The Epidemiology of Platelet Transfusions: An analysis of platelet use at 12 U.S. Hospitals

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Running Head: Epidemiology of Platelet Transfusion

Abstract

Background: Using the REDS-III recipient and donor databases, we performed a retrospective analysis of platelet use in 12 U.S. hospitals that were participants in REDS-III.

Study Design and Methods: Data were electronically extracted from participating transfusion service and blood center computer systems, and from medical records of the 12 REDS-III hospitals. All platelet transfusions from 2013-2016 given to patients 18 and older -were included in the analysis.

Results: There were 28,843 inpatients and 2,987 outpatients who were transfused with 163,719 platelet products (103,371 apheresis, 60,348 whole blood derived). 93.5% of platelet ~~product~~s were leukocyte reduced and 72.5% were irradiated. 46% were transfused to patients with an ICD 9/10 diagnosis of leukemia, MDS or lymphoma. The general ward and the ICU were the most common issue locations. Only 54% of platelet transfusions were ABO identical; and 60.6% of platelet transfusions given to Rh negative patients were Rh positive. The most common pre-transfusion platelet count range for inpatients was 20,000-50,000/µL, for outpatients it was 10,000-20,000/µL. Among ICU patients, 35% of platelet transfusion episodes had a platelet count of greater than 50,000/µL, this was only 8% for general ward and 2% for outpatients. The median post-transfusion increment ranged from 12,000-20,000/µL for inpatients, and from 17,000-27,000/µL for outpatients.

Conclusions: These data from one of the largest reviews of platelet transfusion practice to date provide guidance for where to focus future clinical research studies [i.e. platelet use for moderate thrombocytopenia (20,000 to 100,000/µL), anticoagulation and platelet use in oncology patients, platelet use prior to a procedure] and platelet Blood Management programs.

Key words: platelet transfusions, transfusion episode, platelet count increment, encounter

Introduction

Platelets are a commonly transfused blood product with recent American Red Cross data estimating approximately 7,000 units of platelets being transfused daily in the United States; the majority of these are apheresis platelets[1-3]. Recently, platelet use has plateaued following a number of years in which it showed annual increase. This is in sharp contrast to the dramatic decrease in red cell transfusions over the past decade. Indications for platelet use vary and, in an attempt to improve clinical practice, several clinical practice guidelines for platelet transfusion have been published [4,5,6]. The evidence supporting the recommendations in these guidelines is most robust in the hematology/oncology and stem cell transplant settings where prophylactic use of platelets at specific platelet count thresholds is common. Results are somewhat equivocal concerning the benefit of this practice[7-10]. Furthermore, even with these diagnoses, the evidence for transfusion in specific clinical scenarios (e.g. lumbar puncture, invasive procedures, concomitant anti-coagulation therapy, moderate thrombocytopenia) is weak or not available. There are even fewer data with regard to the efficacy and thresholds for appropriate platelet transfusions in surgical or trauma settings.

In the 2015 AABB Platelet Transfusion Guidelines, the authors commented that large databases could assist with providing background information to inform the design of clinical trials or observational studies on platelet transfusion practice. However, analyses of large databases that contain granular information on platelet use has been lacking. We are aware of only a few including the Society of Thoracic Surgery database on blood use in cardiac surgery that have provided substantial data on platelet use[11-15].

Furthermore, a 2012 study from the United Kingdom which compared local practice with national standards found differences in practice versus standards. The authors indicated the need for reinforcement of guidelines for prophylactic platelet transfusion in hematological disease and for screening of platelet use in cardiac surgery[16]. Given these limited studies and the potential for extending existing Patient Blood Management programs for red cell transfusion into the realm of platelet transfusion practice (provided that current usage patterns are well understood), we performed a retrospective observational data analysis of platelet use in 12 U.S. hospitals that were participants in the Recipient and Donor Epidemiology Study-III (REDS-III).

