distribution table and all statistically significant tests were done using statistical package for social science SPSS-21.

Inclusion Criteria
1. Children up to 18 years of age with acute lymphoblastic leukaemia that had indications for platelet transfusion

Exclusion Criteria
1. Participants, unwilling to comply with the study procedure, were not included.

RESULTS
This cross-sectional study was conducted in the Department of Clinical Pathology in collaboration with the Department of Transfusion Medicine and Department of Paediatric Haemato-Oncology Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total of 81 children with acute lymphoblastic leukemia were enrolled in this study according to the inclusion criteria. These 81 patients were assessed before and after transfusion of platelet concentrate (PC) to evaluate platelet increment. A total of 81 subjects were included in this study and age ranged from 1 to 15 years with mean 6.0±3.7 (±SD) (Table-I) Among them 52 were found male and 29 females. The male female ratio was found 1.8:1 (Table-II). Regarding the blood group it was observed that most of the subjects had B positive (+ve) 26(32.00%), followed by O positive (+ve) 24(29.63%), A positive (+ve) 22(27.16%) and 6(7.41%) had AB positive (+ve). Each one O(-ve) 1(1.2%), A(-ve) 1(1.2%), B(-ve) 1(1.2%) case were also found (Table-III). It was observed that fresh platelet concentrates (FPC) or day-0 platelets were transfused in 47 children with acute lymphoblastic leukaemia (ALL) (58%) and one day's (Day-1) stored platelet concentrates (SPC) were transfused in 7(8.6%), Day-2 in 10(12.3%), Day-3 in 9(11.1%), Day-4 in 6(7.4%) and Day-5 in 2(2.5%) acute lymphoblastic leukaemia children. Stored platelet concentrates (day 1-5) were transfused in 34 children. In 27 cases both fresh and stored platelet concentrates were transfused. According to transfusion of fresh or stored platelet concentrates n= =81 (Table-IV). It was observed that 2 units of platelet concentrate (PC) were transfused in 40 (49%) ALL children, among them fresh platelet concentrates (FPC) were transfused in 24

children, whereas stored platelet concentrates (SPC) were transfused in 16 children. 27 children of ALL were transfused with I unit of PC; FPC and SPC were 17 and 10 respectively. 13 ALL children were transfused 3 units of PC, FPC and SPC were transfused in 6 and 7 respectively. 4 units SPC were transfused in 1 child. 17+ 48+18 =83 units FPC (Day-0) was transfused in 17+24+6=47 children and 10+32+21+67 units of SPC were transfused in 34 ALL children. Total 83+67=150 units of PCs were transfused in 8l ALL children (Table-V). Forty-seven children were transfused with fresh or 0 day's platelet concentrates, their mean Pre-transfusion platelet count, post transfusion count at 1 hour ($Post_{1h}$) and 24 hours ($Post_{24h}$) were 13.6×10^9/L, 48.7×10^9/L and 60×10^9/L respectively. Thirty-four children were transfused with 1–5-day's stored PC. (Day-1) stored platelet concentrates (SPC) were transfused in 7, Day-2 in 10, Day-3 in 9, Day-4 in 6 and Day-5 in 2 acute lymphoblastic leukaemia children. Mean pre-transfusion platelet count, post transfusion platelet counts at 1 hour and 24-hour after transfusion of l-5-day's stored platelet concentrates were shown in Figure 1. There were of significant differences between fresh platelet concentrate and 1-5 day's stored platelet concentrates (p>0.05) (Figure-1). Mean percent platelet recovery at 1 hour (PPR_{1h}) was 51.2 and at 24 hour (PPR_{24h}) was 35.2 after transfusion of fresh platelet concentrate (FPC). In cases of l day's SPC, (PPR_{1h}) and (PPR_{24h}) values were 48.9 and 35.7; in 2 day's SPC (PPR_{1h}) and (PPR_{24h}) were 52.6 and 38.8; in 3 day's SPC (PPR_{1h}) and (PPR_{24h}) were 47.8 and 34.2, in 4 day's SPC (PP_{1h}) and (PPR_{24h}) were 51.I and 55.2, in 5 day's SPC (PPR) $_{1h}$ and (PPR_{24h}) were 41.9 and 30.3 respectively. These are shown in Figure-2. On the basis of percent platelet recovery at 1 hour and 24 hours, there were no significant differences between fresh platelet concentrates and 1-5 day's stored platelet concentrates (Figure-2). Mean Corrected Count increment at 1 hour (CCI_{1h}) was 20.5×10^9/L and at 24 hour (CCI_{24h}) was 15.5×10^9/L after transfusion of fresh platelet concentrate (FPC). In cases of 1 day's SPC, (CCI_{1h}) and (CCI_{24h}) values were 19.2×10^9/L and 13.7×10^9/L; in 2 day's SPC (CCI_{1h}) and (CCI_{24h}) were 21×10^9/L and 15.5×10^9/L in 3-day's SPC (CCI_{1h}) and (CCI_{24h}) were 19.17 and 13.6; in 4 day's SPC (CCI_{1h})

