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

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Received: 28 November 2021
Accepted: 27 February 28, 2022

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DOI 10.5001/omj.2022.81

Abstract

Background: Platelet refractoriness complicates the platelet transfusion which is an essential part in management of thrombocytopenia in patients with hematological disorders. It is associated with adverse clinical outcomes and increased health care costs. **Objective:** A prospective study to determine the effectiveness of cross matched-compatible platelets in group of patients refractory to platelets from random donors and to evaluate HLA- mediated refractoriness. **Methods:** 40 patients with different hematological disorders requiring platelet transfusions who were refractory to random platelets were included in this study. They received 60 ABO-compatible platelet transfusions, either leuco-reduced or random donor platelets stored not more than 72 hours. A solid-phase red cell adherence technique (SPRCA) was used for platelet cross-matching. The corrected count increment (CCI) was used to monitor the effectiveness of each platelet transfusion with a cut –off value of $5x10^3$ /µL at 1 hour and $2.5x10^3$ /µL at 24 hours. Anti HLA antibodies were assessed using ELISA technique. **Results:** Out of 60 crossmatches, 78.3% (47/60) were compatible and 21.7% (13/60) were incompatible. Among 47 compatible results, 63.8% (30/47) showed adequate CCI and 36.2% (17/47) showed inadequate CCI at 1h post transfusion. Among the incompatible results, 23.1%

(3/13) had adequate CCI and 76.9% (10/13) had inadequate CCI. Significant improvements were found in the mean CCI when comparing cross matched-compatible platelets and incompatible platelets either at 1hour or 24 hours ($p=0.009$ and $p<0.001$ respectively).From the forty studied patients, HLA alloimmunization was present in 18 patients (45%) and absent in the remaining 22 patients (55%). In absence of HLA alloimmunization, patients showed significantly better responses at 1h and 24h ($p=0.001$ and $p=0.015$) respectively. There was better sensitivity of platelet cross matching with random donor platelet concentrates than single donor platelet concentrates .**Conclusion:** Platelet cross matching using SPRCA technique and HLA screening are effective and rapid tools for better management of patients refractory to platelet transfusions.
Keywords: Platelets, refractoriness, SPRCA, HLA.

Introduction

Platelet transfusion is an essential part of the treatment in 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 allogenic platelets.[3, 4] It is associated with a number of adverse outcomes including longer hospital stays[5], increased risk of bleeding [6, 7], and decreased survival[7] as well as higher inpatient hospital costs.[3, 5] The current incidence of platelet refractoriness ranges from 5% to 14% in hematological patients.[8-11] The problem is greater in patients with multiple transfusions, as (30–70%) of them become refractory to random donor platelet transfusions.[12-14]

Platelet transfusion refractoriness causes are multifactorial, with 80% being attributed to non-immunological causes, and 20% to immunological causes.[15-17] The latter is often attributed to the presence of antibodies to human leukocyte antigens (HLA) and/or human platelet antigens (HPA). A number of 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, 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 in identifying HLA-matched donors for some patients.[20] In addition, the techniques of HLA typing 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 cross-matching assays are relatively of low-cost and rapid alternative to the HLA-matched approach for the management of platelet refractoriness.[22-24] Cross-matching 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 cross-matching at many institutions, it is still not implemented as a tool for management of refractory patients in Egyptian institutions. Here, we present transfusion-related outcomes observed at Alexandria main university hospitals, to determine whether platelet cross-matching can effectively identify platelet units that will improve the post-transfusion platelet counts.

Aim of the work

The study was done to evaluate the role of platelet cross matching assay in the management of patients with hematological disorders refractory to platelet transfusion, and the effect of HLA- mediated platelet refractoriness**.**

Materials and Methods

This prospective study was conducted on 40 patients with different hematological disorders (24 males and 16 females), from which 28 were adults and 12 were pediatrics. Their age ranged from (6 to 73 years) with a median age of 34.0 years and they were

identified as refractory after receiving random-donor platelet transfusions. All of them presented to the hematology unit of Alexandria main university hospitals between May 2020 and March 2021. They received a total of 60 ABO-compatible platelet transfusions (ranged from 1 to 4 transfusions per patient). Platelets were stored at 20-24 °C with continuous agitation for a maximum of 3 days. Patients with evidence of non-immunological causes of platelet refractoriness were excluded. This study received approval of the Medical Ethics Committee of the Faculty of Medicine, Alexandria University, Egypt. A written informed consent was obtained from each patient (guardian) participating in the study. Platelet cross-matching was performed for all patients who were selected to be refractory to random platelet transfusion based on their 24-hour post-transfusion corrected count increment (CCI) of less than 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)] x [body surface area (m2)]/ [platelet dose transfused (10^{11})].

