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Evaluation of Human Leucocyte Antigen Mediated Platelet Transfusion Refractoriness and Platelet Crossmatching Assay in Patients with Hematologic Disorders

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ABSTRACT

Objectives: Platelet refractoriness complicates the platelet transfusion, which is essential for managing thrombocytopenia in patients with hematological disorders. It is associated with adverse clinical outcomes and increased health care costs. We conducted a prospective study to determine the effectiveness of cross-matched compatible platelets in a group of patients refractory to platelets from random donors and to evaluate human leukocyte antigen (HLA)-mediated refractoriness. ***Methods:*** This prospective study was conducted on 40 patients with different hematological disorders requiring platelet transfusions who were refractory to random platelets and presented to the hematology unit of Alexandria's main university hospitals between May 2020 and March 2021. They received 60 ABO-compatible platelet transfusions, either leuco-reduced or random donor platelets, stored for no more than 72 hours. A solid-phase red cell adherence technique (SPRCA) was used for platelet crossmatching. The corrected count increment (CCI) was used to monitor the effectiveness of each platelet transfusion with a cut-off value of $5 \times 10^3/\mu L$ at 1 hour and $2.5 \times 10^3/\mu L$ at 24 hours. Anti-HLA antibodies were assessed using the enzyme-linked immunosorbent assay technique. ***Results:*** Out of 60 cross matches, 47 (78.3%) were compatible, and 13 (21.7%) were incompatible. Among 47 compatible results, 30 (63.8%) showed adequate CCI and 17 (36.2%) showed inadequate CCI at 1-hour post-transfusion. Among the incompatible results, 3 (23.1%) had adequate CCI and 10 (76.9%) had inadequate CCI. Significant improvements were found in the mean CCI when comparing cross-matched compatible platelets and incompatible platelets at 1hour or 24 hours ($p = 0.009$ and $p < 0.001$, respectively). From the 40 studied patients, HLA alloimmunization was present in 18 patients (45.0%) and absent in the remaining 22 patients (55.0%). In the absence of HLA alloimmunization, patients showed significantly better responses at 1 hour and 24 hours ($p = 0.001$ and $p = 0.015$, respectively). There was better sensitivity of platelet crossmatching with random donor platelet concentrates than single donor platelet concentrates. ***Conclusions:*** Platelet crossmatching using SPRCA and HLA screening are effective and rapid tools for better management of patients' refractory to platelet transfusions.

Platelet transfusion is an essential part of treating hematological malignancies, marrow failure, and hematopoietic stem cell transplantation.[1,2] Platelet transfusion refractoriness (PTR) can be defined as failure to achieve a satisfactory platelet count in a patient after two or more consecutive transfusions of allogeneic platelets.[3,4] It is associated with a number of adverse outcomes including longer hospital stays,[5] increased risk of bleeding,[6,7] decreased survival,[7] and higher inpatient hospital costs.[3,5] The current incidence of PTR ranges from 5% to 14% in hematological patients.[8–11] The problem is greater in patients with multiple transfusions as 30%–70% become refractory to random donor platelet (RDP) transfusions.[12–14]

PTR causes are multifactorial, with 80% attributed to non-immunological causes and 20% to immunological causes.[15–17] The latter is often

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attributed to antibodies to human leukocyte antigen (HLA) and/or human platelet antigens (HPAs). Several approaches have been developed to address the problem of immune-mediated platelet refractoriness. One of the most frequently used methods is HLA matching, which is highly effective and represents the routine approach to the management of refractory patients in a number of institutions.[18,19] HLA matching requires the availability of large numbers of HLA-typed donors.[2] Even large blood suppliers periodically have difficulty identifying HLA-matched donors for some patients.[20] In addition, HLA typing techniques are time-consuming and costly. Also, it has been reported that about 40%–50% of HLA-matched platelet transfusion events do not result in adequate increments.[21]

Platelet crossmatching assays are a relatively low-cost and rapid alternative to the HLA-matched approach for the management of platelet refractoriness.[22–24] Crossmatching assays have been used for the identification of candidate platelet donors and may be beneficial for patients in whom refractoriness is due to HPA alloimmunization.[25]

Despite the routine use of platelet crossmatching at many institutions, it is still not implemented as a tool for the management of refractory patients in Egyptian institutions.

