Original article

An audit of platelet transfusion indications in acute leukaemia patients: six-year experience at an Academic Centre

José C. Jaime-Pérez, Gerardo García-Salas, Grecia A. Turrubiates-Hernández, Dalila M. Alvarado-Navarro, Luis J. Marfil-Rivera, David Gómez-Almaguer

Department of Haematology, Faculty of Medicine and University Hospital "Dr. Jose Eleuterio Gonzalez", Autonomous University of Nuevo Leon, Monterrey, Mexico

Background - Platelet transfusion plays a critical role in the supportive treatment of acute leukaemia patients who receive chemotherapy and haematopoietic stem cell transplantation (HSCT). There are few studies assessing appropriateness of platelet transfusion in this population. An audit was conducted to determine how appropriately platelets are transfused in acute leukaemia patients at a tertiary care health institution.

Materials and methods - A six-year retrospective audit was conducted in acute lymphoblastic (ALL) and acute myeloid leukaemia (AML) patients in an Academic Centre. Episodes were assessed as either appropriate or inappropriate based on guidelines from the British Society for Haematology (BSH). Pre-transfusion platelet count, transfusion indication, World Health Organization (WHO) bleeding score, and antibiotic use were all documented.

Results - Overall, 745 platelet transfusion episodes in 154 patients were audited. The proportion of episodes appropriately indicated according to BSH guidelines was 75.3%. Paediatrics and Internal Medicine had the lowest and highest proportion of appropriateness by department at 63.9% and 86.8%, respectively. The best alignment to guidelines was found on the wards (82.3%). Inpatient cases were significantly better indicated (p=0.002), whereas therapeutic and HSCT-related transfusions were not. The majority of inappropriate transfusions had a pre-transfusion count >20×10^9/L without a valid justification (45.1%), whereas appropriate episodes were mainly accounted for by a pre-transfusion count <10×10^9/L (69%).

Discussion - The 25% rate of inappropriate platelet transfusion in acute leukaemia patients underscores the learning needs of physicians, particularly those in training, regarding adequate use of platelets in haematologic malignancies to optimise its utilisation and patient outcome.

Keywords: *platelet transfusion, audit, acute lymphoblastic leukaemia, acute myeloblastic leukaemia, BSH guideline.*

INTRODUCTION

Blood transfusion support is essential in the care of leukaemia patients since it helps to manage toxicity and myeloablation secondary to intense chemotherapy and conditioning regimens for haematopoietic stem cell transplantation (HSCT)[1]. This is especially true for platelet transfusion.

Arrived: 16 February 2020
Revision accepted: 17 July 2020
Correspondence: José Carlos Jaime-Pérez
e-mail: carjaime@hotmail.com

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Efficient and sustainable platelet utilisation, especially in a limited-resource setting, is important since platelets are a scarce resource. Platelets are difficult to stock because of their short half-life and are among the costliest products in transfusion medicine. Furthermore, their inappropriate use carries risks, such as infection, alloimmunisation, allergic reactions, transfusion-related acute lung injury, and febrile non-haemolytic reactions, as well as transfusion-associated graft-versus-host disease in immunosuppressed patients[2].

The importance of adequate platelet transfusion has been addressed mainly because of the increasing demand for this procedure. Around 2.2 million platelet doses are transfused annually in the United States[2]. Haematology patients are intensive platelet users, constituting 28-66%[3-6] of all transfusion episodes, and this trend is likely to persist with improved survival and more aggressive therapeutic approaches.

The quality of platelet transfusion practice is assessed through periodic audits based on standardised and evidence-based guidelines. Specific guidelines to this end have been issued by the British Society for Haematology (BSH)[7] and the American Association of Blood Banks (AABB)[2]. A platelet threshold of $<10\times10^9$/L for prophylactic transfusions has become widely accepted[8].

Several clinical audits have determined that appropriate platelet transfusion varies widely, from 46-87% in high-income nations[4,9-12] and from 19-96.2% in low- and middle-income countries[13,14]. Information regarding the quality of platelet transfusion in haematology patients is scarce and is only available for 50-72% of procedures carried out in industrialised countries[8,15], whereas no information is available from low-middle income countries.