After performing platelet cross matching, complete blood picture was done at 1h and at 24 hours after platelet transfusion. CCI was calculated. Other formulae to calculate the increment such as 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

Platelet cross-match assays were performed using solid-phase red-cell adherence (SPRCA) technique with Capture-P Ready Screening (Immucor, Norcross, GA, USA) on the automated apparatus (NEO; Immucor 4th generation) for the detection of IgG

antibodies to platelet specific antigens. Briefly, 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 are 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. 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 positive test shows adherence of indicator red cells to the part or the entire reaction surface and considered incompatible.

Detection of HLA class I antibodies

Patients serum samples were collected at -80c for HLA antibody detection using ELISA technique (Glory ScienceCo., Ltd, Del Rio, TX, USA). ELISA was performed according to the manufacturer's instruction using Biorad PW 40 microplate washer and PR 4100 microplate reader.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to investigate the association between the categorical variables. Alternatively, Fisher's Exact correction test was applied when the expected cell counts were less than 5. Odd ratio was used to calculate the ratio of the odds and 95% Confidence Interval of an event occurring in one risk group to the odds of it occurring in the non-risk group. And sensitivity, specificity, PPV, NPV and accuracy for agreement was used. Significance of the obtained results was judged at the 5% level.

Results

Patients characteristics and clinical data 60% (24/40) of refractory patients were males and 40% (16/40) were females. Their age ranged from (6 to 73 years) with a median age of (34.0 years). 70% of the studied patients had aplastic anemia, 20% had AML and 10% had ALL.

Platelet transfusion outcomes

There were significant differences between patients who received cross matched compatible and those who received cross matched incompatible platelets regarding 1 hour and 24 hours post transfusion platelet count, post transfusion PI, CCI and PPR ($p < 0.05$ for all).(fig 1 and 2).suppl. table 2

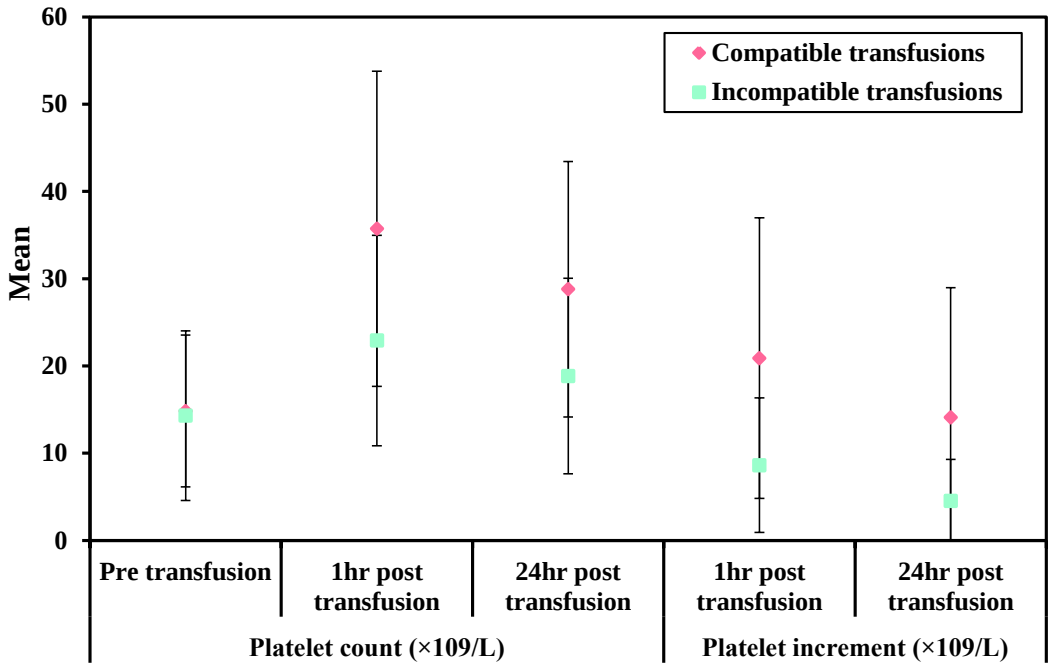

Figure 1: Laboratory data of all transfusion events in patients under study according to platelet count ($\times 10^9$/L) and platelet increment (PI).