Here, we present transfusion-related outcomes observed at Alexandria's main university hospitals to determine whether platelet crossmatching can effectively identify platelet units that will improve the post-transfusion platelet counts.

Moreover, We sought to evaluate the role of platelet crossmatching assay in the management of patients with hematological disorders refractory to platelet transfusion and the effect of HLA-mediated platelet refractoriness.

METHODS

This prospective study was conducted on 40 patients with different hematological disorders (24 males and 16 females), of which 28 were adults and 12 were pediatrics. Their age ranged from 6 to 73 years, with a median age of 34.0 years. They were identified as refractory after receiving RDP transfusions. All were presented to the hematology unit of Alexandria's main university hospitals between May 2020 and March 2021. They received 60 ABO-compatible platelet transfusions (ranging from one to four transfusions per patient). Platelets were stored at 20–24 °C with continuous agitation for a maximum of three days. Patients with evidence of non-immunological causes of platelet refractoriness were excluded. This study received approval from the Medical Ethics Committee of the Faculty of Medicine, Alexandria University, Egypt. Written informed consent was obtained from each patient/guardian participating in the study. Platelet cross-matching was performed for all patients selected to be refractory to random platelet transfusion based on their 24-hour post-transfusion corrected count increment (CCI) of < 2500/μL after at least two consecutive transfusions. The CCI was calculated using the following formula:[26]

CCI = [post-transfusion platelet count (10^9/L) - pre-transfusion platelet count (10^9/L)] × [body surface area (m^2)]/ [platelet dose transfused (10^{11})].

After performing platelet crossmatching, a complete blood picture was done at one hour and 24 hours after platelet transfusion. CCI was calculated. Other formulae to calculate platelet increment (PI) and percentage platelet recovery (PPR) were also calculated.[20,27] Pre- and post-transfusion platelet counts were estimated on Advia 2120i hematology analyzer (Siemens, Germany), and patients' prior transfusion history was accessed from hospital records.

Platelet cross-match assays were performed using the solid-phase red cell adherence (SPRCA) technique with Capture-P Ready Screening (Immucor, Norcross, GA, USA) on the automated apparatus (NEO; Immucor 4 th generation) for the detection of IgG antibodies to platelet specific antigens. Briefly, the serum is incubated in platelet-coated wells to allow antibodies, if present, to bind to the platelets. Unbound immunoglobulins (Igs) are then washed from the wells and replaced with a suspension of anti-IgG-coated indicator red cells. Centrifugation brings the indicator red cells in contact with antibodies bound to the immobilized platelets. The negative test shows a button of indicator red cells at the bottom of the test well with no readily detectable area of adherence and is considered compatible, while the positive test shows adherence of indicator red cells to part of or the entire reaction surface and is considered incompatible.

Patients' serum samples were collected at -80 °C for HLA antibody detection using the enzyme-linked immunosorbent assay (ELISA) technique (Glory Science Co., Ltd, Del Rio, TX,

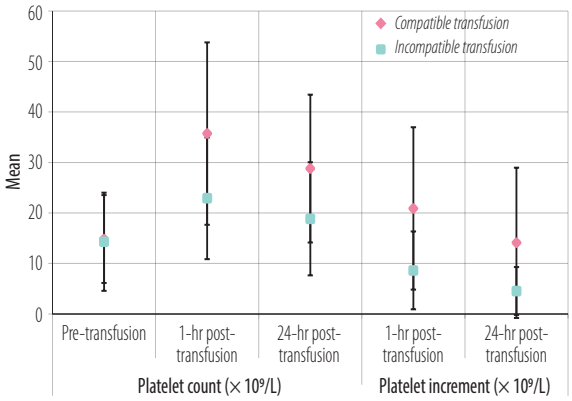

Figure 1: Laboratory data of all transfusion events in patients under study according to platelet count (× 10^9/L) and platelet increment.

