Original Article

Prevention of platelet transfusion refractoriness by platelet antigen gene matching: a systematic review and meta-analysis

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Background: To investigate the prevention of platelet transfusion refractoriness (PTR) by platelet antigen gene matching using literature search and meta-analysis.

Methods: PubMed (2000.1–2021.8), Embase (2000.1–2021.8), Cochrane (2010.1–2021.8), and the Chinese Biomedical Literature Database CBM (2010.1–2021.8) were selected as the search database platform. The keywords (HLA/Human leukocyte antigen), (HPA/Human platelet alloantigens), (genotyping/cross-match), platelet transfusion (PLT), and (CCI/Corrected Count Increment) were used for the joint search. After the literature was screened for inclusion and exclusion criteria, the Cochrane intervention handbook was used for bias risk assessment, and Revman 5.3.5 software was used for analysis to obtain the statistical forest plot and funnel plot.

Results: The preliminary results revealed 255 publications, and seven (297 patients in total) were finally included in the quantitative analysis. A total of five publications reported comparison of the 1 h CCI index of HLA or HPA gene matching and PLT after random selection, and the heterogeneity test showed statistical difference (I^2=49%, P=0.10). The combined statistical analysis results were: (MD =8.57, 95% CI: 7.30–9.80, Z=13.30, P<0.00001), and while six publications reported the effective rate index of PLT, and the heterogeneity test showed no statistical difference (I^2=43%, P=0.12). The fixed effect mode was used to compare the effective rate of the two intervention methods (OR =4.90, 95% CI: 3.50–6.86, Z=9.23, P<0.00001).

Discussion: HLA or HPA gene matching can improve the increment after PLT and reduce the incidence of ineffective PLT.

Keywords: Platelet transfusion (PLT); gene matching; ineffective platelet transfusion (ineffective PLT); meta-analysis

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Introduction

Platelet transfusion (PLT) is a blood transfusion method to prevent and treat thrombocytopenia caused by disease to maintain coagulation function (1). However, platelet transfusion refractoriness (PTR) after multiple transfusions is widespread and seen when the platelet count in serum is not significantly higher after transfusion, or the platelet survival time is short. This not only wastes platelet resources, but also delays the patient's condition and aggravates their economic burden (2). Some studies (3) in cancer patients and those with hematological diseases have

statistically shown the ineffective rate of blood transfusion to be 7–34%. Among the many factors causing PTR, alloimmunization caused by antibodies to platelet surface antigens is one of the important factors, accounting for about 25% to 50% (4). Platelet alloantigens mainly include ABO blood group antigens, human leukocyte antigens (HLA), and human platelet alloantigens (HPA) (5), and blood group crossmatching is often used in clinical practice to reduce immune infusion reactions, although it cannot be completely avoided. With the development of polymerase chain reaction (PCR) molecular diagnostic technology, platelet antigen typing has been gradually stabilized and applied in clinical genotyping and polymorphism investigation (6). In this study, we investigated the role of gene matching in platelet matching and the prevention of PTR by meta-analysis. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2603).

Methods

Literature inclusion criteria

Literature type

The included publications were randomized controlled trials (RCTs), quasi-randomized controlled clinical trials (CCTs), or non-randomized controlled trials (NRCTs). There was no requirement on whether a blind method was adopted for the study.

Study subjects

Patients included in the study were those requiring PLT due to different disease types, including acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, and breast cancer, regardless of age or gender, or whether PTR had occurred during PLT before.

Intervention measures

The intervention group and control group were clearly specified in the literature, HLA or HPA gene matching was performed before PLT, PCR technique was used as the genotyping technique for the intervention group, and routine serological ABO matching or random selection without any matching was performed for the control group.

Outcome measures

The following indicators were used: (I) corrected count increment (CCI), which was calculated by the observed value of CCI detected within 1–4 h after PLT: CCI = [(posttransfusion PLT count within 1 h of completion of transfusion – pretransfusion PLT count) × body surface area]/number of PLTs transfused. (II) Effective rate of PLT: PTR was defined as the CCI value $<5\times10^9$/L within 1–4 h. The effective rate of PLT was calculated as (total cases – PTR cases)/total cases.

Literature exclusion criteria

(I) Case analyses, investigations, reviews, guidelines, and other literature without data indicators; (II) literature in which there were no intervention measures, or studies with missing indicators or in which the data could not be transformed or used.