Methods

The infrastructure of the NHLBI Recipient Epidemiology and Donor Evaluation Study III (REDS-III) Domestic program has been described previously[17]. REDS-III is a consortium of hubs, each consisting of a blood center and two to four affiliated hospitals, a single central laboratory, and a data coordinating

center. Data from 12 US hospitals comprising the REDS-III Recipient Database, which has been previously described in detail[18], were utilized to study recipient characteristics of platelet transfusions. A linked Components database was used to study blood donor and product characteristics. Data studied included those extracted electronic data from participating transfusion service/blood center (Components) and electronic health records from each participating hospital (Recipient) using a conserved specification created by the REDS-III program. All inpatient and outpatient platelet transfusions between January 2013 and December 2016 were included in the analysis, excluding transfusions among patient less than 18 years of age.

Information on ~~component~~ product~~s and~~ manufacturing, including leukoreduction, irradiation, and donor blood group and type were extracted from the REDS-III Components database. Linkage of blood components to transfusion recipients was performed using an obfuscated blood product donation identifier assigned at the domestic hubs. Recipient factors were extracted from the REDS-III Recipient Database demographics table. Patient ABO and Rh blood type and pre- and post-transfusion laboratory data were collected from the Laboratory table. Patient location within the hospital, medication use, and mortality were assessed using the transfers, medication, and encounter tables, respectively. Diagnosis codes were extracted from the table of the same name and collated into HCUP categories (e.g. Diseases of the Circulatory System). Aggregated data were assessed for normality. Mean and standard deviation were used to describe normally distributed data, whereas median and interquartile range (IQR) were used to describe the non-normally distributed data. Data manipulation was performed in SAS.

Definitions

Patient encounter: A patient encounter was defined as any unique inpatient admission or outpatient visit that was documented with a unique start date and time and with a discharge date. Many patients had multiple encounters.

Transfusion episode: All platelet ~~product~~s issued within an 8 hour interval beginning with issuance of the first platelet ~~product~~ for the encounter.

Pre-transfusion Platelet Count: the nearest platelet count up to 24 hours prior to the first transfusion of the episode for inpatients; and up to 48 hours for outpatients.

Post-transfusion Platelet Count: the nearest platelet count up to 24 hours after the last platelet transfusion of the episode for inpatients; up to 48 hours for outpatients. Occasionally a post-platelet count for one episode is the pre-transfusion platelet count for the next transfusion episode.

ABO type specific platelet transfusions: the ABO type of the patient and the platelet product were identical (i.e. A to A, O to O).

ABO ~~compatible platelet transfusions~~major mismatch: the ABO type of the patient and the platelet product were not identical and there was no donor plasma antibody incompatibility (i.e. A to O, B to O).

ABO ~~incompatible platelet transfusions~~minor mismatch: the ABO type of the patient and the platelet product were not identical and there was donor plasma incompatibility (i.e. O to A, A to B).

Platelet product: one apheresis platelet or a pool of whole blood derived platelets (WBD).

Results

Tables 1 and 2 list patient and product characteristics. 163,719 individual platelet ~~product~~s (103,371 apheresis, 60,348 whole blood derived (WBD)) were transfused into 31,821 individual patients (60.5% males, 39.5% female). Patients 50-69 years were the most common age group to be transfused with platelets. The most common locations for platelet transfusion were the General Ward (52.7%), followed by the Intensive Care Unit (28.2%) and the Operating Room (12.6%). The top three broad categories by diagnosis codes (inpatient only) were Hematology/Oncology, Circulatory system, and Injury and Poisoning. 93.5% of the platelet ~~product~~s were leukocyte reduced, while 72.4% were irradiated. The majority of patients received at least one other type of blood product with red blood cells being the most common, followed by plasma and cryoprecipitate. The mean number (over the entire four year study period) of RBC units administered to patients who received at least one platelet over the four years of data collection was 6.3 (SD 11.1), for plasma 3.5 (SD 12.8) while 2.6% of patients receiving a platelet transfusion also received cryoprecipitate (Data not shown). Of the 31,821 patients during the four year study period, 15.8% had expired by the end of the study period.

