Brunei International Medical Journal

OFFICIAL PUBLICATION OF THE MINISTRY OF HEALTH, BRUNEI DARUSSALAM

Volume 15 29 December 2019 (3 Jamadilawal 1441H)

CLINICAL AND TRANSFUSION RELATED FACTORS INFLUENCING POST-TRANSFUSION PLATELET RESPONSE AMONG THROMBO-CYTOPENIC PATIENTS IN MALAYSIA.

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ABSTRACT

Introduction: Most clinicians are inclined to request platelet transfusion for thrombocytopenic patients with bleeding or at high risk of bleeding. Many factors that may influence post-transfusion platelet increments have been proposed, but the specific prediction of increment for each patient is quite difficult. Hence, this study was carried out to determine the factors that may influence post-transfusion platelet increment in thrombocytopenic patients. **Methods:** This is a retrospective review of 97 thrombocytopenic patients who received a total number of 351 platelet transfusions over a period of two years. The clinical and transfusion related factors were evaluated based on post-transfusion platelet response measured by corrected count increment (CCI) calculated at one and 24 hours post-transfusion. Simple logistic regression and multiple logistic regression tests were used for statistical analyses and p values of <0.05 were considered significant. **Results:** The mean age of patients were 42.6±20.8 years and the majority were Malays (92.8%). Patients diagnosed with malignancies constitutes 63.9% of the total subjects and 66.1% had good CCI with mean CCI of $15.8x10^9$/L. The predictive factors of poor CCI were disseminated intravascular coagulopathy (DIC) (adjusted OR=5.31; CI=3.06, 9.24; p<0.001) and platelet shelf age of ≥4 days (adjusted OR=2.2; CI=1.29, 3.75; p=0.004). **Conclusion:** DIC and older platelet shelf age gave inferior post-transfusion platelet response. Thus, fresh platelet concentrates (≤3 days) are highly recommended in thrombocytopenic patients as they showed better post-transfusion platelet response.

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Brunei Int Med J. *2019;15:73-145-152*

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

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Official Publication of the Ministry of Health, Brunei Darussalam

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Keywords: **ABO blood-group system, Disseminated intravascular coagulation, Platelet, Platelet transfusion, Thrombocytopenia**.

INTRODUCTION

Thrombocytopenic patients are at risk for bleeding as platelets function has been well established to provide an endothelial supportive function to prevent or stop bleeding by plugging gaps in the injured endothelium of blood vessels.[1] Most clinicians are very keen at managing most thrombocytopenic patients with bleeding or those who at high risk of bleeding, with platelet transfusion since platelet transfusion may reduce the incidence of

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fatal haemorrhages.[2] Most institutions set a standard for platelet transfusion as prophylactic at the threshold platelet level of less than 20 x 10^9/L and to treat active bleeding independent of platelet levels based on specific patient needs.[3]

A platelet transfusion is considered successful when the post-transfusion platelet response (p-TPR) shows corrected count increment (CCI) of >7.5x10^9/L at 1 hour and >4.5x10^9/L at 20-24 hours post-transfusion, or percentage platelet recovery (PPR) of >30% at 1 hour and >20% at 20-24 hours post-transfusion.[4] However, the dilemma becomes evident when the desired p-TPR fails to be reached even after standard calculations for such transfusions have been applied. Many factors have been suggested to influence the CCI of platelet transfusion. It has been found that splenomegaly, use of antiplatelet and transfusions of non-identical ABO platelet gave poor p-TPR.[2,5] Even though many other factors had been proposed, prediction of p-TPR can be difficult in those patients with multiple factors that bear their own weightages to influence the increment.

Furthermore, such data are not easily available in our population as previous studies on p-TPR and CCI have never been carried out before. Although many studies had proposed few factors that influenced p-TPR, those factors might vary depending on different population and their local platelet transfusion guideline practices. This study was carried out to determine the factors that may lead to poor p-TPR in thrombocytopenic patients in our centre.