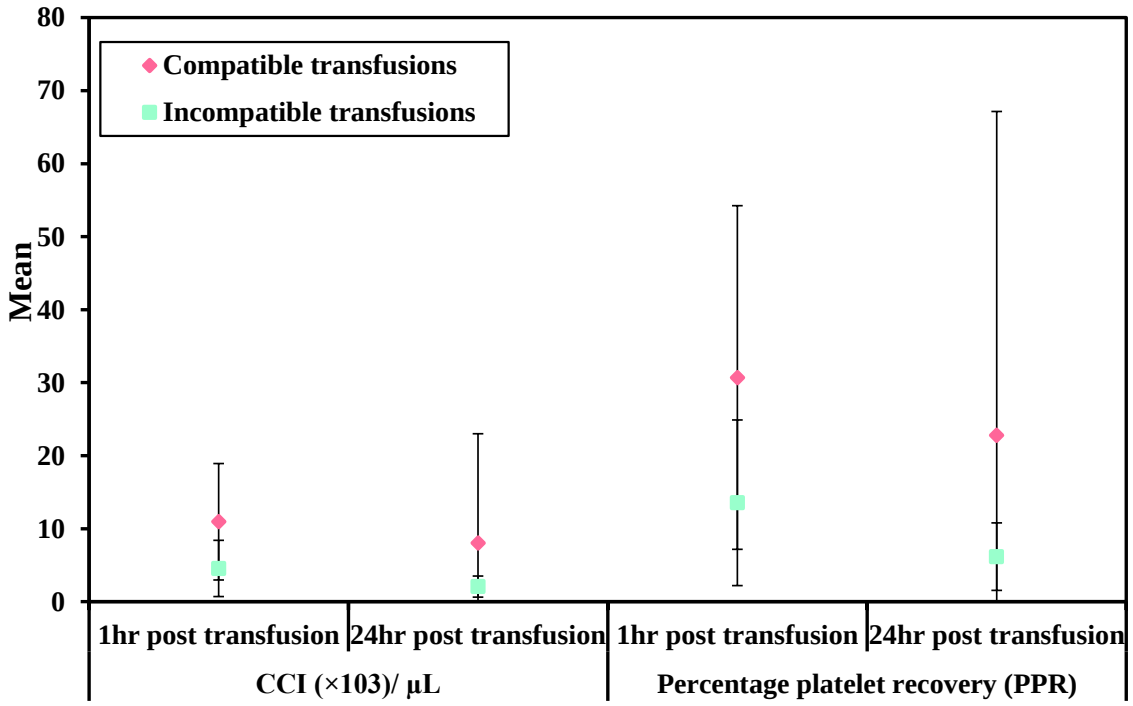

Figure 2: Laboratory data of all transfusion events in patients under study according to CCI ($\times 10^3$/uL) and percentage PLT recovery (PPR).

Table I shows platelet transfusion response after cross-matching. Compatible transfusions showed better response than incompatible transfusions at both 1h and 24h for all studied patients (total of adults and pediatrics).Pediatric results are not significant either at 1h or 24h (p= 0.525, p =0.081) respectively.

Table I: Comparison between cross matched compatible transfusions and cross matched incompatible transfusions at 1h and 24h post transfusion

		Platelet cross matching		
		Compatible transfusions	**Incompatible transfusions**	**p**
CCI ($\times 10^3$)	**1hr 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%)	
	24hr post transfusion	**(n = 47)**	**(n = 13)**	
	Good response(>2.5)	44 (93.6%)	3 (23.1%)	