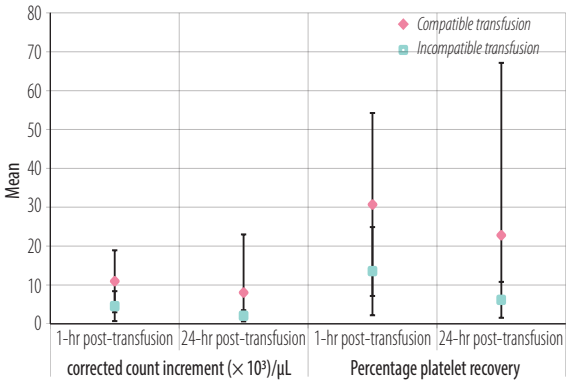

Figure 2: Laboratory data of all transfusion events in patients under study according to corrected count increment (× 10^3/µL) and percentage platelet recovery.

USA). ELISA was performed according to the manufacturer's instruction using Bio Rrad PW40 Microplate Washer and PR 4100 microplate reader.

Data were analyzed using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Categorical data were represented as numbers and percentages. We used the chi-square test to investigate the association between the categorical variables. Alternatively, Fisher's exact correction test was applied when the expected cell counts were less than five. We used odds ratio (OR) to calculate the ratio of the odds and 95% CI of an event occurring in one risk group to the odds of it happening in the

Table 1: Comparison between cross-matched compatible and incompatible transfusions at one hour and 24 hours post-transfusion.

Transfusion	Platelet cross-matching, n (%)		*p*-value
	Compatible transfusions	Incompatible transfusions	
CCI (× 10^3)			
1-hour post-transfusion	n = 47	n = 13	
Good response (> 5)	30 (63.8)	3 (23.1)	0.009*
Poor response (< 5)	17 (36.2)	10 (76.9)	
24-hour post-transfusion	n = 47	n = 13	
Good response (> 2.5)	44 (93.6)	3 (23.1)	< 0.001[FE*]
Poor response (< 2.5)	3 (6.4)	10 (76.9)	
CCI (× 10^3)			
1-hour post-transfusion	n = 35	n = 10	
Good response (> 5)	22 (62.9)	2 (20.0)	0.029[FE*]
Poor response (< 5)	13 (37.1)	8 (80.0)	
24-hour post-transfusion	n = 35	n = 10	
Good response (> 2.5)	33 (94.3)	2 (20.0)	< 0.001[FE*]
Poor response (< 2.5)	2 (5.7)	8 (80.0)	
CCI (× 10^3)			
1-hour post-transfusion	n = 12	n = 3	
Good response (> 5)	8 (66.7)	1 (33.3)	0.525[FE]
Poor response (< 5)	4 (33.3)	2 (66.7)	
24-hour post-transfusion	n = 12	n = 3	
Good response (> 2.5)	11 (91.7)	1 (33.3)	0.081[FE]
Poor response (< 2.5)	1 (8.3)	2 (66.7)	

*CCI: corrected count increment; FE: Fisher's exact. *Statistically significant at p ≤ 0.05.*

Table 2: Role of platelet crossmatching as a predictor of platelet refractoriness.

CCI, × 10³	Platelet crossmatching, n (%)		*p*-value	OR (95% CI)
	Compatible transfusions (n = 47)	Incompatible transfusions (n = 13)		
1-hour post-transfusion				
Good response (> 5)	30 (63.8%)	3 (23.1%)	0.015*	1.000
Poor response (< 5)	17 (36.2%)	10 (76.9%)		5.882 (1.421–24.355)
24-hour post-transfusion				
Good response (> 2.5)	44 (93.6%)	3 (23.1%)	< 0.001*	1.000
Poor response (< 2.5)	3 (6.4%)	10 (76.9%)		48.889 (8.569–278.920)

*CCI: corrected count increment; OR: odds ratio. *Statistically significant at p ≤ 0.05.*

non-risk group. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for agreement was used. The significance of the obtained results was judged at the 5% level.