MATERIALS AND METHODS

Study background

This is a retrospective cohort study involving 97 thrombocytopenic patients with various clinical diagnoses (Table I) treated at our centre. Over the course of two years from centre. Over the course of two years from January 2014 until December 2015, the patients received a total of 351 courses of platelet concentrate (PC) transfusions. Non-probability sampling was used and the study subjects were selected based on the availability of records from the computerized transfusion record system (MyTransfusi) and patients' medical records.

For the retrospective analysis, the clinical factors taken into consideration included patient's demographic data (sex, age, weight, race, and height) and presence of certain conditions including malignancy, splenomegaly, fever, disseminated intravascular coagulopathy (DIC) and bleeding. Transfusion factors were also considered and these including type of PC (random or apheresis), shelf age of the issued PC and ABO compatibility.

Platelet concentrates

Patients were transfused with a dose of PC either from the platelet rich plasma preparation of random donors (random platelet, RP) or single apheresis donor (apheresis platelet, AP). The selection of a PC supply was based on ABO compatibility and availability of products during the PC transfusion request. PC were stored in blood bags (Terumo Penpol, Belgium) at room temperature (22-24^{o}C) on a flatbed shaker for 1-5 days. The number of transfused platelets was measured at the time of transfusion. We further classified PC into two groups, either fresh or old. Based on previous studies, we studied few cut-off values for the shelf age of PC. For this study, the shelf age of 1-3 days and 4-5 days were considered as fresh and old PC respectively.[6-8]

Post-transfusion platelet response (p-TPR) measurement

The p-TPR was measured by CCI (x10^9/L). The CCI was calculated as the difference between basal and post-transfusion platelet count at 1 and 24 hour (platelet increment, PI), multiplied by the body surface area (BSA) in square metres (m^2) and divided by the

dose of platelet transfused ($x10^{11}$) (PD).[4] The calculation of the BSA utilized the Mosteller's formula.[2]

$$CCI = PI \times BSA \times PD^{-1}$$

Good p-TPR or successful transfusion was defined as CCI >$7.5x10^9$/L at 1 hour or >$4.5x10^9$/L at 20 to 24 hours.[4] Thus, poor response was defined as CCI ≤7.5 $x10^9$/L at 1 hour or ≤4.5 $x10^9$/L at 20 to 24 hours.

The platelet count was measured using the Haematology analyser, Sysmex XE-5000 (Sysmex Corporation, Kobe Japan). Pre and post-transfusion platelet counts in 1 hour or 20 to 24 hours post-transfusion were obtained for the measurement of PI.

Statistical analysis

The data was analysed using Statistical Package for the Social Software (SPSS) version 22. The descriptive results were expressed as frequency and percentage or mean and standard deviation (SD) and range. Simple logistic regression (SLR) and multiple logistic regression (MLR) analysis were used to determine the potential factors that might influence p-TPR. Any variables with *p*-value <0.25 by SLR were considered for further MLR analysis and *p*-value less than 0.05 was considered statistically significant.

Ethical consideration

Ethical approval was obtained from the Universiti Sains Malaysia Human Research and Ethics Committee (HREC) before this study was commenced with the reference number of USM/JEPeM/15010003.

RESULTS

The mean age of patients were 42.6±20.8 years and majority were Malays (92.8%) with equal gender distribution. Patients diagnosed with malignancies constituted 63.9% of the total subjects included in the study of Which majority were haematological malignancies (Table I). The mean pre-transfusion platelet count was $30.5x10^9$/L. About 2/3rd of the PC transfusion events had good CCI (66.1%) with a mean CCI of $15.8x10^9$/L (Table I). The transfused PC characteristics included majority of patients received transfusion of ABO-identical PC (80.1%), PC aged 1-3 days (62.4%) and the use of random PC (72.9%) (Table II).

Factors influencing poor p-TPR

Based on univariate analysis, p-TPR showed significant associations with DIC (crude OR=4.22, p<0.001), bleeding (crude OR=1.91, p=0.009) and shelf age of platelets (crude OR=0.83, p=0.009). The other potential clinical and transfusion factors had no significant association with poor CCI.