The objective of this study was to evaluate the utilisation of platelet transfusion in patients with acute leukaemia at an Academic hospital according to BSH guidelines.

MATERIALS AND METHODS

A retrospective, cross-sectional audit of platelet transfusions in acute leukaemia patients was performed from 1st of January 2013 to 31st of March 2019 (a period of six years and three months) at an Academic Centre. Platelet transfusions at our university hospital are mostly indicated by residents who receive an induction course on blood banking and transfusion medicine at the beginning of the residency programme, as well as a summarised guideline for transfusion of blood products. Decisions to transfuse are regularly discussed with senior staff.

Random (RDP) and single (SDP) donor platelet transfusions issued to patients diagnosed with either acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML) were studied, regardless of age, sex or number of episodes per patient. Both inpatient and outpatient transfusions were included. All platelets transfused to patients with acute leukaemia were leukoreduced. Formal approval of the study was obtained from the institutional ethics and research committees.

Data were retrieved from the patients' chart files and the blood bank's electronic records, and then abstracted into a database. Patient data included age, sex and haematologic diagnosis. Transfusion data included date, location where it took place, which department ordered the transfusion (ordering department), type of platelet product (RDP or SDP), concomitant drug use, and pre- and post-transfusion platelet count. Prophylactic transfusions were defined as those given: (i) to non-bleeding patients; (ii) prior to a procedure; or (iii) in cases of a grade 1 World Health Organization (WHO) bleeding score. Pre-transfusion platelet counts were defined as those measured on the day of transfusion or the day before; otherwise, the pre-transfusion count was recorded as unknown. Likewise, post-transfusion counts were recorded if they were available within the first 24 hours after transfusion. Pre-transfusion counts recorded in the patient files were compared with those on the blood bank's request forms, since they were expected to coincide. Acute bleeding, if present, was assessed according to the WHO bleeding score[2,16].

The BSH adult guideline[7] was used as the adjudication tool to evaluate transfusion compliance, since it is more recent and encompasses most co-existing conditions of ALL and AML patients, including concomitant use of antibiotics; furthermore, the BSH guideline for children is compatible with most key indications in the ALL group and its use was deemed appropriate for adjudication of paediatric ALL transfusions[17]. Each transfusion episode was adjudicated as appropriate or inappropriate. When a pre-transfusion platelet count was not recorded, the episode was deemed inappropriate by default.

Statistical analysis was performed using IBM SPSS 22

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Statistics for Windows v. 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA), including determining appropriateness by transfusion indication, patient location, the ordering department, concomitant drug use, and transfusion in the setting of HSCT. Pre-transfusion counts were also recorded according to category. Categorical variables were summarised as frequencies and percentages, and continuous variables as means with standard deviation (SD) or as medians with interquartile range (IQR) if data were skewed. The normality of data distribution was tested with the Kolmogorov-Smirnov test and the Shapiro-Wilk test. The χ^2 test was used for comparison of categorical values, and the Mann-Whitney-Wilcoxon test and the Kruskal-Wallis test for comparison of numerical data. $p<0.05$ was considered statistically significant.

RESULTS

A total of 745 platelet transfusion episodes from 154 acute leukaemia patients were audited. The age of patients ranged from one to 75 years (median: 17.5 years; mean: 23.6 years). Sixty-nine (44.8%) patients were children (<16 years) and 55% were males (**Table I**).