Table 3 lists platelet transfusions by ABO and Rh product and patient type. For ABO only, 54.1% of transfusions were ABO-identical ranging from 49.5% for group O to 19.4% for group AB patients. For all group O platelets, 29.7% (11,435) were transfused to non-type O patients, while 47.0% (25,689) of all group A platelets were given to non-type A patients, with most going to group O patients, a major mismatch. Overall, 16% of platelet transfusions were ABO ~~incompatible~~ minor mismatch in that there were ABO antibodies in the donor plasma directed against corresponding antigens on the transfused recipient's red cells. For Rh, 9.8% of all Rh positive platelets were transfused to Rh negative patients. Rh negative patients were commonly transfused with Rh positive platelets; 60.6% of their platelet transfusions were Rh positive.

The mean number of platelet products transfused per episode for inpatients was 1.30 (range 1-24). 78% of platelet transfusion episodes were comprised of 1 platelet product, 17% two platelet

products, 2.5% three platelet products and 1.9% of four or more. There were 77 episodes where 10 or more platelet products were transfused.

Table 4 depicts pre-platelet transfusion count with post-transfusion platelet count increment for inpatient and outpatient episodes. Figures 1 and 2 present similar results for the General Ward and ICU. The most common pre-transfusion platelet count range for inpatients was 20,000-50,000/µL; for outpatients, it was 10,000-20,000/µL. The range of 20,000-50,000/µL was most common for the General Ward and ICU, but not for the OR which had a higher pre-transfusion platelet count. 42% of platelet transfusion episodes for inpatients had a platelet count of 20,000/µL or less. Among ICU patients 35% of platelet transfusion episodes had a pre-transfusion platelet count >50,000 vs. 8% for the general ward and only 2% for outpatients. Disregarding inpatients with pre-transfusion platelet count greater than 100,000/µL, the median post-transfusion increment ranged from 12,000-20,000/µL across patient groups with different pre-transfusion platelet levels. For outpatients, the median increment ranged from 17,000-27,000/µL. For inpatients the median time from time of issue to post-platelet count was 6.9 hours, and for outpatients, it was 16 hours. Almost half of the outpatient episodes did not have a pre or post count that fit the definition for inclusion.

There were 5,983 episodes where patients were on anti-platelet medications (aspirin and/or Clopidogrel). The median pre-transfusion platelet count for these patients was 83,000/µL (42,000-180,000/µL, IQR) while for patients not on anti-platelet medication the median pre-transfusion platelet count was 19,000/µL (11,000-43,000/µL, IQR).

46% of all platelet units were transfused to patients who had a primary or secondary ICD9/10 diagnosis code of leukemia, myelodysplastic syndrome (MDS) or lymphoma. These patients were transfused, on average, more platelets per encounter and per total study period (Table 5).

Discussion

The REDS-III Recipient and Component databases represent one of the largest data sets available addressing both component and patient clinical characteristics, and we estimate it represents roughly 3-5% of all platelets transfused annually in the United States[2,3]. Other large international databases are available that have been used to address a number of donor and patient transfusion issues, but may lack the granularity and depth of the REDS-III database[11-15,19]. Our data confirm that apheresis platelets are the most common platelet transfusion product, though our data shows less apheresis use than national surveys due to one of the four HUBS manufacturing large numbers of WBD platelets. Not surprisingly, nearly all platelet ~~product~~s were leukocyte reduced since all apheresis platelet ~~product~~s are automatically leukocyte reduced by apheresis technology. Irradiation of platelet

~~product~~s is common, partly reflecting high platelet use in the oncologic/stem cell transplant setting. The General Ward (mainly representing oncology and stem cell transplant patients) and ICU dominated as the locations for platelet transfusions and have similar transfusion practices. Any Patient Blood Management program addressing platelet transfusion practice will need to primarily focus on these two locations.

Post-transfusion platelet count increments were under 20,000/µL for the majority of inpatient transfusion regardless of location. Data from the recent PLADO trial showed a similar but slightly higher 4 hour platelet increment for their median and high dose arms[20]. The differences may reflect a lesser acuity of illness in their patients compared to our study or the shorter interval for post-transfusion platelet counts vs. 6.9 hours in this study. Outpatient transfusions led to a higher median post-transfusion platelet count increment, most likely reflecting a lower severity of illness than in the inpatient setting. We selected post platelet transfusion platelet count increments as the measure of platelet count rise rather than corrected count increments (CCI) because they reflect the "real life values" upon which physicians make decisions. CCI are most useful in determining platelet refractoriness, a condition not studied in this project.