Based on multivariate analysis, only DIC (adjusted OR=5.31, p<0.001) and shelf age of day 4-5 of PC (adjusted OR=2.17, p=0.002) were found to be the independent predictors for poor p-TPR. Patients with DIC were 5.31 times more likely to have poor p-TPR with low CCI than those without DIC. Similarly, patient who were transfused with older shelf age PC of ≥4 days were 2.17 times more likely to have poor p-TPR with low CCI compared with those receiving fresh PC of ≤3days. (Table III).

DISCUSSION

Majority of thrombocytopenic patients in this study showed good CCI with a mean CCI of $15.8x10^9$/L. This result showed good correlation with most other literatures whereby reported mean CCI were within range of 10.0 to 20.0 $x10^9$/L.[2,9] Thus, it is generally accepted worldwide that most patient have good CCI after platelet transfusion. However, thorough investigations are needed to evaluate this group of patients with poor increment for proper platelet transfusion plan to prevent any severe morbidity or mortality related to

Table I: Patients characteristic (n=97).

Variable	Frequency (%)	Mean (SD)	Range
Age (years)*		42.6 (20.8)	2-82
Height (m)*		1.5 (0.2)	0.75-1.75
Weight (kg)*		55.1 (18.1)	8-96.4
Gender			
Male	49 (50.5)		
Female	48 (49.5)		
Race			
Malay	90 (92.8)		
Non-Malay	7 (7.2)		
Blood group			
O	39 (40.2)		
B	27 (27.8)		
A	26 (26.8)		
AB	5 (5.2)		
Diagnosis			
Haematological malignancy	38 (39.2)		
AML	6		
ALL	9		
CML	2		
MM	7		
Lymphoma	14		
Non-haematological malignancy	24 (24.7)		
Breast Ca	5		
GIT Ca	5		
GUT Ca	7		
Brain Ca	3		
Others malignancy	4		
BM failure	6 (6.2)		
ITP	6 (6.2)		
Infection	10 (10.3)		
Massive bleeding	5 (5.2)		
Others	8 (8.2)		
Splenomegaly			
Yes	13 (13.4)		
No	84 (86.6)		
Pre-transfusion platelet count (x10^9/L)[a]*		30.5 (32.3)	
Good CCI / poor CCI		27.1 (26.7) / 37.2 (40.3)	
Post-transfusion platelet count (x10^9/L)[a]*		47.6 (39.4)	
Good CCI/poor CCI		54.7 (41.7) / 33.8 (30.5)	
CCI (x10^9/L)[a]*		15.8 (24.5)	0-28.2
Good	232 (66.1)		
Poor	119 (33.9)		

* mean (SD); [a] based on 351 PC transfusion event
m=meters; kg=kilogram; BSA=body surface area, m^2=meter square; AML=acute myeloid leukaemia; ALL=acute lympho-blastic leukaemia; CML=chronic myeloid leukaemia; MM=multiple myeloma; GIT=gastrointestinal teract; GUT=genitor-urinary tract; Ca=cancer BM=bone marrow; ITP=idiopathic thrombocytopenic purpura; CCI=corrected count increment

Table II: The characteristics of transfused platelet concentrate (n=351).

Variable	Frequency (%)
ABO identical	
Yes	281 (80.1)
No	70 (19.9)
Age of PC	
D1-3 / D4-5	219 (62.4)/132 (37.6)
D1-2 / D3-5	134 (38.2)/ 217(61.8)
Type of PC	
Random platelet	256 (72.9)
Apheresis platelet	95 (27.1)

PC=platelet concentrate, D=day

thrombocytopenia in future. Many studies had been performed worldwide to determine the clinical and laboratory factors which may contribute to poor p-TPR and some studies reported differences in term of the significant factors encountered.

