Original Article

The Availability of LCT-Crossmatched Platelets for Patients with Platelet Refractoriness

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Abstract:

Background: *Platelet refractoriness is defined as the repeated failure to obtain satisfactory response to platelet transfusion which is the cause of serious clinical complication usually found in multi-transfused patients. There are many causes of platelet refractoriness that can be divided into immune and non-immune. The main immune cause is human leukocyte antigens (HLA) alloimmunization. Other immune causes include human platelet antigens (HPA) alloimmunization and ABO incompatibility. Many strategies are used to provide appropriate or compatible platelet units for alloimmunized patients.* ***Objective:*** *To evaluate the availability of crossmatch-compatible platelets by lymphocytotoxicity test (LCT) for patients with platelet refractoriness and its association with panel reactive antibody (PRA) of LCT tests.* ***Materials and Methods:*** *Altogether, 1,316 laboratory record data of the patients with immune platelet refractoriness who requested for HLA antibody detection and cross-match compatible platelet for transfusion were retrospectively reviewed. An available request was defined that the number of compatible platelet units should be more than 1 therapeutic dose, which was 10 kg body weight/ unit of platelet concentrate (PC) or 1 unit of single donor plateletpheresis (SDP).* ***Results:*** *Of 1,077 requests for compatible platelets from 128 patients, 86.4% could be responded by LCT-crossmatched compatible platelet units. However, 23 patients had never received any compatible platelet by LCT-crossmatch. Median PRA of LCT tests was significantly higher in the requests with no compatible platelet available than the requests with compatible platelets [96% (86-100) vs 34% (1-67), $p < 0.01$]. The panel reactivity of greater than or equal to 70% was significantly associated with the unavailability of compatible platelets.* ***Conclusion:*** *LCT-crossmatched compatible platelet transfusion was available for the majority of patients with alloimmune platelet refractoriness.*

Keywords : ● *Platelet refractoriness* ● *Lymphocytotoxicity test* ● *Crossmatched platelet*

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นิพนธ์ต้นฉบับ

ความสามารถในการหาเกล็ดเลือดที่เข้ากันได้สำหรับผู้ป่วยที่มีภาวะเกล็ดเลือดต่ำที่ไม่ตอบสนองต่อการให้เกล็ดเลือดโดยการทดสอบความเข้ากันได้ด้วยวิธีลิมโฟไซโตท็อกซิกซิตีย์

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ภาควิชาเวชศาสตร์การธนาคารเลือด คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