Surprisingly, a pre-transfusion platelet count of 20,000-50,000 was the most common platelet count prior to transfusion. This was true for both General Ward and ICU. Current recommendations for prophylactic platelet transfusion for oncology and bone marrow transplant are 10,000/µL and for minor bleeding, 20,000/µL[4,5]. Transfusions in the 20,000/µL to 100,000/µL range is an area that requires further study in that evidence based data is limited and weak. ~~There are virtually no good evidence based data that address platelet transfusion practice for these patients.~~ In the ICU setting there are a large number of platelet transfusion episodes for pre-transfusion platelet counts of 50,000-100,000/µL or greater than 100,000/µL. Again the evidence based data for this practice is weak. A recent United Kingdom observational study of thrombocytopenia and platelet transfusion in the ICU reported that greater than 40% of platelet transfusions were given with a patient platelet count >50,000/µL similar to the 35% we observed. Many platelet transfusions were given to non-bleeding patients, and platelet count increments were similar to our data for ICU patients. They concluded the importance of the need for improved evidence for platelet use in this population of patients[21]. A more recent retrospective, three academic center study of patients transfused with platelets in the ICU demonstrated that platelet transfusions were not associated with increased risk of death in critically ill patients. They found that median pre-transfusion platelet count was 55,000/µL for medical ICU patients and 95,000/µL for general surgery patients. They emphasized the need for further prospective studies to address the benefits and harms of platelet transfusions in critically ill patients[11].

Our data demonstrate that only 54.1% of platelet transfusions were ABO type specific. 29.7% of type O platelets were transfused to non-type O patients. These practices illustrate the difficulty that collection centers have in maintaining an adequate platelet inventory that would allow for more type-specific transfusion. Though the risk of a severe or even life-threatening hemolytic transfusion reaction is very low, it is clear that with 1 in 10 platelet transfusions being an O platelet to a non-O patient and 16% overall ABO antibody ~~incompatibility~~minor mismatch, our data indicates exposure to this risk is occurring on a daily basis. There are also reports of adverse outcomes when patients receive non-ABO type specific ~~blood product~~platelets, including decreases in platelet increment, increased alloimmunization, and increase in febrile reactions[22,23]. Pai et al recently reported the transfusion of ABO non-identical blood is associated with worsened mortality outcomes in group A patients. The mechanism was not clear, though it was thought unlikely to be due to donor plasma products~~components~~, this explanation could not be ruled out[24]. Our data show that use of non-type specific platelet transfusions is common, supporting the need for further studies to clarify the risk for adverse events. Our data are similar to a recent BEST Collaborative international survey which demonstrated wide variability in practices associated with the transfusion of ABO ~~incompatible~~ mismatched platelets[19]. Though we did not analyze the impact of major mismatched platelets on platelet increment, Triulzi et. al. analyzed this as part of the Platelet Dose Study (PLADO). They demonstrated that there was a small (approximately 25%) but statistically significant decrease in corrected count increment for major mismatched platelets. However, they importantly demonstrated that there was no impact on the risk of bleeding when compared to ABO identical platelets[25]. In our study, 60.6% of all transfusions given to Rh negative patients were Rh positive thereby posing the risk of anti-D alloimmunization. A review of this topic in the 2017 ASCO guidelines for platelet transfusion in cancer patients states that whereas older literature indicated a rate of anti-D alloimmunization of greater than 7%, current studies suggest a much lower alloimmunization rate of about 1%[4].

The number of patients on anti-platelet therapy continues to rise. Our data demonstrate that patients on aspirin and/or Clopidogrel had pre-transfusion platelet counts significantly higher than for patients not on these medications. The higher pre-transfusion platelet count for ICU and surgery patients may be partly reflected by use of these drugs for patients undergoing cardiac surgery. Although the impact of these drugs on platelet function is well-understood, the efficacy of platelet transfusion to prevent or treat bleeding is poorly understood, and is in definite need of further clinical evaluation as suggested in a recent review of this ~~clinical~~ issue[2~~5~~6].