RESULTS

Sixty percent (24/40) of refractory patients were males, and 40.0% (16/40) were females. Their age ranged from 6–73 years, with a median age of 34.0 years. Seventy percent of the studied patients had aplastic anemia, 20.0% had acute myeloid leukemia, and 10.0% had acute lymphoblastic leukemia.

There were significant differences between patients who received cross-matched compatible and those who received cross-matched incompatible platelets in one hour and 24 hours post-transfusion platelet counts, post-transfusion PI, CCI, and PPR ($p < 0.05$ for all) [Figures 1 and 2 and supplementary Table 1].

Table 1 shows platelet transfusion response after crossmatching. Compatible transfusions showed a better response than incompatible transfusions at both one hour and 24 hours for all studied patients (total of adults and pediatrics). Pediatric results are not significant either at one hour or 24 hours ($p = 0.525$, $p = 0.081$, respectively).

Also, patients who received cross-match incompatible platelets showed higher risk to develop poor response either at one hour (OR = 5.882, 95% CI: 1.421–24.355) or 24-hour post-transfusion (OR = 48.889, CI: 8.569–278.920) as shown in Table 2.

Moreover, patients with HLA alloimmunization showed higher risk to develop poor response either at one hour (OR = 7.442, 95% CI: 2.356–23.376) or 24 hours post-transfusion (OR = 5.882, CI: 5.882–24.355) [Table 3].

Regarding platelet cross-matching, adequate CCI for compatible units was higher than incompatible units for both RDP and single donor platelet at one hour or 24 hours [Table 4]. Characteristics of transfusion events are shown in supplementary Table 2.

DISCUSSION

Platelet transfusion therapy is lifesaving for patients with hematological disorders, but platelet

Table 3: Human leukocyte antigen (HLA) alloimmunization as predictor of platelet refractoriness.

CCI× 10³	HLA alloimnunization, n (%)		*p*-value	OR (95% CI)
	Present (n = 27)	Absent (n = 33)		
1-hour post-transfusion				
Good response (> 5)	8 (29.6)	25 (75.8)	0.001*	1.000
Poor response (< 5)	19 (70.4)	8 (24.2)		7.422 (2.356–23.376)
24-hour post-transfusion				
Good response (> 2.5)	17 (63.0)	30 (90.9)	0.015*	1.000
Poor response (< 2.5)	10 (37.0)	3 (9.1)		5.882 (5.882–24.355)

*CCI: corrected count increment; OR: odds ratio. *Statistically significant at p ≤ 0.05.*

Table 4: Crossmatching as a predictor to response to platelet transfusion regarding the type of platelet donation at one hour and 24 hours post-transfusion.

Variables	Adequate CCI, n (%)	Inadequate CCI, n (%)	Sen.%	Spe. %	PPV%	NPV%	Acc. %
1-hour post-transfusion CCI, × 10^3							
Cross-match, SDP type							
Compatible (-ve)	15 (93.8)	5 (71.4)	28.6	93.6	66.7	75.0	73.9
Incompatible (+ve)	1 (6.3)	2 (28.6)					
Cross-match, RDP type							
Compatible (-ve)	15 (88.2)	12 (60.0)	40.0	88.2	80.0	55.6	62.2
Incompatible (+ve)	2 (11.8)	8 (40.0)					
24-hour post-transfusion CCI, × 10^3							
Cross-match, SDP type							
Compatible (-ve)	19 (95.0)	1 (33.3)	66.7	95.0	66.7	95.0	91.3
Incompatible (+ve)	1 (5.0)	2 (66.7)					
Cross-match, RDP type							
Compatible (-ve)	25 (92.6)	2 (20.0)	80.0	92.6	80.0	92.6	89.2
Incompatible (+ve)	2 (7.4)	8 (80.0)					

CCI: corrected count increment; SDP: single donor platelet; RDP: random donor platelet; Sen.: sensitivity; Spe.: specificity; PPV: positive predictive value; NPV: negative predictive value; Acc.: accuracy.

refractoriness always poses a challenge due to alloimmunization to HLA and HPAs. A commonly used alternative to HLA-matched platelets is the transfusion of cross-match compatible platelets.[23,28] There are surprisingly few reports describing the benefit obtained from using SPRCA assays to identify cross-matched compatible platelets.[1,13,22,29]

However, there is a paucity of Egyptian literature on platelet crossmatching and platelet refractoriness with RDP transfusion for patients with hematological disorders.