บทนำ *ภาวะเกล็ดเลือดต่ำที่ไม่ตอบสนองต่อการให้เกล็ดเลือด (platelet refractoriness) หมายถึง ภาวะที่เกิดจากการให้เกล็ดเลือดแก่ผู้ป่วยซ้ำแล้วนับจำนวนเกล็ดเลือดภายหลังการให้จะไม่เพิ่มขึ้นเท่าที่ควรทำให้เกิดภาวะแทรกซ้อนทางการแพทย์อย่างรุนแรง พบในผู้ป่วยที่ได้รับเลือดและหรือเกล็ดเลือดเป็นประจำ สาเหตุที่ทำให้เกิด platelet refractoriness มีทั้ง immune และ non-immune สาเหตุส่วนใหญ่ของ immune มาจากการถูกกระตุ้นให้สร้างแอนติบอดีต่อ human leukocyte antigen (HLA) ส่วนสาเหตุอื่นๆ ได้แก่ การถูกกระตุ้นให้สร้างแอนติบอดีต่อ human platelet antigen (HPA) และการได้รับเกล็ดเลือดซึ่งมีหมู่เลือด ABO ไม่ตรงกัน การรักษาเพื่อให้ได้ผลดีจึงควรให้เกล็ดเลือดที่เข้ากันได้ให้กับผู้ป่วยเหล่านี้* ***วัตถุประสงค์*** *เพื่อประเมินความสามารถในการหาเกล็ดเลือดที่เข้ากันได้สำหรับผู้ป่วยที่มีภาวะเกล็ดเลือดต่ำที่ไม่ตอบสนองต่อการให้เกล็ดเลือดโดยการทดสอบความเข้ากันได้ด้วยวิธีลิมโฟไซโตท็อกซิกซิตีย์ และศึกษาความสัมพันธ์กับ panel reactive antibody (PRA)* ***วัสดุและวิธีการ*** *ศึกษาข้อมูลย้อนหลังจำนวน 1,316 ข้อมูลของผู้ป่วยที่มีภาวะเกล็ดเลือดต่ำที่ไม่ตอบสนองต่อการให้เกล็ดเลือด ซึ่งมีการขอให้ตรวจหา HLA antibody และขอ crossmatch compatible plateletโดยการมีเกล็ดเลือดที่เข้ากันได้ให้ผู้ป่วยหมายถึงจะต้องมีผลการตรวจที่ได้ปริมาณเกล็ดเลือดที่เข้ากันได้ด้วยการทดสอบความเข้ากันได้ด้วยวิธีลิมโฟไซโตท็อกซิกซิตีย์เพียงพอต่อการรักษาด้วยการให้เกล็ดเลือด 1 ครั้ง ซึ่งถ้าเป็นการให้ platelet concentrate (PC) จะให้ในขนาดน้ำหนักตัวผู้ป่วย 10 กิโลกรัมต่อ PC 1 ยูนิตหรือหากเป็น single donor plateletpheresis (SDP) จะให้ในขนาด 1 ยูนิตต่อครั้ง* ***ผลการศึกษา*** *สามารถหาเกล็ดเลือดที่เข้ากันได้จากการทดสอบความเข้ากันได้ด้วยวิธีลิมโฟไซโตท็อกซิกซิตีย์ได้ร้อยละ 86.4 ของการขอเกล็ดเลือดทั้งหมด 1,077 ครั้ง จากผู้ป่วย 128 คน อย่างไรก็ตามมีผู้ป่วยจำนวน 23 คนที่ไม่สามารถหาเกล็ดเลือดที่เข้ากันได้จากการทดสอบด้วยวิธีนี้ เมื่อศึกษาเปรียบเทียบผล PRA พบว่าในการทดสอบที่เกล็ดเลือดเข้ากันไม่ได้มีค่าสูงกว่าการทดสอบที่มีเกล็ดเลือดเข้ากันได้อย่างมีนัยสำคัญทางสถิติ [96% (86-100) vs 34% (1-67), $p < 0.01$] ซึ่งการมีผล PRA ที่มากกว่าหรือเท่ากับร้อยละ 70 มีความสัมพันธ์กับการหาเกล็ดเลือดที่เข้ากันไม่ได้อย่างมีนัยสำคัญทางสถิติ* ***สรุป*** *สามารถหาเกล็ดเลือดที่เข้ากันได้ให้ผู้ป่วยที่มีภาวะเกล็ดเลือดต่ำที่ไม่ตอบสนองต่อการให้เกล็ดเลือดส่วนใหญ่ได้โดยการทดสอบความเข้ากันได้ด้วยวิธีลิมโฟไซโตท็อกซิกซิตีย์*

คำสำคัญ : ● *Platelet refractoriness* ● *Lymphocytotoxicity test* ● *Crossmatched platelet*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2560;27:225-31.

Introduction

Platelet refractoriness is a serious clinical complication found in multi-transfused patients, which transfused platelet survival is shortened and platelet increment is lower than expected.[1] One hour-correct count increment (1h-CCI) following appropriate platelet transfusion is generally used as an objective measurement to make a diagnosis of platelet refractoriness. A 1-h CCI less than 5,000-7,500 on two consecutive platelet transfusions suggests the diagnosis of platelet refractoriness.[1-3] The impact of platelet transfusion failure on survival and bleeding complication has been shown as significantly reduce median survival time and 3.4 times increase relative risk of bleeding.[4] There are many causes of platelet refractoriness such as splenomegaly, bleeding, fever, infection, disseminated intravascular coagulation, receiving heparin or amphotericin, increasing number of platelet transfusion, positive lymphocytotoxicity antibody, ABO-incompatibility, platelet storage (48 hours or less) and large dose of platelet transfusion, which can be divided into immune and non-immune causes.[3,5-6] Alloimmunization following blood transfusion or pregnancy, which cause by alloantibodies against human leukocyte antigens (HLA) and/or human platelet antigens (HPA), is a major etiology of immune platelet refractoriness. HLA antibodies are more common cause of immune platelet refractoriness than HPA antibodies. However, not all patients with anti-HLA develop clinical platelet refractoriness.[5-6] Leukocyte reduction of cellular blood products (red cells and platelets) is proved to significantly decreased HLA alloimmunization and immune platelet refractoriness.[5,7-8]