Our study has a number of limitations. Although the number of platelet transfusions evaluated is extremely large, it represents only 12 hospitals in the U.S. and is weighted towards academic medical

centers. Though the study was epidemiological in nature, the lack of data on the efficacy to prevent or treat bleeding is evident. Because of inability to match ~~component~~ product and recipient ABO and Rh type for all products, the number of platelet transfusions for evaluation by ABO and Rh type was reduced. Diagnosis and procedure codes were not the emphasis of this paper so data are limited to general diagnostic codes. Platelet transfusions on the General Ward were assumed to represent mainly Hematology/Oncology and stem cell transplant patients, though we have no direct proof that is so. Platelet transfusions in pediatric patients were not part of this study, so no comment can be made as to platelet transfusion practice in pediatric patients.

In summary, our data represent one of the largest studies of platelet transfusion practice to date. Despite some weaknesses, this database has a wealth of information concerning platelet transfusion practices in the inpatient and outpatient setting, using data from both community hospitals and academic institutions. This study has emphasized areas of platelet transfusion practice that are poorly defined. It will lead to the creation of new clinical research questions as well as to help direct platelet Patient Blood Management Program efforts. Opportunities for further research include platelet use for moderate thrombocytopenia (platelet counts between 20,000 and 100,000/µL), anticoagulation and platelet use in oncology patients, platelet use prior to a procedure, and the role of platelet transfusions for patients on anti-platelet medications. Finally, these data highlight “real world” versus controlled trial studies and provide epidemiologic and laboratory data to support new initiatives to improve platelet transfusion practice.

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Table 1. Characteristics (by number and %) of patients with an encounter that included a platelet transfusion

Number of Patient-Total	31,821
Inpatients	28,843 (91%)
Outpatients	2,978 (9%)
Male (%)	19,264 (60.5%)
Female (%)	12,554 (39.5%)
Age (Years) 18-29	1,475 (4.6%)
30-49	4,425 (13.9%)
50-69	15,265 (48.1%)
70 & >	10,656 (33.4%)
Race (%) White	23,876 (75%)
Black	3,177 (9.9%)
Asian	843 (2.6%)
Other	3,925 (12.3%)
Alive at last encounter	26,803 (84.2%)
Dead at last encounter*	5,018 (15.8%)

*Hospital mortality at any time during the four year study interval

Table 2. Platelet products issued, location issued and broad ICD 9/10 Diagnosis Codes

Platelet Products (Units)-Total	163,719
Apheresis	103,371 (63%)
Whole Blood Derived	60,348 (37%)
Leukocyte Reduced	93.5%
Irradiated	72.5%
Outpatient	25,582 (16%)
Inpatient	138,137 (84%)
General ward	72,787 (52.7%)
ICU	38,944 (28.2%)
OR	17,370 (12.6%)
Emergency Department	4,504 (3.3%)
Other procedure suite	291 (0.2%)
Other	4,241 (3.0%)
ICD 9/10 Diagnosis Code: Inpatient (%)	
Disease of the Circulatory System	23.2%
Neoplasms	18.6%
Diseases of blood & blood forming organs	5.6%
Injury & Poisoning	16.2%
Disease of Digestive System	9%
ICD 9/10 Diagnosis Code: Outpatient (%)	
Neoplasms & Diseases of blood & blood forming organs	83%

Table 3. Platelet transfusions by ABO and Rh product type

Platelet Product ABO Type						
Patient ABO	**A**	**B**	**AB**	**O**	**Total**	**% ABO Identical**
A	**28,927**	3,546	2,444	7,518	42,435	**68.1**
B	3,969	**6,598**	1,276	2,944	14,787	**44.7**
AB	3,227	665	**1,173**	973	6,038	**19.4**
O	18,493	6,593	2,377	**27,001**	54,464	**49.5**
Total	54,616	17,402	7,270	38,436	117,724	**54.1**

Platelet Product Rh Type				
Patient Rh	**Rh Positive**	**Rh Negative**	**Total**	**% Rh "Identical"**
Rh Positive	**69,663**	6,216	75,879	**91.8**
Rh Negative	7,548	**4,912**	12,460	**39.4**
Total	77,211	11, 128	88,339	**84.4**