Our study showed that in our population, DIC was the most significant predictor of poor CCI with an adjusted OR ranging from 3.06 to as high as 9.24. Based on our data, clinicians should choose a higher dose of platelet transfusion in patients with DIC. Most previous studies have reported significant association with poor p-TPR with low CCI and this was suggested to be related to platelet refractoriness.[10-12] It has been known that DIC is a major contributor in increasing platelet consumption and requiring extensive platelet transfusion support.[13] However, two previous studies did not find an association between DIC and poor post-transfusion platelet response.[2,6]

Our study also demonstrated significant association of poor CCI with older shelf

Table III: Factors influencing poor post transfusion platelet response (CCI <7.5x10^9/L at 1 hour or <4.5 x10^9/L at 24 hours) by multivariate analysis.

Variable	Frequency		SLR		MLR	
	Good CCI	Poor CCI	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (years)*,[a]	42.6 (20.7)	42.1 (23.5)	1.00 (0.99,1.01)	*0.698*	-	-
Weight (kg)*,[a]	55.9 (17.8)	45.9 (20.4)	1.00 (0.99,1.01)	*0.930*	-	-
Height (m)*,[a]	1.5 (0.2)	1.5 (0.2)	1.28 (0.36,4.5)	*0.706*	-	-
Gender (male/female)[a]	45/45	4/3	1.20 (0.77,1.88)	*0.414*	-	-
Race (Malay/non-Malay)[a]	85/5	5/2	1.02 (0.8,1.3)	*0.883*	-	-
ABO group (O/non-O)[a]	36/54	3/4	1.01 (0.85,1.21)	*0.908*	-	-
Malignancy (yes/no)[b]	172/60	85/34	0.87 (0.53,1.43)	*0.588*	-	-
DIC (yes/no)[b]	**35/197**	**51/68**	**4.22 (2.53,7.04)**	***<0.001***	**5.31 (3.06,9.24)**	***<0.001***
Fever (yes/no)[b]	105/127	64/55	1.41 (0.90,2.19)	*0.131*	0.96 (0.57,1.63)	*0.889*
Bleeding (yes/no)[b]	**53/179**	**43/76**	**1.91 (1.18,3.10)**	***0.009***	1.5 (0.86,2.63)	*0.156*
Splenomegaly (yes/no)[b]	31/201	23/96	1.55 (0.86,2.81)	*0.145*	1.50 (0.79,2.84)	*0.218*
Type of PC (RP/AP)[b]	169/63	87/32	1.01 (0.62,1.67)	*0.958*	-	-
ABO Identical (yes/no)	186/46	95/24	1.02 (0.59,1.77)	*0.940*	-	-
Age of platelet (D4-5/D1-3)	**76/156**	**56/63**	**1.83 (1.16-2.87)**	***0.009***	**2.17 (1.33,3.56)**	***0.002***
Age of platelet (D3-5/D1-2)	137/95	80/39	1.42 (0.90,2.26)	*0.136*	1.02 (0.53,1.96)	*0.961*

* mean (SD); [a] based on 97 thrombocytopenic patients; [b] based on 351 PC transfusion event
SLR=simple logistic regression, MLR=multiple logistic regression; CCI=corrected count increment; DIC=disseminated intravascular coagulopathy; PC=platelet concentrate; RP=random platelet; AP=apheresis platelet; D=day

age PC of more than three days compared to fresh PC. PC more than three days old were 2.17 times more likely to be associated with poor CCI. Previous study also reported similar finding where they found a significant decline in CCI for platelet stored for more than three days.[7] Storage period of PC contributed to platelet concentrate viability and subsequently influenced p-TPR.[8] In optimal conditions and gentle agitation, at day five of age, the intravascular recovery was approximately 51% and half-life of stored platelets was 3.1 days.[9] Till now there is no definitive classification of the term of fresh PC based on period of storage. Based on our study, we can suggest that three days old PC or less can be considered as fresh platelet, and is mostly suitable for patients who need higher p-TPR. Other studies described PC within 48 hours post collection as the standard fresh PC.[6,8]