Many strategies are used to provide appropriate platelet units after the diagnosis of alloimmune platelet refractoriness was given, which can be classified to HLA-matched platelet, HLA antigen-negative platelet and crossmatch compatible platelet. Several methods can be used for platelet-crossmatched test; complement-dependent cytotoxicity (CDC) or lymphocytotoxicity test (LCT), solid phase red cell adherence assay (SPRCA), flow cytometric crossmatched test and enzyme-linked immunosorbent assay (ELISA).[9] Lymphocytotoxicity test is originally used for identifying compatible donors for kidney transplantation. Later on, HLA-matched platelet transfusion, lymphocytotoxic antibodies and compatible lymphocytotoxic donor-recipient pairs were identified to be related with platelet transfusion response.[10-14] Nevertheless, the efficacy of LCT-crossmatched platelet transfusion for patients with platelet refractoriness was varied between studies.[13-14] In Thailand, universal leukocyte reduction has not been implemented and the use of leukocyte-depleted blood component is less than 10%, the percentage of alloimmunization in patients who requested for platelet antibody detection by SPRCA at the National Blood Centre, Thai Red Cross Society was 55.82% in the year 2001 and increased to 63.78% in the year 2016.[15-16] Both studies reported that the majority of alloimmunization cases comprised HLA alloimmunization (89.01% and 97.53%, respectively).

In our institution, Siriraj Hospital, LCT has been implemented as a donor-recipient-crossmatched test for kidney transplantation since 1973 and employed to detect HLA antibodies and identify compatible platelet components for patients who were refractory to platelet transfusion since 1986. The prevalence of platelet refractoriness patients with lymphocytotoxic antibody was 133 cases in the period of 3 years (2012-2014), which was 37.5% of patients with platelet transfusion failure. Although the limitation of LCT test is generally addressed, regarding only complement-dependent cytotoxic HLA antibodies can be detected, the efficacy of LCT-crossmatched platelet transfusion was mentioned in Makechay's study that satisfactory platelet transfusion response was significantly reached in LCT-crossmatched group more than random platelet group (51% vs 30 %, $p < 0.05$).[17] We aimed to study the ability to provide compatible platelets for patients with alloimmune platelet refractoriness by using LCT-crossmatched method and the association between panel reactivity of LCT-crossmatched tests and the availability of compatible platelets.

Materials and Methods

Patients

The data record of 1,316 requests from 128 patients with platelet transfusion failure and suspected to have immune platelet refractoriness from January 2012 to December 2014 were retrospectively reviewed of medical and laboratory record data. Laboratory record data of these patients who requested for HLA antibody detection and crossmatch compatible platelet transfusion were retrieved and analyzed. This study was approved by the Siriraj Institutional Review Board.

Lymphocytotoxicity test (LCT)

Five milliliters of CPDA blood were collected from donors and centrifuged at 1,000 X *g* for 10 minutes. Then, the buffy coats were collected, and mixed with equal volume of phosphate buffer solution (PBS), layered on top of 2.5 mL of Lymphoprep (Fresenius Kabi Norge As, Oslo, Norway), and centrifuged at 1,000 X *g* for 15 minutes. Mononuclear cell interfaces were collected and washed three times with phosphate buffer saline (PBS). Contaminated platelets were eliminated by precipitation with bovine thrombin and contaminated red blood cells were lysed using pre-warmed ammonium chloride solution (HLA technical workshop, April 8-10, 1991, Bangkok, Thailand). Mononuclear cells were adjusted to the working concentration at $2x10^3$cells/μL in 10% HIBS-RPMI. The viability of the mononuclear cells was estimated using erythrosine B dye in a white blood cells counting chamber, viability more than 80% can be used. One microliter of donor lymphocytes were incubate with 1 μL of patient's serum, negative and positive control serum for 30 minutes at room temperature in Terasaki trays. Thereafter, 5 μL of rabbit complement for HLA class I (One lambda Inc, Canoga Park, USA) was added to each well and incubated for 60 minutes at room temperature and 5 μL of eosin dye was added and left for 2 minutes. Finally, 8 μL of formaldehyde was added to stop the reaction. The tray was covered with mineral oil and left at least one hour on agitator at room temperature before the reaction were read by using the inverted phase-contrast microscope (Diaphot 200, Nikon, Tokyo, Japan). The reactions were considered positive reaction when dead cells in each well were more than 21% of the total, following the American Society for Histocompatibility and Immunogenetics (ASHI) standard grade reading.[18]