Details of transfusion episodes are summarised in **Table II**. Overall, 643 platelet transfusion episodes using 2,698 concentrates pooled into 685 RDP units, as well as 102 episodes using SDP units, were administered; they constituted 86.3% and 13.7% of all episodes, respectively. Each patient received a mean of 4.8 transfusions in the study period. Paediatric transfusions comprised 46% (n=343) of cases, and male transfusions accounted for 58.7% (n=437). Sorted by ordering department, 48.1% of the transfusions were ordered by the Haematology Department, 32.6% by Internal Medicine, and 19.3% by the Paediatric Department. When grouped according to patient location, 50.9% were transfused on the wards, 42% in the outpatient clinic, and 7.1% in the Intensive Care Unit (ICU). Ninety-seven percent of episodes were prophylactic and 3% were therapeutic. Bleeding episodes were categorised according to the WHO classification into grade 1 (109 of 133), grade 2 (20 of 133), and grade 3 or 4 (4 of 133); grades 2-4 were included in the therapeutic group. The percentage of SDP use differed significantly among departments: 20.4% in Haematology, 9.5% in Internal Medicine, and 4.2% in Paediatrics ($p<0.001$). There was also a non-significant difference between children (11.7%) and adults (15.4%) ($p=0.14$).

The median pre- and post-transfusion counts were 10.1×10^9/L (IQR=6.6-15.7$\times10^9$/L) and 21×10^9/L (IQR=11-34$\times10^9$/L), respectively; the median increase from pre- to post-transfusion count was 9×10^9/L (IQR=1.8-21$\times10^9$/L). When sorted by pre-transfusion platelet intervals, most transfusions took place in the ranges of 0-10$\times10^9$/L (49.5%) and 11-20$\times10^9$/L (36.1%).

Of the 745 episodes audited, 561 (75.3%) were considered appropriately indicated according to BSH guidelines.

Table I - *Demographic characteristics of 154 patients with acute leukaemia who received platelet transfusion in an Academic Centre*

Characteristic	N (%)
Total	154 (100)
Gender	
Female	68 (44.2)
Male	86 (55.8)
Age	
<16 years	69 (44.8)
≥16 years	85 (55.2)
Haematopoietic transplant	
Not transplanted	93 (60.4)
Transplanted	61 (39.6)

Table II - *Characteristics of 745 platelet transfusion episodes in 154 acute leukaemia patients sorted by location and ordering department in an Academic Centre*

Characteristic	N (%)	Appropriateness (%)	p
Total	745 (100)		
Admission status			
Inpatient episode	432 (58.0)	343 (79.4)	<0.001
Outpatient episode	313 (42.0)	218 (69.6)	
Patient location			
Outpatient clinic	313 (42.0)	218 (69.6)	<0.001
Ward	379 (50.9)	312 (82.3)	
Intensive Care Unit	53 (7.1)	31 (58.5)	
Ordering department			
Haematology	358 (48.1)	258 (72.1)	<0.001
Internal Medicine	243 (32.6)	211 (86.8)	
Paediatrics	144 (19.3)	92 (63.9)	
Indication			
Prophylactic	721 (96.8)	539 (74.8)	0.06
Therapeutic	24 (3.2)	22 (91.7)	
Type of product			
Random donor platelets	643 (86.3)	486 (75.6)	0.066
Single donor platelets	102 (13.7)	75 (73.5)	

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Thirty-four (4.6%) cases were deemed inappropriate due to the lack of a pre-transfusion platelet count. The proportion of appropriate transfusions was compared by ordering department and patient location (**Figure 1**). The ordering department with the lowest appropriateness rate was Paediatrics (63.9%), whereas the highest rate corresponded to Internal Medicine (86.8%); the difference between the three departments was statistically significant (p<0.001). Transfusions in adults adhered significantly better to guidelines (83.8%) than those in children (65.3%) (p<0.001). Regarding patient location, transfusion compliance was lowest in the ICU (58.5%) and highest on the ward (82.3%); the difference between locations was also significant (p<0.001).

Conversely, transfusion appropriateness according to location was more uniform and not statistically different when analysing adults separately (ICU 75%, outpatient clinic 81.1%, ward 87.8%; p=0.07), whereas greater differences were observed in the paediatric group, and these retained significance (ICU 23.5%, outpatient clinic 56.3%, ward 76.4%; p<0.001). Adjudication by indication (prophylactic *vs* therapeutic) and haematologic diagnosis is shown in **Table III**. Therapeutic transfusions had the highest rate of appropriate platelet use (91.7%), whereas prophylactic episodes had a lower rate (74.8%), although this difference did not reach significance (p=0.06). Therapeutic transfusions were also more compliant when sorted by age in both children (80%) and adults (94.7%), but neither reached significance (data not shown). Conversely, transfusions in AML were more appropriately used (84%) than in ALL (68.8%) (p<0.001), and this difference persisted in the paediatric group when analysed separately (p=0.02). When pre-procedure transfusions were analysed separately from the rest of the prophylactic episodes, they had a rate of appropriateness of 90.9%. Furthermore, inpatient transfusions had a higher rate of appropriateness (79.4%) than outpatient episodes (69.6%) (p=0.002).