	Poor response (<2.5)	3 (6.4%)	10 (76.9%)	^{FE}p <0.001*
CCI ($\times 10^3$)	**1hr post transfusion**	**(n = 35)**	**(n = 10)**	
	Good response (>5)	22 (62.9%)	2 (20%)	$^{FE}p=$ 0.029*
	Poor response (<5)	13 (37.1%)	8 (80%)	
	24hr post transfusion	**(n = 35)**	**(n = 10)**	
	Good response(>2.5)	33 (94.3%)	2 (20%)	^{FE}p <0.001*
	Poor response (<2.5)	2 (5.7%)	8 (80%)	
CCI ($\times 10^3$)	**1hr post transfusion**	**(n = 12)**	**(n = 3)**	
	Good response (>5)	8 (66.7%)	1 (33.3%)	$^{FE}p=$ 0.525
	Poor response (<5)	4 (33.3%)	2 (66.7%)	
	24hr post transfusion	**(n = 12)**	**(n = 3)**	
	Good response(>2.5)	11 (91.7%)	1 (33.3%)	$^{FE}p=$ 0.081
	Poor response (<2.5)	1 (8.3%)	2 (66.7%)	

FE**: Fisher Exact**
*: Statistically significant at $p \leq 0.05$

Also, patients who received cross match incompatible platelets showed higher risk to develop poor response either at 1h (OR=5.882, 95% CI=1.421-24.355) or 24h post transfusion (OR=48.889, CI=8.569 - 278.92) as shown in table II.

Table II: Role of platelet cross matching as predictor of platelet refractoriness

CCI ($\times 10^3$)	**Platelet cross matching**		**p**	**OR (95%CI)**
	Compatible transfusions (n = 47)	**Incompatible transfusions (n = 13)**		
1hr 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)
24hr 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 – 278.92)

OR: Odds ratio
CI: Confidence interval
*: Statistically significant at $p \leq 0.05$

Moreover, patients with HLA alloimmunization showed higher risk to develop poor response either at 1h (OR=5.442, 95% CI=2.356-23.376) or 24h post transfusion (OR=5.882, CI=5.882 - 24.355). Table (III)

Table III: HLA alloimmunization as predictor of platelet refractoriness

CCI ($\times 10^3$)	HLA Alloimnunization		p	OR (95%CI)
	Present (n = 27)	Absent (n = 33)		
1hr 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)
24hr post transfusion				
Good response (>2.5)	17 (63.0%)	30 (90.9%)	0.015*	1.000
Poor response (<2.5)	10 (37%)	3 (9.1%)		5.882 (5.882 – 24.355)

OR: Odds ratio
CI: Confidence interval
p: p value for comparing between **Present** and **Absent**
*: Statistically significant at $p \leq 0.05$

Platelet cross matching-SPRCA and outcome of each type of platelet transfusions

Regarding platelet cross matching, adequate CCI for compatible units was higher than incompatible units for both RDP and SDP either at 1h or 24h. Table IV.

Table IV: Cross matching as predictor to response to PLT transfusion regarding the type of PLT donation at 1h and 24hr post transfusion

		Adequate CCI	Inadequate CCI	Sen. %	Spe. %	PPV %	NPV %	Acc. %
1hr post transfusion CCI ($\times 10^3$)								
SDP type	**Cross match**							
	Compatible (-ve)	15 (93.8%)	5 (71.4%)	28.57	93.75	66.67	75.0	73.91
	Incompatible (+ve)	1 (6.3%)	2 (28.6%)					
RDP type	**Cross match**							
	Compatible (-ve)	15 (88.2%)	12 (60%)	40.0	88.24	80.0	55.56	62.16
	Incompatible (+ve)	2 (11.8%)	8 (40%)					

		24hr post transfusion CCI (×10^3)						
SDP type	**Cross match**							
	Compatible (-ve)	19 (95%)	1 (33.3%)	66.67	95.0	66.67	95.0	91.30
	Incompatible (+ve)	1 (5%)	2 (66.7%)					
RDP type	**Cross match**							
	Compatible (-ve)	25 (92.6%)	2 (20%)	80.0	92.59	80.0	92.59	89.19
	Incompatible (+ve)	2 (7.4%)	8 (80%)					

CCI: Corrected count increment SDP: Single donor platelet RDP: Random donor platelet

Sen.: Sensitivity Spe.: Specificity Acc.: Accuracy
PPV: Positive predictive value
NPV: Negative predictive value

Discussion

Platelet transfusion therapy is life-saving for patients with hematological disorders, but platelet refractoriness always poses a challenge due to alloimmunization to HLA and human platelet antigens (HPAs).A commonly used alternative to HLA matched platelets is the transfusion of cross-match - compatible platelets.[23, 28] Given the widespread use of cross-matched platelets, there are surprisingly few reports describing the benefit obtained from using a SPRCA assay to identify cross matched-compatible platelets.[1, 13, 22, 29]

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

The present 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 cross matching assay. Additionally, patients who received compatible platelets showed better post transfusion platelet count and CCI than incompatible transfusions at both 1&24 hours.