and (CCI_{24h}) were 18.2 and 14.1; in 5 day's SPC (CCI_{1h}) and (CCI_{24h}) were l6.8 and 12.1 respectively. These are shown in figure-3. On the basis of corrected count increment at 1 hour and 24 hours, there were no significant differences between fresh platelet concentrates and 1-5 day's stored platelet concentrates (Figure-3). It was observed that 81 cases were transfused either fresh or stored PC or both and 15 (18.5%) cases were below the lower limit of CCI and PPR after 1 hour or 24 hours of transfusion. Among the 47 cases who were transfused fresh platelet concentrates (FPC), 7 (15%) cases were below the lower limit of CCI and PPR after 1 hour or 24 hours of transfusion. Thirty-Four (34) cases were transfused with stored platelet concentrates (SPC) and 8(23.5%) cases were found refractory. P value was 0.504 which was statistically not significant (Figure-4).

Table-I: Demographic characteristics of the study population (N=81)

Age (in years)	n	%
1-5	40	49.38
6-10	31	38.27
12-15	10	12.35
Mean ±SD	6.0±3.7	
Range (Min-Max)	(1-15)	

Table-II: Gender distribution of the study subjects (N=81)

Gender	n	%
Male	52	64.20
Female	29	35.80
Ratio	1.8:1	

Table-III: Blood group distribution of study subjects (N=81)

Blood group	n	%
B(+ve)	26	32.00
O(+ve)	24	29.63
A(+ve)	22	27.16
AB(+ve)	6	7.41
O(-ve)	1	1.2
A (-ve)	1	1.2
B (-ve)	1	1.2

Table-IV: Distribution of the study subjects according to fresh platelet concentrates (FPC) and stored platelet concentrates (SPC) transfusion (N=81)

Type of Platelet concentrates (PC)	Day of storage	n	%
Fresh PC (day-0) n=47	Day-0	47	58.0
Stored PC (day 1-5) n=34 Day -1	Day-1	07	08.6
	Day-2	10	12.3
	Day-3	09	11.1
	Day-4	06	07.4
	Day-5	02	02.5

Table-V: Distribution of study subjects according to number of units of platelet concentrate (PC) transfused (N=81)