Our study revealed that mean post-transfusion count and CCI observed with the compatible platelet products were significantly higher than those observed in the same patients given randomly selected platelets before crossmatching assay. Additionally, patients who received compatible platelets showed better post-transfusion platelet count and CCI than incompatible transfusions at one and 24 hours.

The mean CCI of 10.96 × 10^3 achieved at 1-hour with compatible platelets in our study corresponds to a mean post-transfusion platelet count of 35.7 × 10^9/L, which is sufficient to avoid spontaneous bleeding. This CCI response to cross-matched units was significantly higher than that to comparable random platelet units for these patients, demonstrating benefits from crossmatch compatibility. The response to compatible platelets seen in our study is also consistent with that in prior studies that demonstrated a significant improvement in CCI using the SPRCA method to crossmatch platelets.[22,29–33]

Sayed et al,[33] assessed the predictive value of a flow cytometric platelet crossmatching in 39 patients with acute leukemia (26 adults and 13 children). The transfusion response was better in children than in adults ($p = 0.041$). This is in contrast to our findings, which showed a better response in adults than children at both one hour and 24 hours post-transfusion ($p = 0.029$ and $p < 0.001$, respectively). Pediatric results were not significant either at one hour or 24 hours ($p = 0.525$ and $p = 0.081$, respectively). This may be attributed to differences in method sensitivity or the small number of pediatric patients in our study and needs to be studied in a larger group.

Platelet transfusion response was evaluated using the CCI, which was calculated at one hour and 24 hours post-transfusion. The cut-off values used were 5 × 10^3/μL at one hour and 2.5 × 10^3/μL at 24 hours in accordance with other studies.[23,31,33,34] However, many studies used 7500/μL at one hour and 5000/μL at 24 hours as cut-offs.[35–39] The lower cut-off values were used in this study due to endemic bilharzia and hepatitis C virus infection in the Egyptian people.

Platelet crossmatching was found to be a good predictor of transfusion response. A good response was reported in 63.8% of compatible transfusions, which was significantly higher than incompatible

platelets (23.1%) at one hour or 24 hours ($p = 0.015$ and $p < 0.001$, respectively).

Our results were consistent with Rebulla et al,[22] who used SPRCA automated technique and reported good response in 68% of evaluable transfusions. Sayed et al,[33] reported a good response in 57.7% of compatible transfusion events, which may be due to the use of flow cytometric platelet crossmatching, a more sensitive method for crossmatching.

Anti-HLA antibodies were present in 45.0% of our patients. Kiefel et al,[40] analyzed the sera of all patients using two techniques, monoclonal antibody immobilization of platelet antigens and complement-dependent lymphocytotoxicity (CDC), and observed anti-HLA antibodies in 42.9% of hemato-oncology patients. Moreover, Laundy et al,[41] reported that 45%–70% of chronically transfused patients developed antibodies to HLA class I antigens using flow cytometry and CDC assay.

A multi-centric trial to reduce alloimmunization to platelets study found that the incidence of HLA alloimmunization was 3%–4% and 13%–14% in chronic recipients of leukoreduced and non-leukoreduced platelets, respectively.[34,42] The high percentage of alloimmunization in our studied patients could be explained by the frequent use of RDP concentrates in our institution.

In our study, 11 females had a history of conception among the 16 females under the study. In addition, anti-HLA antibodies were present in seven females with six of those females having multiple pregnancies.

In agreement with previous studies, we found that platelet cross-matching was the best predictor for transfusion response, followed by HLA alloimmunization using multivariate analysis.[31,33]

Finally, platelet crossmatching using SPRCA assay showed higher sensitivity with RDP concentrates than SDP concentrates. Regarding RDP type of platelet transfusions, the assay showed 80.0% sensitivity, 92.6% specificity, 80.0% PPV, and 92.6% NPV at 24 hours post-transfusion. While for SDP type, crossmatching assay showed 66.7% sensitivity, 95.0% specificity, 66.7% PPV, and 95.0% NPV.