Database and search strategy and literature screening

PubMed (2000.1–2021.8), Embase (2000.1–2021.8), Cochrane (2010.1–2021.8), and the Chinese Biomedical Literature Database CBM (2010.1–2021.8) were selected as the search database platforms. The keywords (HLA/Human leukocyte antigen), (HPA/Human platelet alloantigens), (genotyping/cross-match), platelet transfusion, (CCI/Corrected Count Increment) were used for joint searching to obtain the list of publications in English. Two researchers reorganized the literature list, read the title and abstract one by one according to the inclusion and exclusion criteria, eliminated obviously non-conforming literature, obtained the full text of the remaining literature for full-text reading, continued screening, and obtained the final included literature list.

Literature quality evaluation and risk of bias evaluation

The Cochrane Handbook of Interventions (7) was used to evaluate the risk of bias in the included studies, which were divided into six aspects: (I) whether randomization was performed; (II) whether a blind method was used; (III) whether there was a hidden scheme; (IV) a description of the phenomenon of loss to follow-up in the scheme; (V) selective reporting bias; (VI) other biases, which were described as “yes”, “no”, and “unclear”.

Data extraction

The two researchers read the full text and extracted literature data from the text independently, which included

the following: (I) basic characteristics of the literature: publisher, publication time, fund source; (II) study characteristics: study time, study site, study type; (III) object characteristics: number of patients, gender ratio, age, primary disease; (IV) intervention characteristics: intervention method in the intervention group, intervention method in the control group; (V) outcome measures: outcome types and data. The obtained data was transformed to facilitate the subsequent meta-analysis, such as data shown in %, being transformed into an actual case number.

Statistical analysis

Revman 5.3.5 was used for the meta-analysis. Inverse variance statistics were used for continuous variables (CCI count), and mean method and 95% CI: were used to report statistics. The Mantel-Haenszel statistical method was used for binary variables (effective rate), and OR value and 95% CI: were used to report statistics. The above differences were statistically significant at $P<0.05$. Every publication reporting the 1h CCI count after transfusion was included for the CCI meta synthesis, and those reporting the effective rate of transfusion were included for the effective rate synthesis. Forest plot descriptive statistics were used for comparison, I^2 analysis and Q test were used for literature heterogeneity, $I^2>50\%$ or $P<0.1$ were used to indicate the heterogeneity of results, and a random effect model was used to obtain OR values, otherwise fixed effect was used to obtain OR value. If heterogeneity between publications was suggested, sensitivity analysis was performed using a subgroup analysis method, and a funnel plot was used to indicate publication bias.

Results

Literature screening results

In this study, 255 publications (PubMed 68, Embase 43, Cochrane 52, and CBM 92) were preliminarily searched. The titles and abstracts were read for duplicate removal, and 169 publications that obviously did not meet the requirements (non-controlled study, no intervention group, or no outcome measures) were removed, five of which were excluded due to a full text retrieval fail. The full text of the remaining 77 publications was then read, resulting in 70 being removed as they did not include outcome measures. This left seven publications with a total of 297 patients to be included in the final quantitative analysis, as shown in *Figure 1*. The basic characteristics, intervention measures, and outcome measures of the seven publications is shown in *Table 1*.

Literature bias assessment

Only publications (11) mentioned the use of randomization, without necessarily detailing the specific method. None of the publications mentioned whether there was classification concealment or a blind method implementation, and the phenomenon of case loss was reported in only three publications (8,9,11), although the data was still complete because the case loss was not included in the outcome statistics. There were no selective reporting in all included studies results, and other risk of bias was unknown, as shown in *Table 2*.

Meta-analysis results

Comparison of 1-hour CCI between PLT after gene matching and unmatched transfusion

A total of five publications (9-13) reported the CCI index at 1 h after infusion. As the heterogeneity test showed statistical difference ($I^2=49\%$, $P=0.10$), publications were divided into two subgroups according to the intervention method: HLA genotyping and HPA genotyping. The internal heterogeneity of HLA genotyping subgroup showed no statistical difference (HLA matched: $I^2=0\%$, $P=0.53$), the fixed effect analysis was used, result showed the HLA genotyping could significantly improve the CCI value at 1 h (HLA matched: MD =9.00, 95% CI: 7.69–10.32, $Z=13.44$, $P<0.00001$. HPA matched subgroup result: MD =3.20, 95% CI: −1.40–7.80, $Z=1.36$, $P=0.17$). The merged statistical analysis results were: (MD =8.57, 95% CI: 7.30–9.83, $Z=13.30$, $P<0.00001$), as shown in *Figure 2*.