Unit of PC	Number of patients	No. of patients transfused FPC	No. of patients transfused SPC	Percentage
1	27	17	10	33.3
2	40	24	16	49.4
3	13	06	07	16.0
4	01	00	01	01.3
Total	**81**	**47**	**34**	
Mean±SD	1.8±07			
Range (Min-Max)	(0.7-1.8)			
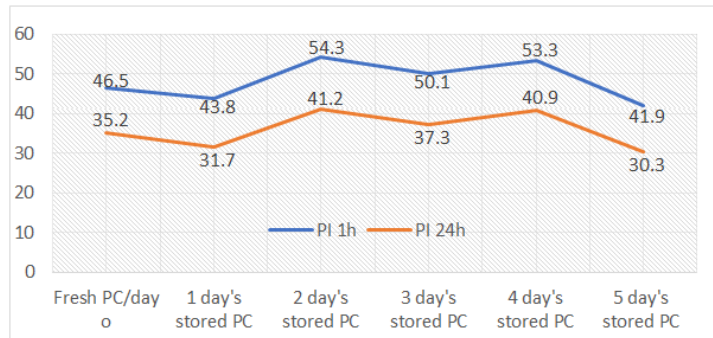
Figure-1: Line diagram showing Pre- transfusion platelet count, post transfusion platelet counts at 1 hour and 24 hours after transfusion of Fresh platelet concentrates (day 0 PC) and 1-5 days stored platelet concentrates
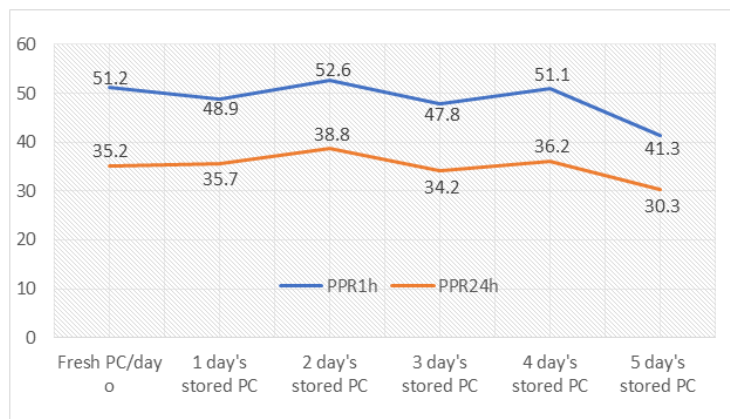
Figure-2: Line diagram showing percentage platelet recovery at 1-hour (PPR_{1h}) and 24 hours (PPR_{24h}) after transfusion of fresh platelet concentrates (day 0 PC) and1-5 day's stored platelet concentrates
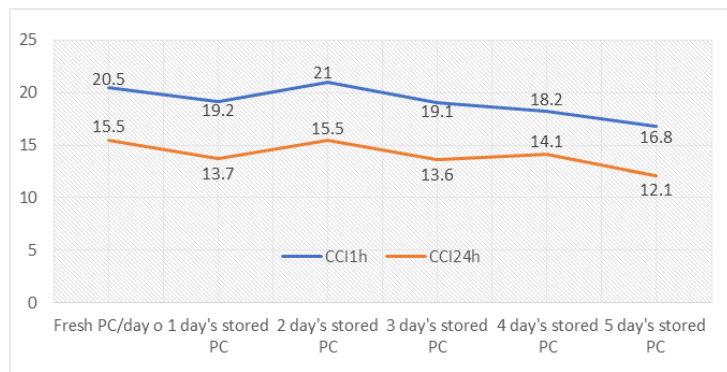
Figure-3: Corrected count increment at 1 hour (CCI 1hr) and 24 hours (CCI 24h) after transfusion of fresh platelet concentrates (day 0 PC) and 1-5 day's stored platelet concentrates
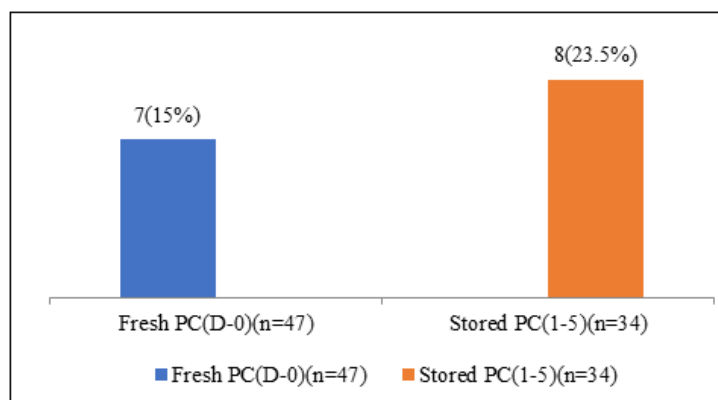
Figure-4: Bar diagram showing the Platelet refractory cases of the study patients

DISCUSSION

Patients suffering from different malignancies utilize the majority of platelet products and the increasing numbers of platelets used over the past two decades were in patients being supported during chemotherapy [12]. Leukemia patients, often depend on platelet transfusion while they are undergoing chemotherapy [13].

Early in the 20th century; freshly drawn whole blood was the only source of viable platelet [12]. It is now standard practice to transfuse both fresh and stored platelet concentrates.[14] Changes in platelet count, pH, presence or absence of bacteria and platelet indices in 5 day's stored platelet concentrates (PC) were evaluated in previous studies [15, 16].

In vivo effectiveness of fresh platelet concentrates (FPC) as well as stored platelet concentrates (SPC) after transfusion in childhood acute lymphoblastic leukemia in Bangladesh has been evaluated in the present study. Thrombocytopenia was associated with chemotherapy for childhood acute lymphoblastic leukemia. Children who required platelet transfusion were enrolled in this prospective type of cross-sectional study. The sample size was 81 in the present study, where age ranged from 1 to 15 years with mean 6.0 ± 3.7 ($\pm SD$). Maximum 36(50%) cases were found 1-5 years age groups among them 52 were male and 29 females. Predominance of age group 1-5 years and male gender were in accordance with the study of Ries LAG *et al*., [17].