Table 4. Pre-platelet transfusion count (range and median count within that range) with post-transfusion increment by episode

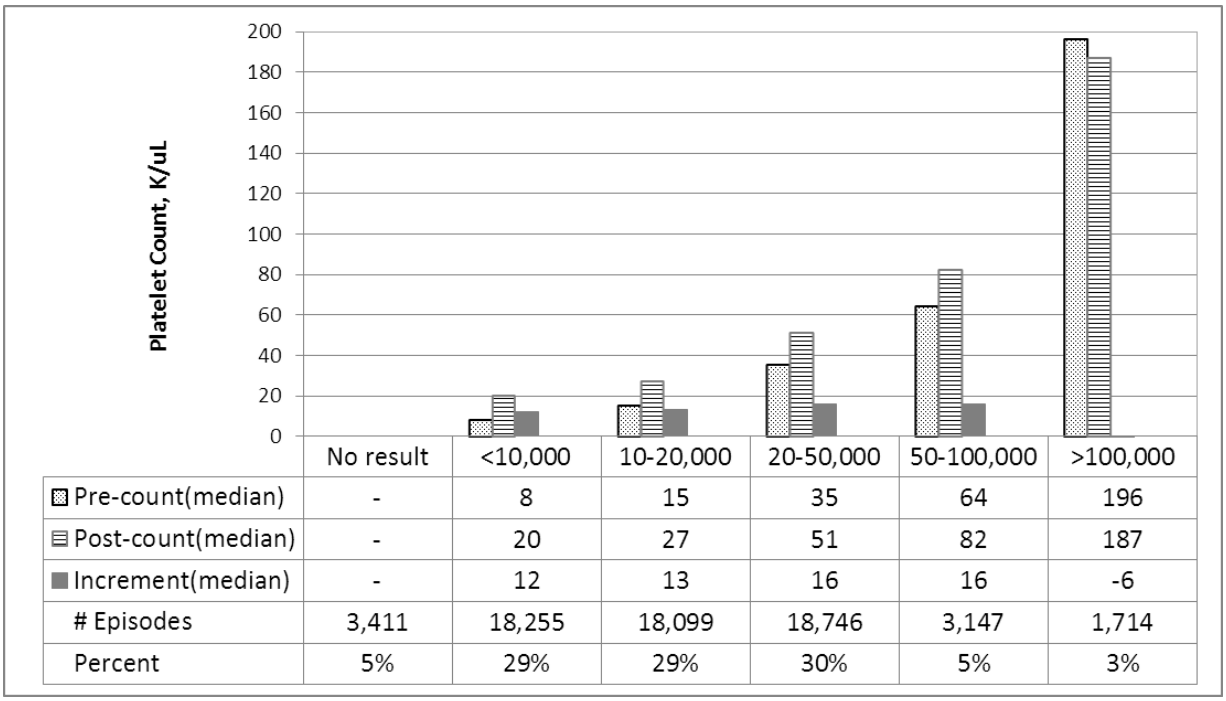
	Pre-Tx Plt Ct per ul (Median)	Total Episodes	% of Total	Median Post-Tx Plt Ct Increment per ul*
Inpatient Transfusions	No results	9,689	9%	
	≤10,000 (8,000)	21,367	20%	12,000
	>10,000-20,000 (15,000)	23,390	22%	13,000
	>20,000-50,000 (36,000)	30,046	28%	17,000
	>50,000-100,000 (68,000)	11,223	11%	20,000
	>100,000 (187,000)	10,204	10%	-6,000
Outpatient Transfusions	No results	11,038	47%	
	≤10,000 (7,000)	4,128	17%	27,000
	>10,000-20,000 (15,000)	5,906	25%	24,000
	>20,000-50,000 (29,000)	2,300	10%	20,000
	>50,000-100,000 (61,000)	222	1%	17,000
	>100,000 (189,000)	136	1%	-7,500
*Median time from time of issue to post-platelet count: 6.9 hours (inpatients) 1.6 hours (outpatients)				

Table 5. Platelet use in patients with ICD 9/10 diagnosis of Leukemia, MDS and Lymphoma