Comparison of the effective rate of PLT after gene matching and unmatched transfusion

This index was reported in six publications (8-11,13,14), and the heterogeneity test showed no statistically significant difference ($I^2=43\%$, $P=0.12$) using the fixed-effect mode, and the obtained effective rate of the two intervention methods was compared (OR =4.90, 95% CI: 3.50–6.86, $Z=9.23$, $P<0.00001$), as shown in *Figure 3*.

Analysis of publication bias

Subgroup analysis was performed for five publications with heterogeneity in “Comparison of 1-hour CCI between

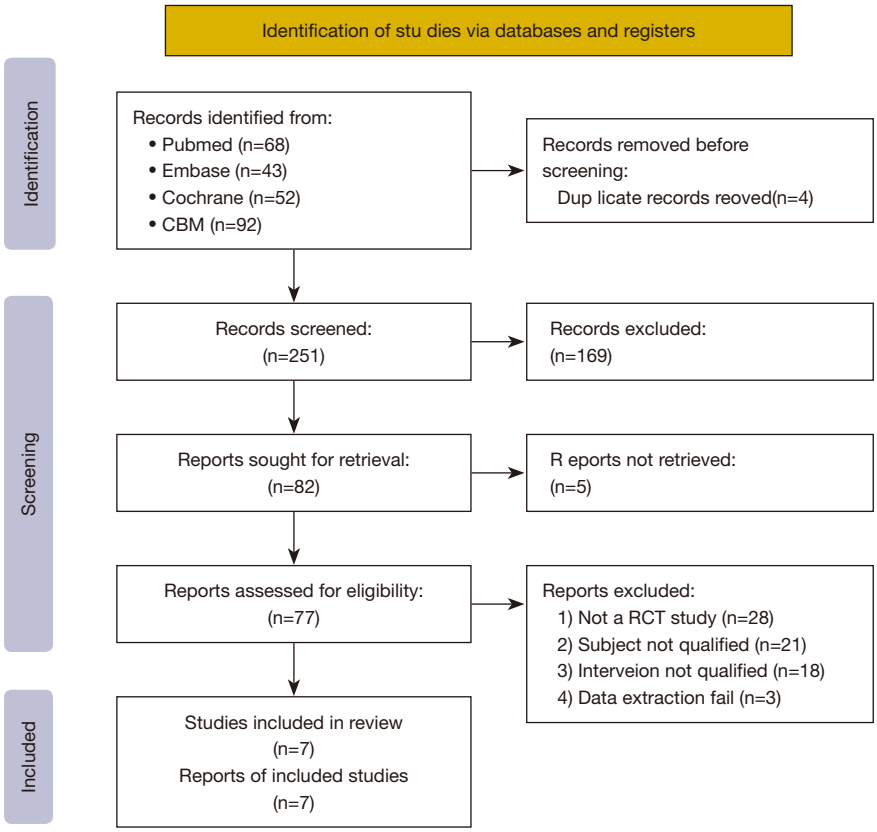

Figure 1 Identification and inclusion flow chart.

PLT after gene matching and unmatched transfusion", and there was no statistically significant internal heterogeneity between the two subgroups, suggesting that the sensitivity analysis results were stable. As there was no statistical heterogeneity in the six included publications in analysis of the infusion response rate, a funnel plot was used to represent the publication bias analysis. The literatures showed asymmetric distribution, suggesting that there may be publication bias, as shown in *Figure 4*.

Discussion

PLT is an important supportive therapy for blood disease. However, after multiple transfusions, platelet antibodies, such as HLA antibodies and HPA antibodies, may be produced, increasing the incidence of PTR and reducing the utilization rate of platelet resources (15). Allo-antibodies against HLA and HPA could lead to allo-immune reaction against platelet antigens, which would accelerate platelet destruction and decrease the platelet count due to antibodies fixation on incompatible platelet antigens (16). In a study conducted by Liu *et al.* (17), 156 patients received multiple platelet transfusion, 74 of them found antibodies positive, 47.4% patients contained HLA antibodies, and 8.3% patients contained both HLA and HPA antibodies. In some cases for the immunodeficient patients graft-versus-host disease can be induced by blood products that contain live lymphocytes, it is imperative to monitor the immunological consequences of transfusion in order to deter the disadvantageous side effects (18).

One traditional immunohematological methods to reduce the transfusion reactions was the simplified sensitized erythrocyte plateleterology assay (SEPSA), in a study (19) manual Polybrene test and SEPSA test before platelet transfusion efficiently reduced immune transfusion reactions to 1.6%. Another meta analysis introduced 1,502 patients and identified ABO matching for platelet (PLT) transfusion could result in a higher PLT increment and reduce the PTR significantly (20). But these methods still could not completely avoid the occurrence of immune response, therefore, it is necessary to accurately identify platelets antigen type before PLT transfusion.