HLA antibody detection

When patients had platelet transfusion failure, 1 h-CCI less than 5,000 was required in order to give the diagnosis of immune platelet refractoriness. Then, HLA antibody detection by LCT antibody screening test was allowed to be requested. For HLA antibody detection, at least 20 random whole blood donors were used as a set of screening cells. Results were reported in term of the percentage of panel reactivity or panel reactive antibody (PRA), which was calculated by using the number of positive reactions divided by the total number of screening cells multiplying with 100. For example, if there are 12 positive reactions from 24 screening cells, the panel reactivity will be 50%. When the patients have panel reactivity greater than or equal to 70%, which is considered as a critical value, the physician will be notified to find out the appropriate strategies to get suitable platelet transfusion.

Platelet crossmatching

After the diagnosis of immune platelet refractoriness had been given (1h-CCI less than 5,000 and positive of LCT antibody screening test), LCT for platelet-crossmatch was requested. All whole blood donors whose platelet concentrate (PC) and donors of single donor platelet by apheresis (SDP), who had the same blood group as the patients and had platelet units available on that days, were retrieved to use as donors in platelet-crossmatched LCT tests. Platelet units, PC and SDP, with negative reaction on the LCT tests with patient's serum, were hold and issued for those patients. Panel reactivity from platelet-crossmatched LCT tests was calculated and greater than or equal to 70% panel reactivity was also notified to the physicians as a critical value.

Availibity of LCT-crossmatch-compatible platelet

All platelet-crossmatched LCT tests were reviewed. An available request was defined as a request which platelet units, PC or SDP, were compatible and ready for issued more than 1 dose, which was 10 kg body weight/unit of PC or 1 unit of SDP. Percentage of availability was calculated using number of available requests divided by the total number of requests multiplying with 100.

Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0, Chicago, IL, USA) under MUIT network. Characteristics of the patients are shown as percentage, mean ± standard deviation (SD) and median (IQR) when normal distribution was not observed. The chi-square test was used to compare with groups. The associated risk was presented as an odd ratio (95% confidence interval). For comparison PRA between groups of availability, which was non-parametric data, the Kruskal-Wallis test was used. P-value < 0.05 was considered statistically significant.

Results

A total of 1,316 requests for LCT tests were reviewed, 270 were requests for HLA antibody detection and 1,077 were requests for crossmatch compatible platelet transfusion, (31 requests for both antibody screening and platelet crossmatch). These 1,077 requests came from 128 patients, who were previously given the diagnosis of immune platelet refractoriness according to our criteria (1 h-CCI less than 5,000 and positive of LCT antibody screening test). Patient characteristics were shown in Table 1 and the availability of compatible platelets according to blood groups was presented in Table 2. Of these, 930 (86.4%) of the requests can be responded by LCT-crossmatched compatible platelet units, comprising of platelet concentrate, single donor platelet or both; however, 17.0% of crossmatch compatible platelet units were not issued due to patients' condition change.

Only 1,057 LCT tests had been done to search for compatible platelet units because 20 requests can be responded using compatible platelets from previous platelet-crossmatched requests. Median panel reactivity of LCT tests were significantly higher in the request with no compatible platelet available, 96% (86-100) vs 34% (1-67), p < 0.01. Panel reactivity greater than or equal 70% was usually used as a cut off for critical value. This study showed an odd ratio was 58.64 (95%CI: 28.28-121.59) when panel reactivity ≥ 70% was used as a critical value that no compatible platelet would be available (Table 3).