Thirty-four children with acute lymphoblastic leukaemia were transfused with 1-5 day's stored platelet concentrates (SPC) whereas fresh platelet concentrates (FPC) to 47 children. Their mean ($\pm SD$) age was 1-5 years, total 150 units of PC were transfused (87 FPC and 63 units SPC). Pre-transfusion platelet count, post-transfusion PLT increment after 1 & 24 hours. Pre transfusion platelet count, post transfusion PLT increment after 1 hour and 24 hours of FPC versus SPC ranged (2-35 and 1-30; 15-61 and 5-90; 10-95 and 2-75)x109/L respectively. These results reflected that there were no significant differences between FPC and SPC (P>0.05). In addition, mean ($\pm SD$) post transfusion corrected count increments (CCI's) in both groups were 20.1 ± 10.1 versus 18.6 ± 6.1 ($\pm SD$) at 1 hour and 15.5 ± 9.1 versus 13.5 ± 8 at 24 hours, respectively. When the two were compared, there were no significant differences (P>0.05). In contrast, Peter Salonen K *et al*., [18], Lazarus *et al*., [19] and Vallejo's *et al*., [20] found poor platelet responses in their studies. Lazarus *et al*., [20] studied with eighteen chemotherapy induced adult patient of leukemia and aplastic anaemia. These patients had received many transfusions in the past. He also concluded that the multi-transfusion may be influenced the transfusion response. Gentle agitation is another factor that influenced the platelet transfusion response 1973. On the other hand, results of this study of FPC and SPC were in accordance with the other studies of Murphy *et al*., [21], Hogge *et al*., [22] and Dijkstra-Teikstra MJ *et al*., [23]. On the basis of percent platelet recovery (PPR's), FPC versus SPC in this study were 51.2 ± 25.4 versus 47.5 ± 16.9 at 1-hour FPC 38.8 ± 22.6 versus 32.8 ± 14.6 at 24 hours respectively. In a study with AML patients, Rebull P *et al*., [24] transfused 2-4 day's SPC and percent platelet recovery at 1hour & 24 hours (42 ± 9.9) values were apart from the recommended lower limits of AABB and BCSH [11] Furthermore, here were no significant differences between P values of FPC and SPC (P>0.05).

The recommended limit of corrected count increment is 7.5 x10^9/L at 1 hour or PPR 30.9%. After 24 hours; the lower values should be 4.5×10^9/L and 20% respectively. 15(18.52%) cases were found below these recommended values in 81 study subjects. Among them, 7(15%) cases were platelet refractory out of 47 children who were transfused FPC and 8(23.5%) cases were platelet refractory out of 34 children transfused with SPC. According to day of storage, 2 cases in I day's SPC, I in 2 day's SPC, 2 in 3 day's SPC and 2 in 4 day's SPC were found below the lower limit of effective platelet transfusion, whereas in 5 day's SPC all the cases showed effective platelet transfusion. In 13 cases, both CCI and PPR at 1 hour and 24 hours of transfusions were below the lower limit. In these cases,

poor platelet responses might be due to immune causes of platelet refractoriness. In one case transfused with FPC, CCI was found >7.5 x10^9/L at 1 hour but <4.5 x10^9/L after 24 hours. Non immune cause of platelet refractoriness might be the cause of poor platelet response in this case [11]. But actual causes of poor platelet response could not be ruled out without complete evidences of patients' clinical conditions Such as Sepsis, presence of hyper splenomegaly, bleeding grade according to WHO criteria, DIC, amphotericin B [25]. Schiffer CA *et al*., have shown that CCI <7.5x10^9/L in 3-5 day's SPC were 13.2-15% and 3.7-5% in 1-2 day's PC[5]. Slichter SJ et al had ruled out 143(27%) refractory cases after analyzing 528 patients [26]. Peter-Salonen K et al have shown that 34% better recoveries have been achieved with FPC than SPC [18]. It was evident that researcher found various ranges of platelet refractoriness due to different age, diseases, and clinical conditions. The frequency of refractoriness observed in the study of Fabris F *et al*., [27], Legler T [28], Novotny VMJ [29] found 24% to 34% in range.

From this study it was observed that 1-5 day's stored platelet-rich-plasma platelet concentrate (PRP-PC) was as effective as fresh PC to obtain acceptable platelet increment in childhood acute lymphoblastic leukemia. However, corrected count increments an-percent platelet recovery are important tools to evaluate platelet refractoriness and refractory frequency.

LIMITATIONS OF THE STUDY
There were some limitations in the present study. The major difficulty encountered during this study unavailability of patients which were transfused 4- and 5-day's stored platelet concentrates. This made the limitation of data analysis in these groups. It was inconvenient to take samples strictly at 1 hour and 24 hours of transfusions. Samples that could not be measured within 4 hours of collection were kept in refrigerator at 4^0C in EDTA tubes. This sampling procedure could therefore affect the platelet count.

CONCLUSION
The current study assessed CCI and PPR in children with ALL. In vivo quality of newly generated platelet concentrate (PC) versus preserved platelet concentrate (up to 5 days). The FPC found 14.9% platelet refractory cases and 20.5% in SPC. Based on post transfusion platelet increase, percentage platelet recovery and corrected count increment after 1 hour and 24 hours, it is determined that 1-5 day preserved PRP-PCs are equally effective as fresh PRP-PCs for adequate platelet increment.

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