Table 1 Statistics of characteristics of included studies

Author	Region	Total samples	Number of transfusions	Basic characteristics of included patients			Observation group		Primary outcome measures
				Sex ratio (male: female)	Age (years)	Primary disease	Gene matching	Control group	
Seike *et al.* (8), 2020	Okayama, Japan	16	354	1:15	51 [42–67]	Hematopoietic stem cell transplantation	HLA-A, B	ABO only	1 infusion effective rate
Rioux-Massé *et al.* (9), 2014	Minnesota, USA	64	202	12:20	39.5 [9–67]	Acute myelogenous leukemia	HLA-A, B1U, or B1X	ABO only	1 CCI 1 h after infusion, 2 infusion effective rate
Gavva *et al.* (10), 2019	Washington, USA	94	489	12:82	55 [20–84]	Acute leukemia	HLA	Random selection	1 CCI 1 h after infusion, 2 infusion effective rate
Salama *et al.* (11), 2014	Mansoura, Egypt	40	120	16:24	37.6±13.35	Acute myelogenous leukemia	HLA-A, B	Random selection	1 CCI 1 h after infusion, 2 infusion effective rate
Hyun *et al.* (12), 2009	Seoul, Korea	16	71	–	–	–	HLA-A, B	Random selection	1 CCI 1 h after infusion
Li *et al.* (13), 2007	Changsha, China	44	44	–	–	–	HPA 1-5, 15	Random selection	1 CCI 1 h after infusion, 2 infusion effective rate
Liu *et al.* (14), 2014	Mudanjiang, China	23	63	–	–	–	HPA 1-17	Random selection	1 infusion effective rate

–, not mentioned; HLA, human leukocyte antigen; HPA, human platelet alloantigen; CCI, corrected count increment.

Table 2 Risk bias assessment based on the Cochrane Handbook of Interventions

Study	Randomization or not	Hide classification	Whether blind method is applied	Whether the outcome data is complete	Optional reporting	Other bias
Seike *et al.* (8), 2020	N	U	U	Y	N	U
Rioux-Massé *et al.* (9), 2014	N	U	U	Y	N	U
Gavva *et al.* (10), 2019	N	U	U	Y	N	U
Salama *et al.* (11), 2014	Y	U	U	Y	N	U
Hyun *et al.* (12), 2009	N	U	U	Y	N	U
LI *et al.* (13), 2007	U	U	U	Y	N	U
Liu *et al.* (14), 2014	N	U	U	Y	N	U

Y, yes; N, no; U, unclear.

Platelets antigen type matching also called genotyping is an effective way of reducing the incidence of PTR by transfusing genotypically matched platelets to patients who produce antibodies (21). In this study, the merged effect results showed that the CCI value (1–4 h) after HLA gene matching was significantly higher than that of patients without matching (randomly selected), and the merged statistics value were MD =9.00, 95% CI: 7.69–10.32,

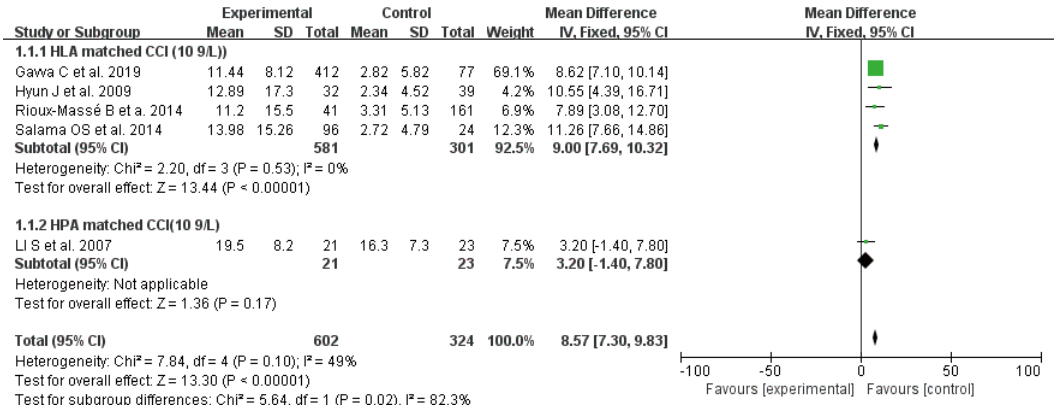

Figure 2 Comparative analysis of 1-h CCI between platelet transfusion after gene matching and unmatched transfusion. CCI, corrected count increment.