Reasons for appropriate and inappropriate platelet transfusions, as well as their sorting by location and age categories, are shown in **Table IV**. Inappropriate transfusions were mainly those with a pre-transfusion count >20×10⁹/L without additional justification (45.1%). On the other hand, a pre-transfusion count below the standard prophylactic threshold <10×10⁹/L accounted for the most appropriate transfusions (69%).

Table III - *Comparison of platelet transfusion appropriateness for 154 patients by transfusion classification and type of acute leukaemia*

Characteristic		ALL (%)	AML (%)	p
Total				
Appropriate	561 (75.3)	293 (68.8)	268 (84.0)	<0.001
Inappropriate	184 (24.7)	133 (31.2)	51 (16.0)	
Prophylactic				
Appropriate	539 (74.8)	285 (68.3)	254 (83.6)	<0.001
Inappropriate	182 (25.2)	132 (31.7)	50 (16.4)	
Therapeutic				
Appropriate	22 (91.7)	8 (88.9)	14 (93.3)	0.703
Inappropriate	2 (8.3)	1 (11.1)	1 (6.7)	

ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia.

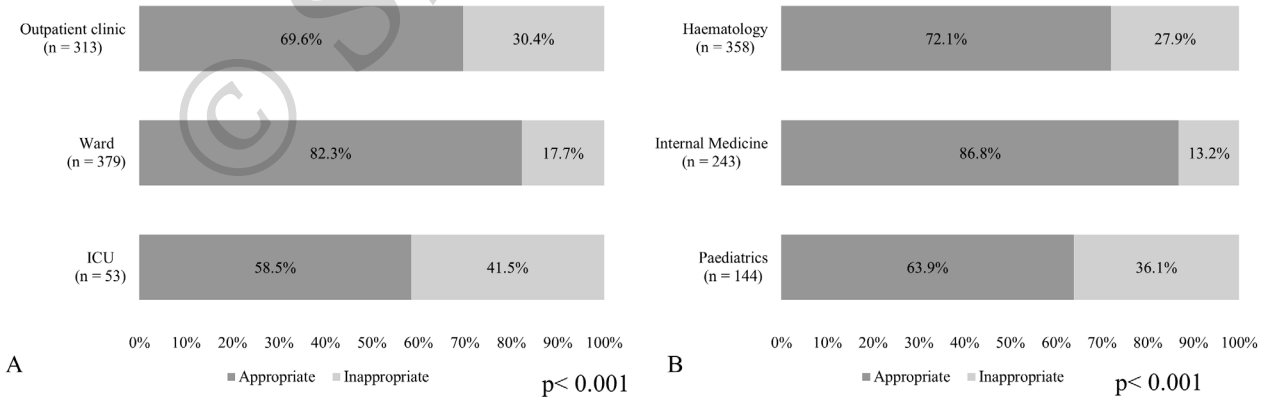


Figure 1 - Comparison of appropriateness of 745 platelet transfusion episodes in 154 acute leukaemia patients according to patient location and ordering department
(A) Patient location and (B) Department. ICU: Intensive Care Unit.

Blood Transfus 2021; 19: 37-44 DOI 10.2450/2020.0045-20

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There was no difference in appropriateness between transfusions issued after an HSCT (76.8%; 106 of 138) and those not related to an HSCT (75%; 455 of 607) (p=0.65), nor was there a significant difference in pre-transfusion platelet counts between HSCT-related (median=10×10^9/L) and non-HSCT-related (median=10.2×10^9/L) (p=0.86) cases.