The mean CCI of 10.96 x 10^3 achieved at 1hour with compatible platelets in our

study corresponds to a mean post transfusion platelet count of 35.72 x 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 cross-match compatibility. The response to compatible platelets seen in our study is also consistent with that in prior studies which demonstrated a significant improvement in CCI by using the SPRCA method to cross-matched platelets.[22, 29-33]

Sayed et al.[33] assessed the predictive value of a flow cytometric platelet cross matching in 39 patients with acute leukemia (26 adults and 13 children), transfusion response was better in children than in adults (p=0.041) and this in contrast to our findings, which showed better response in adults than children at both 1h and 24 h post transfusion (p=0.029 and p<0.001respectively).Pediatric results were not significant either at 1h or 24h (p= 0.525, p =0.081) respectively. This is may be attributed to difference in method sensitivity or the small number of pediatric group of patients in the current study and need to be studied on larger group.

Platelet transfusion response was evaluated using the corrected count increment (CCI) which was calculated at 1-h and 24-h posttransfusion. Cut off values used were $5x10^3$ / µL at lh and $2.5x10^3$ µL at 24 h which are in accordance with other studies such as TRAP study group, Rubella et al, Sayed et al and salama et al. [23, 31, 33, 34] However, many studies used 7500/ µL at lh and 5000 / µL at 24 h as cut off.[35-39] The lower cut off values were used in the present study due to endemic bilharziasis and HCV infection in the Egyptian people.

Platelet cross matching was found to be a good predictor of transfusion response. Transfusion of compatible platelets was more successful in 63.8% of transfusion than incompatible platelets 23.1% at lh and 24h ($p=0.015$, $p <0.001$) respectively.

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

Anti-HLA antibodies were present in 45 % of our studied patients. Kiefel et al.[40], analyzed the sera of all patients by two techniques, MAIPA and complement dependent lymphocytotoxicity (CDC), 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 flowcytometry and CDC assay.

On other hand, multi centric TRAP study found that the incidence of HLA alloimmunization was 3-4% and 13-14% in chronic recipients of leucoreduced and non-leucoreduced 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 the present study, 11 females had previous history of conception from the 16 females under the study. Anti HLA antibodies were present in 7 females, from them 6 females had multiple pregnancies.

In agreement with Salama et al and Sayed *et al*, we found that platelet cross-matching was the best predictor for transfusion response, followed by HLA-alloimmunization by using multivariate analysis.[31, 33]

Finally, platelet cross matching using SPRCA assay showed higher sensitivity with RDP concentrates than SDP concentrates. Regarding RDP type of platelet transfusions, the assay showed 80% sensitivity, 92.59% specificity, 80% PPV and 92.59% NPV at 24h post transfusion. While for SDP type, cross matching assay showed 66.67% sensitivity, 95% specificity, 66.67% PPV and 95% NPV.

This was similar to the study conducted by Elhence et al,[39] on 31 refractory patients using MACE technique for platelet cross-matching. Their study showed high clinical sensitivity of 88%, and NPV of 93.2% respectively. 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 negative predictive value demonstrates the greater chance of an adequate response with cross-matched-compatible platelets, and also to improve the outcome of response in refractory patients.

Recommendation 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 crossmatching to reduce the risk of alloimmunization and to improve the outcome of response in refractory patients.

Conclusion Platelet cross matching using a commercially available solid phase red cell adherence technique and HLA screening are effective, useful and rapid tools for better management of patients refractory to platelet transfusions.

Acknowledgements:

The authors thank all patients who have been involved in this study, hematology and blood bank team members and colleagues who assisted this research.

Funding: This research did not receive any funding.

Conflict of interest: The authors declare that they have no conflict of interest.

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