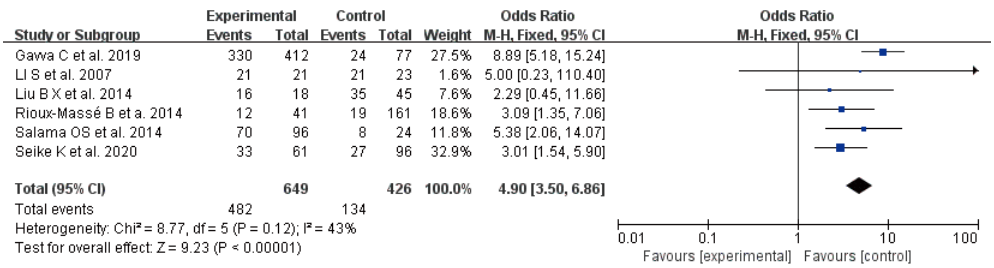

Figure 3 Comparative analysis of the effective rate of platelet transfusion after gene matching and unmatched transfusion.

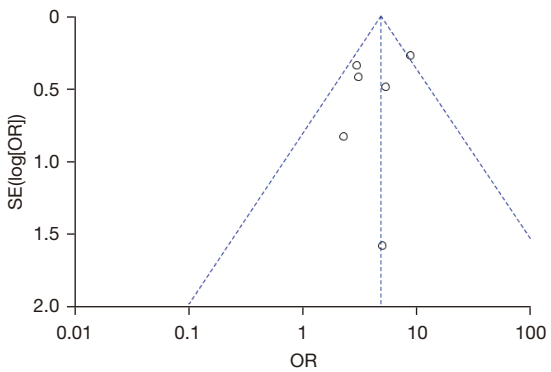

Figure 4 Funnel plot of the comparison of the effective rate of platelet transfusion after gene matching and unmatched transfusion.

Z=13.44, P<0.00001. The CCI (1–4 h) after HPA gene matching was also higher than that of the control group (MD =3.20, 95% CI: −1.40–7.80, Z=1.36, P=0.17), but the difference was not statistically significant. However, for the infusion response effective rate (without PTR), the results after gene matching compared with the randomly selected group were OR =4.90, 95% CI: 3.50–6.86, Z=9.23, P<0.00001, suggesting the former could improve the infusion response effective rate.

However, as compatible PLTs with the same genetic matching still cannot avoid PTR production due to antibodies during the next transfusion, the most fundamental solution is to transfuse platelets matched for ABO blood groups, HLA, and HPA to eliminate PTR caused by alloimmunization (22). In the report by Xia *et al.* (23), 23 patients were matched simultaneously with ABO blood groups, HLA-A and HLA-B, and HPA1-6/15, and the percentage of platelet transfusion recovery (PPR) of patients was significantly higher than that of the concurrent control group. However, due to different outcome measures, such studies were not included in this meta-analysis.

The situation of PTR for platelet transfusions patients benefits from human leukocyte antigen (HLA)-matched platelet transfusions, however, differences in ethnic

background of patients and donors could hamper the availability of sufficient numbers of HLA-matched donors for all patients. In a study conducted by Kreuger *et al.* (24), for 10.3% patients who have African American background, fewer donors were available, which meant that more donors with the same ethnic ground were required to ensure the availability of HLA-matching transfusion.

HPAs are specific antigens carried by platelet glycoproteins, currently there are more than 22 kinds of alloantigens found, which called platelet antigen polymorphism. Some of them related to PTR. In a study by Zhou *et al.* (25), the HPA-1, -2, -3, -4, -5 and -15 polymorphisms were all associated with the platelet count. In the study (14), all the platelet antigen polymorphisms HPA 1-17 were engaged in matching before transfusion, which significantly reduced the antibodies and prevented PTR.

Among the controlled clinical studies included in this study, only one publication mentioned randomization (method unknown), but neither the allocation method nor the blind method was mentioned, and the overall quality was low, which may have caused the implementation bias in the analysis. As only 297 patients were included for further analysis, with few samples, the funnel plot showed asymmetric left-right distribution, suggesting there may be some risk of publication bias. Therefore, future studies on this topic still need to include more high-quality controlled clinical studies for analysis.

Conclusions

In PLT, the use of HLA or HPA gene matching can improve the increment after PLT and reduce the incidence of ineffective PLT. However, due to the small sample size and quality of included literature in this meta-analysis, more controlled clinical studies are needed for in-depth discussion.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2603

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2603). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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