This was similar to the study conducted by Elhence et al,[39] on 31 refractory patients using the modified antigen capture enzyme technique for platelet crossmatching. Their study showed high clinical sensitivity of 88% and NPV of 93.2%. The clinical sensitivity of 80% and NPV of 92.6% for RDP concentrates in the current study suggest that the test may be a valuable tool for better selection of RDP units, as the high NPV demonstrates a greater chance of an adequate response with cross-matched compatible platelets, and also to improve the outcome of response in refractory patients.

We recommend that for patients who need frequent platelet support, if SDP transfusions are not available, it is better to provide the patients with compatible units of RDP concentrates after cross-matching to reduce the risk of alloimmunization and improve the outcome of the response in refractory patients.

CONCLUSION

Platelet crossmatching using a commercially available SPRCA technique and HLA screening are effective, useful, and are rapid tools for better management of patients' refractory to platelet transfusions.

Disclosure

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Supplementary tables

Table 1: Comparison between cross-matched compatible and incompatible transfusions according to laboratory data of all transfusion events.

Transfusion events	Platelet cross matching		U	*p*-value
	Compatible transfusions (n = 47)	Incompatible transfusions (n = 13)		
Platelet count, 10^9/L				
Pre-transfusion	14.8 ± 8.7	14.3 ± 9.7	283.00	0.686
1-hr post-transfusion	35.7 ± 18.0	22.9 ± 12.0	174.50*	0.019*
24-hr post-transfusion	28.7 ± 14.	18.8 ± 11.2	174.50*	0.019*
Platelet increment				
1-hr post-transfusion	20. ± 16.0	8.6 ± 7.7	124.50*	0.001*
24-hr post-transfusion	14. ± 14.8	4.5 ± 4.7	98.0*	< 0.001*
CCI, 10^3/μL				
1-hr post-transfusion	10.9 ± 7.9	4.5 ± 3.8	116.00*	0.001*
24-hr post-transfusion	8.0 ± 14.9	2. ± 1.4	55.00*	< 0.001*
Percentage platelet recovery				
1-hr post-transfusion	30.7 ± 23.5	13.5 ± 11.3	132.50*	0.002*
24-hr post-transfusion	22.8 ± 44.3	6.1 ± 4.6	69.50*	< 0.001*

*U: Mann Whitney test; CCI: corrected count increment. *Statistically significant at p ≤ 0.05.*

Table 2: Comparison between cross-matched compatible and incompatible transfusions according to characteristics of transfusion events.

Characteristics	Total (n = 60)	Platelet cross-match	
		Compatible transfusions (n = 47)	Incompatible transfusions (n = 13)
Type of unit, n(%)			
SDP	23 (38.3)	20 (42.6)	3 (23.1)
RDP	37 (61.7)	27 (57.4)	10 (76.9)
Platelet dose transfused, × 10^{11}			
Mean ± SD	3.3 ± 1.7	3.3 ± 1.7	3.4 ± 1.6
Median (min–max)	3 (1.5–10.0)	3 (1.5–10.0)	3 (1.5–6.0)
No of platelet units			
Mean ± SD	6.6 ± 3.3	6.5 ± 3.4	6.8 ± 3.2
Median (min–max)	6 (3–20)	6 (3–20)	6 (3–12)
Storage time units (days), n(%)			
1	30 (50.0)	24 (51.1)	6 (46.2)
2	23 (38.3)	17 (36.2)	6 (46.2)
3	7 (11.7)	6 (12.8)	1 (7.7)
Blood group, n(%)			
O	16 (26.7)	14 (29.8)	2 (15.4)
A	19 (31.7)	13 (27.7)	6 (46.2)
B	16 (26.7)	12 (25.5)	4 (30.8)
AB	9 (15.0)	8 (17.0)	1 (7.7)

SDP: single donor platelet; RDP: random donor platelet.