Concurrent antibiotic and antifungal drugs that justified a higher prophylactic threshold (<20×10^9/L) were used prior to transfusion in 74.1% (552 of 745) of episodes; of these, the prophylactic threshold was affected by the antibiotic therapy only in 28.26% (156 transfusions) (**Table IV**). In addition, platelet transfusion was more appropriately indicated (84.4%) when patients were receiving antibiotics than when they were not (60.1%) (p=0.001) (*data not shown*).

Ninety-five percent of episodes with recorded dates had a pre-transfusion platelet count measured within 24 hours prior to transfusion, 4.6% within 24-48 hours, and 0.4% more than 48 hours apart. Conversely, 81% of episodes with recorded dates had a post-transfusion platelet count measured within 24 hours prior to transfusion, 18.3% within 24-48 hours, and 0.7% more than 48 hours apart.

Pre- and post-transfusion counts sorted by different categories are shown in **Figure 2**. Inappropriate transfusions had a significantly higher pre- and post-transfusion count than appropriate events (p<0.001) (**Figure 2A**). Significant differences in pre- and post-transfusion platelet counts were also seen between ordering departments (p<0.001) (**Figure 2B**). Regarding patient location, there was no significant difference in pre-transfusion platelet counts (p<0.92) but a significant difference was observed in post-transfusion counts (p<0.001). Pre- and post-transfusion platelet counts sorted by indication are shown in **Figure 2C**; neither pre- nor post-transfusion counts differed significantly between prophylactic versus therapeutic groups (p=0.96 and p=0.22, respectively).

Of all inpatient episodes with available pre-transfusion counts in the patient charts, 56.6% (232 of 410) also had such a count recorded in the respective blood bank request form. These were categorised as either: (i) platelet count indicated on the request form and corresponding to the actual platelet count noted in the clinical file (74.1%; 172 of 232); or (ii) platelet count indicated on the request form but differing from the actual file count (25.9%; 60 of 232). These did not differ significantly with regard to transfusion appropriateness (p=0.19). When the pre-transfusion count was indicated on the request form but differed from the actual count, the median deviation in platelet count was 4.5×10^9/L (IQR=2.5-8.9×10^9/L). The clinical file pre-transfusion counts which matched those of their corresponding request forms were significantly

Table IV - *Reasons for inappropriate and appropriate platelet transfusions in 154 acute leukaemia patients by age group and location of transfusion*

Characteristic	Total (%)	Children (%)	Adults (%)	Outpatient (%)	Ward (%)	ICU (%)
Inappropriate						
No pre-transfusion count	34 (18.5)	21 (17.6)	13 (20.0)	12 (12.6)	21 (31.3)	1 (4.5)
Pre-transfusion count 10-20×10^9/L without additional risk factors for bleeding	67 (36.4)	46 (38.7)	21 (32.3)	54 (56.8)	13 (19.4)	0 (0.0)
Pre-transfusion count >20×10^9/L without additional risk factors for bleeding	83 (45.1)	52 (43.7)	31 (47.7)	29 (30.5)	33 (49.3)	21 (95.5)
Appropriate						
Pre-transfusion count <10×10^9/L	387 (69.0)	133 (59.4)	254 (75.4)	162 (74.3)	199 (63.8)	26 (83.9)
Concurrent antibiotic use	156 (28.26)	86 (38.4)	70 (20.8)	53 (24.3)	98 (31.4)	5 (16.1)
Active bleeding (WHO score ≥2)	10 (1.8)	3 (1.3)	7 (2.1)	3 (1.4)	7 (2.2)	0 (0.0)
Before invasive procedure	8 (1.4)	2 (0.9)	6 (1.8)	0 (0.0)	8 (2.6)	0 (0.0)

ICU: Intensive Care Unit; WHO: World Health Organization.