Table 1 Characteristics of the patients with platelet refractoriness

Characteristics of the patients (N = 128)	N
Sex	
Female	75 (58.6%)
Male	53 (41.4%)
Age (mean ± SD) (years)	42.39 ± 20.87
Blood group	
O	66 (51.6%)
A	20 (15.6%)
B	35 (27.3%)
AB	7 (5.5%)
Number of compatible-platelet request, median (range)	4 (1-106)
Percentage of panel reactivity: HLA antibody detection test, median (IQR)	
0% compatible-platelet availability, n = 23	96 (90-100)
> 0%, < 100% compatible-platelet availability, n = 33	66 (50-92)
100% compatible-platelet availability, n = 72	36 (17-78)

Table 2 Availability of crossmatch compatible platelet components

	Blood group (N)				
	O	**A**	**B**	**AB**	**Total**
Request	540	112	393	32	1,077
Platelet component					
Not available	66 (12.2%)	25 (22.3%)	45 (11.5%)	11 (34.4%)	147 (13.6%)
Available	474 (87.8%)	84 (77.7%)	348 (88.5%)	21 (65.6%)	930 (86.4%)
PC	356	76	306	11	749
SDP	81	9	31	8	129
PC & SDP	37	2	11	2	52
Issued platelet component	397 (83.8%)	77 (91.7%)	284 (81.6%)	14 (66.7%)	772 (83.0%)

PC = platelet concentrate; SDP = single donor plateletpheresis; PC & SDP = both of PC and SDP were available

Table 3 Panel reactivity of platelet-crossmatched LCT tests

	Availability of platelet component		OR (95%CI)	p-value
	Available (n = 910)	**Not available (n = 147)**		
Panel reactivity of LCT tests				
PRA < 70%	702 (98.9%)	8 (1.1%)		
PRA ≥ 70%	208 (59.9%)	139 (40.1%)	58.64 (28.28-121.59)	< 0.01

Before the platelet-crossmatched LCT tests were done in order to search compatible platelet units, the patients with history of platelet transfusion failure required CCI calculation and HLA antibody detection. The median (IQR) percentage of panel reactivity of HLA antibody detection tests was 50 (21-86). The patients can be separated into 3 groups according to compatible-platelet availability, including 23 patients with 0% availability, whose none of the request can be responded, 33 patients had > 0% and < 100% availability and 72 patients had 100% availability. The median of panel reactivity of HLA antibody detection tests was significantly different among 3 groups ($p < 0.01$) as shown in Table 1.

Discussion

In hospital blood banks which blood donation center locates at the same place, a number of platelet units are always on hand and therefore one of the practical ways to find platelet units for patients with platelet refractoriness is crossmatch compatible platelets. Many modern methods are applied to identify antibody against donor platelet antigens which can improved transfusion response in alloimmune platelet refractoriness.[19-20] In this study, the majority of requests for compatible platelets can be responded by LCT-crossmatched platelet transfusion (82% of the patients, Table1 and 86.4% of the requested, Table 2). The crossmatched tests were done in both PC donors and SDP donors, which increase opportunity to find compatible platelet units and maximize platelet resource on hand. Our result addressed 86.13% of compatible platelet units were from PC (Table 2), requiring 5 to 6 compatible donors for 1 dose. Even though it is time consuming and labor intensive workload, LCT crossmatch with both PC and SDP has been served the request of patients with platelet refractoriness for many years.

The association between increasing panel reactivity, both from HLA antibody screening and crossmatch tests, the availability of compatible units were addressed in this study. The critical value of greater than or equal 70% panel reactivity was shown to have significance on availability of compatible platelets units. Practically, when the patients have panel reactivity more than 70%, the physicians will be notified, because it is crucial for plan of treatment. If a curative aim of treat-

ment is carried on, active actions such as searching compatible platelets from outer source such as the National Blood Centre, Thai Red Cross Society or LCT-crossmatching and plateletpheresis donation from patient's relatives need to be prearranged. However, if palliative aim is conducted, this is the critical point to patients' end of life, which need to be informed to the patients and their relatives.

Systematic reviews of the utility of crossmatched platelet transfusions revealed the usefulness in increasing platelet count; however, the data is not enough to address impact on hemorrhage and mortality.[20] The follow up of clinical outcome of the patients in this study is undergoing. The impact of lymphocytotoxic antibodies and availability of compatible platelet will be revealed.

Conclusion

LCT-crossmatched compatible platelet transfusion was available for majority of the patients with platelet refractoriness. Patients with panel reactivity greater than or equal to 70% was significantly associated with the unavailability of compatible platelets.

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