Table 5a. Platelet use in patients with ICD9/10 diagnosis of leukemia/MDS			
Mean platelet ~~product~~s transfused during an encounter			
Any primary or secondary diagnosis of leukemia/MDS	# of encounters	Mean p~~roduct~~latelets transfused	Std. Dev
NO	36,060	2.6	5.0
YES	22,742	2.8	5.8
Mean platelet ~~product~~s transfused to each subject			
NO	27,188	3.4	7.87
YES	4,386	14.7	19.41
Table 5b. Platelet use in patients with ICD 9/10 diagnosis of lymphoma			
Mean platelet ~~product~~s transfused during an encounter			
Any primary or secondary diagnosis of lymphoma	# of encounters	Mean p~~roduct~~latelets transfused	Std. Dev
NO	57,774	2.6	5.37
YES	4,028	2.8	5.65
Mean platelet ~~product~~s transfused to each subject			
NO	30,084	4.9	11.2
YES	1,490	7.6	13.3

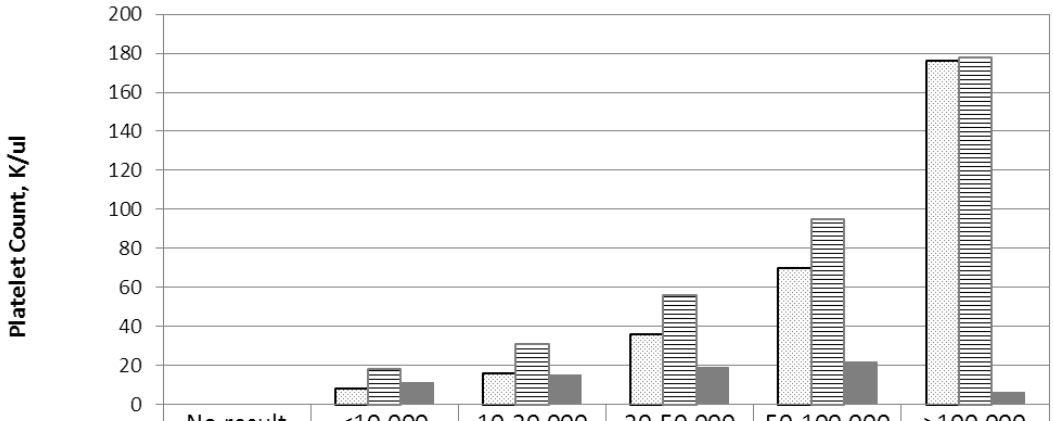
1) 64,400 platelet ~~product~~s transfused with diagnosis of leukemia/MDS
2) 11,286 platelet ~~product~~s transfused with diagnosis of lymphoma
3) 46.2% of all platelet ~~product~~s were transfused with diagnosis of leukemia, MDS and lymphoma combined
4)There were 247 patients who had a primary or secondary diagnosis of both leukemia/MDS and lymphoma, and were not included in Table 5 data

Figure 1.



	No result	<10,000	10-20,000	20-50,000	50-100,000	>100,000
Pre-count(median)	-	8	15	35	64	196
Post-count(median)	-	20	27	51	82	187
Increment(median)	-	12	13	16	16	-6
# Episodes	3,411	18,255	18,099	18,746	3,147	1,714
Percent	5%	29%	29%	30%	5%	3%

Figure 2.



	No result	<10,000	10-20,000	20-50,000	50-100,000	>100,000
Pre-count(median)	-	8	16	36	70	176
Post-count(median)	-	18	31	56	95	178
Increment(median)	-	11	15	19	22	6
# Episodes	1,257	2,309	4,478	9,348	5,974	3,524
Percent	5%	9%	17%	35%	22%	13%

Figure Descriptions

Fig. 1 The pre-platelet, post-platelet count and platelet increment (all median counts) are presented by different pre-transfusion platelet counts. The number of episodes (and % episodes) is also presented. The data are for patients who received a transfusion while an inpatient on the hospital general ward.

Fig. 2 The pre-platelet, post-platelet count and platelet increment (all median counts) are presented by different pre-transfusion platelet counts. The number of episodes (and % episodes) is also presented. The data are for patients who received a transfusion while an inpatient in the hospital ICU.