It is fairly well established that ABO compatibility can affect the adequacy of platelet transfusions.[14-17] Hence, the British Committee for Standards in Haematology and Blood Transfusion Task Force has recommended that platelet transfusion with identical ABO group is the best choice to achieve a good p-TPR.[4] Surprisingly, our study did not showed significant difference of platelet CCI between ABO identical and ABO incompatible group. Two other previous published studies reported similar findings, lending further support to our study.[18,19] In term of clinical application, the discordance of our result with majority of previous studies was not a major concern, since one of the largest studies had reported that poor p-TPR in major mismatched platelet transfusion did not increase the risk of major bleeding in thrombocytopenic patients.[7] Another prospective study showed some advantage in identical ABO platelet transfusion in term of clinical outcome, in which newly diagnosed hematologic diseases recipients of ABO identical platelet resulted in fewer platelet transfusion in the first 30 days compared to those patients who received ABO mismatched platelets.[5]

Splenomegaly is always associated with poor platelet transfusion increment and most studies showed a significant reduction in p-TPR in patients with any degree of splenomegaly.[2] A previous study showed that up to 85% of transfused platelets are destroyed in the spleens of patients with splenomegaly, as opposed to 61% in normal controls.[20] However, our study did not show splenomegaly as a significant factor influencing p-TPR. This can be explained by the small number of subjects with splenomegaly and the median size of spleen of 4 cm which was considered as mild splenomegaly in this study. Fabris et al also found a similar result whereby splenomegaly did not affect the outcome of platelet transfusion.[21]

In this study, the results showed no significant association of p-TPR with malignancy and this was consistent with other previous studies.[2,22] Other variables such as multiple non-HLA specific platelet transfusion or underlying splenomegaly were reported as a contributor for p-TPI in underlying malignancy patient.[2,22]

Fever was also not identified as a significant factor influencing post-transfusion platelet CCI in this study. Two larger studies supported this finding.[23,24] Nevertheless, there were two small studies which showed poor p-TPR which were associated with underlying fever.[25,26] Studies pertaining to bleeding as a factor that needs to be considered as a contributing factor to p-TPR were not scarce. In this study, univariate analysis showed there was a significant association of bleeding with p-TPR with crude odds of 1.91. However, multivariate analysis revealed that the bleeding variable was not significant. A previous study also revealed that bleeding factor showed no association with platelet transfusion efficacy.[2]

Types of PC were observed to give

some effect on p-TPI. AP was more superior in term of transfusion efficacy compared to RP.[27] However, we found that there was no significant association of platelet CCI with type of PC. This result was concordant with other studies which showed AP was not superior to pooled RP.[19,28,29] This can be explained by the fact that current modern preparation of both types of PC can yield similar or almost similar platelet concentration.[30] Hence, specific selection of the type of platelet concentrate to be given to a patient was not a major issue.[29]

This study has several limitations encountered. First is the used of convenient sampling in view of many incomplete or deficient patients' data in their medical record and/or transfusion information system. Furthermore, there was heterogeneity mainly in the variation of the diseases of the study population and a few of the confounding factors (underlying immune mechanism, severity of bleeding) were not included in the study. Therefore, the findings need to be inferred with caution since they might not be representative beyond the reference population of this study.

CONCLUSIONS

In conclusion, patients with DIC and those who received platelet ≥4 days required more platelet transfusions to achieve the desirable platelet increment compared to those without DIC and those who received ≤3 days old PC respectively. Thus, for those patients who require higher post-transfusion increment such as severe thrombocytopenic patient, fresh PC (≤3 days old) is recommended for transfusion. Common calculation for platelet transfusion in targeting desirable level might not be applicable for patients with these factors and clinical judgement is required in terms of specific indication and frequency of transfusion in achieving certain level of p-TPR.

ACKNOWLEDGEMENT

We would like to acknowledge all staff in Transfusion Medicine Unit, Hospital Universiti Sains Malaysia who were involved directly or indirectly in this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest and financial conflict.

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