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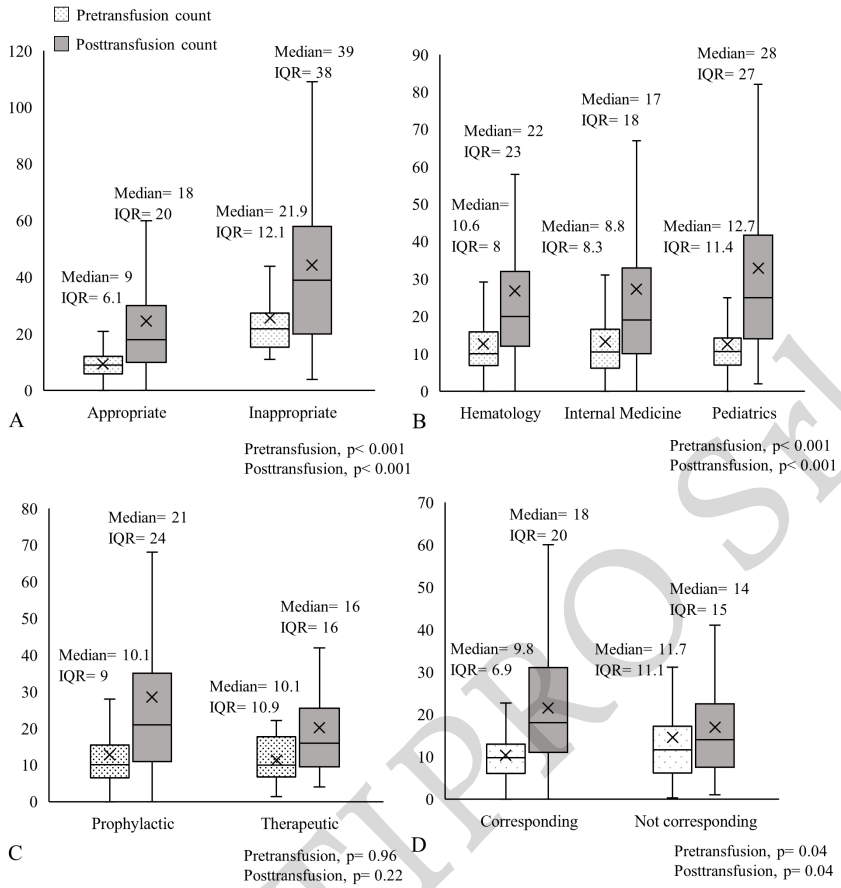


Figure 2 - Pre- and post-transfusion platelet counts for 745 episodes in 154 acute leukaemia patients according to various criteria
(A) Transfusion appropriateness. (B) Ordering service. (C) Transfusion classification. (D) Correspondence of request form count with actual count.

lower (median=9.8×10⁹/L) than those where they did not match (median=11.7×10⁹/L, p=0.04) (**Figure 2D**).

Reported transfusion reactions were present in 2.5% (19 of 756) of all episodes, and more than half consisted of fever and rash (n=10 of 19; 52.6%).

DISCUSSION

This audit focused on platelet transfusions in ALL and AML patients since these are the main haematologic malignancies for which heavy and recurrent platelet transfusion is required. To our knowledge, this is the first audit assessing the appropriateness of platelet use exclusively in acute leukaemia patients.

Around half of the transfusions were indicated by the Haematology Department; this is expected given that they are responsible for treating the studied population and considering that most of these transfusions were prophylactically given to patients prior to chemotherapy or conditioning regimens for HSCT. Regarding patient location, half of the transfusions were performed on the wards, similar to a previous haematology audit[8]. Most transfusions in our acute leukaemia patients (96.8%) were prophylactic, which differs from other audit results showing a range of 35-69%[4,8]. This may be partly because, for the purposes of this audit, bleeding with a non-specified severity was assigned a WHO grade 1, which would exclude these cases from the therapeutic group.

One in every ten transfusions in our audit were platelet pheresis, which is considerably less than the up to 98% reported in high-income countries[18]. Most of these SDP transfusions were indicated by the Haematology Department, and more than half of them were administered in the Outpatient Clinic.

The proportion of transfusion appropriateness in our

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study was 75.3%, which is consistent with results from previous audits that included haematologic patients[8,15]. Our higher proportion of guideline adherence in therapeutic rather than prophylactic episodes is also in line with previous audits[8,19]. Pre-procedure transfusions had a higher rate of appropriateness than the overall prophylactic transfusions; most procedures consisted of lumbar puncture and central venous catheter placement. This is to be expected given the diagnostic and therapeutic approach necessary in haematology patients. In this respect, it is important to note that the recommendation for the use of a higher platelet transfusion threshold in specific circumstances in haemato-oncology patients has been included in recent guidelines[20].

As previously observed[8,21], a transfusion that is not adherent to guideline standards does not necessarily indicate that it is inappropriate, given that some particular patient subgroups (i.e. acute promyelocytic leukaemia) or setting (i.e. an expected platelet count drop below transfusion threshold before the next visit) may warrant a transfusion in spite of not being explicitly accounted for in the guidelines.

Previous audits have suggested that inappropriate prophylactic transfusions are explained by the physicians' tendency to transfuse on the safer side of the transfusion threshold[15,22]. In our study, however, a threshold <20×10^9/L for all prophylactic episodes would only increase appropriateness by 2%. Interestingly, a pre-transfusion platelet count >20×10^9/L without a justifiable reason for transfusion accounted for most of the inappropriate transfusions in the ICU. Although there is no clear explanation for this, it might have been due to under-documentation regarding bleeding or additional risk factors, such as sepsis.

The pre-transfusion platelet count remains the single most important factor in the decision to transfuse, which explained our decision to adjudicate episodes without a recorded pre-transfusion count as inappropriate.

Total and prophylactic platelet transfusions in ALL had a significantly lower rate of appropriateness than AML. No clear explanation for this was identified; however, this could have been due to a more liberal transfusion practice in ALL paediatric patients, who are perceived to be at a higher risk of bleeding. Differences in compliance with guidelines according to haematologic diagnosis have not been previously characterised.

The pre-transfusion count was lower in episodes in which the value recorded in the patient chart matched that of the blood bank order form. This underpins the relation between accurate recording practice and appropriate transfusion itself. Furthermore, over half of the episodes did not have a platelet count recorded on the blood bank form, and of those that did have it but had a different value, the median difference was 4.5×10^9/platelets/L, in contrast with the 9×10^9/L previously reported[14]. On the other hand, the rate of episode documentation in the clinical file was lower than expected at 40%, in agreement with that in the literature. These findings stress the need to improve physician training on the importance of proper and consistent recording for purposes of quality audits.

The difference in transfusion appropriateness between HSCT-related and non-related cases was not significant, and over three-quarters of HSCT-related transfusions were indicated by the Haematology Department. Although transfusion appropriateness has not been assessed in HSCT recipients, the threshold of 10×10^9/L is currently considered adequate[23].

Transfusion reactions were recorded in 2.5% of episodes, which is consistent with previous reports and underscores the need for medical residents to be aware of the possible negative effects of platelet transfusions, which have the highest rate of transfusion-derived complications[24].

This study has limitations. Due to the multiple transfusion episodes registered per patient, appropriateness may be dependent on patient management rather than on separate transfusions, representing a potential statistical bias, which has been previously described[4,10]. Also, the reduced number of therapeutic transfusions might impair the generalisation of our results for episodes in this category.

CONCLUSIONS

Most platelet transfusions in patients with acute leukaemia were appropriate. Findings varied according to patient location and medical department. Ordering and documentation standards need to be improved to prevent inappropriate platelet transfusions. Finally, continuing education on transfusion medicine and reinforcing the application of guidelines by physicians in training will lead to improved, safe, and cost-efficient platelet transfusion practice.

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ACKNOWLEDGEMENTS

The Authors thank Sergio Lozano-Rodriguez, MD, for his critical review of the manuscript.

AUTHORSHIP CONTRIBUTIONS

JCJ-P is responsible for the study concept, design, and supervision, writing the original draft, review and editing. GG-S is responsible for study validation, formal analysis, and writing the original draft. GAT-H is responsible for software validation, and study investigation. DMA-N is responsible for data curation and study investigation. LJM-R is responsible for study supervision and review. DG-A is responsible for writing the article, review and editing.

The Authors declare no conflicts of interest.

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