Review Article

Current trends in platelet transfusions practice: The role of ABO-RhD and human leukocyte antigen incompatibility

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Abstract:

Platelet transfusions have contributed to the revolutionary modern treatment of hypoproliferative thrombocytopenia. Despite the long-term application of platelet transfusion in therapeutics, all aspects of their optimal use (i.e., in cases of ABO and/or Rh (D incompatibility) have not been definitively determined yet. We reviewed the available data on transfusion practices and outcome in ABO and RhD incompatibility and platelet refractoriness due to anti-human leukocyte antigen (HLA) antibodies. Transfusion of platelets with major ABO-incompatibility is related to reduced posttransfusion platelet (PLT) count increments, compared to ABO-identical and minor, but still are equally effective in preventing clinical bleeding. ABO-minor incompatible transfusions pose the risk of an acute hemolytic reaction of the recipient that is not always related to high anti-A, B donor titers. ABO-identical PLT transfusion seems to be the most effective and safest therapeutic strategy. Exclusive ABO-identical platelet transfusion policy could be feasible, but alternative approaches could facilitate platelet inventory management. Transfusion of platelets from RhD positive donors to RhD negative patients is considered to be effective and safe though is associated with low rate of anti-D alloimmunization due to contaminating red blood cells. The prevention of D alloimmunization is recommended only for women of childbearing age. HLA alloimmunization is a major cause of platelet refractoriness. Managing patients with refractoriness with cross-matched or HLA-matched platelets is the current practice although data are still lacking for the efficacy of this practice in terms of clinical outcome. Leukoreduction contributes to the reduction of both HLA and anti-D alloimmunization.

Key words:

ABO-incompatibility, human leukocyte antigen-platelet refractoriness, platelet transfusion, RhD

Introduction

Platelet transfusions have contributed to the revolutionary modern treatment of thrombocytopenia in patients with cancer and hematological malignancies receiving chemotherapy over the past 50 years.[1] However, despite the long-term application of platelet transfusion in therapeutics, all aspects of their optimal use have not been definitively determined yet. One such aspect is platelet transfusion in cases of ABO and/or RhD incompatibility. Currently, there are still no consensus guidelines and recommendations for all issues of platelet transfusions, and a wide variety of practices worldwide is being applied.[2,3] We reviewed the existing data on platelet transfusion practices and their clinical impact in cases of ABO and RhD incompatibility as well as platelet refractoriness due to anti-human leukocyte antigen (HLA) antibodies.

The Role of ABO-incompatibility in Platelet Transfusions

Since the early years of platelet transfusions, platelet ABO-incompatibility was not considered to hinder normal responses. ABO-mismatched platelet transfusion was a common practice for a long time,[4] however, it gradually became apparent that ABO-incompatibility in platelet transfusion not only affects the efficacy of transfusion but is also associated with adverse consequences for the recipient.

Platelets express on their surface antigens of the ABO system while they do not express any antigens of the Rhesus system. The ABH antigens expressed on the platelet surface are a mixture of intrinsic molecules, as a result of endogenous synthesis and extrinsic molecules, as a result of adsorption of soluble antigens found in plasma.[5] A and B determinants are present on intrinsic PLT glycoproteins (GPs), mainly in IIb-IIIa, GPIb-IX-V, GPIa/IIa, GPIVIIIa and Ib.[6,7] Apart from GPs, additional ABH antigens are expressed on platelet membrane glycolipids.[8] ABH expression on PLTs varies dramatically among individuals: A2 individuals express minimal levels of antigens compared to A1 individuals and approximately 5% of A1 and B individuals express very high levels of ABH antigens on their PLTs (high expressors).[9-11] None of the group AB individuals show high expression of both A and B antigens at

the same time. The level of high expression of A and B antigens is related to the level of the respective serum glycosyltransferase activity but not to the secretor (Se) or nonsecretor phenotypes.[11] In addition, expression of ABH antigens on the surface of platelets varies even among the PLT population of the same individual.[12] Interestingly, in apheresis platelets concentrates derived from A1 donors an increase of antigen A expression was noted probably due to the increase of GPIIb-IIIa expression induced by a combination of increased synthesis and release from α granules.[13,14]

The effectiveness of platelet transfusion varies and greatly depends on the type of ABO-incompatibility between the donor and the recipient. A major ABO-incompatibility occurs when donor platelets express antigens of the ABO system that interact with natural anti-A and anti-B antibodies that are present in the plasma of the recipient, e.g., transfusion of Group A platelets to a Group O recipient. In contrast, a minor ABO-incompatibility occurs when donor plasma, containing anti-A and anti-B antibodies, react with the AB antigens present on the red cells and platelets of the recipient, e.g., transfusion of Group O platelets to a Group A or B recipient.

Thus, a platelet transfusion may be ABO-identical (same ABO group donor-recipient), ABO-compatible (with minor ABO-incompatibility or otherwise incompatible plasma) or ABO incompatible (with major ABO-incompatibility).[15]

Transfusion of ABO-identical Platelets Concentrates

Transfusion of ABO-identical PLTs versus nonidentical platelet transfusion practices was reviewed by Shehata *et al*.[16] This review that included three randomized controlled trials and 16 observational studies concluded that although ABO-identical platelet transfusions are associated with higher platelet posttransfusion increment, the overall clinical benefit could not be assessed as none of the included studies assessed mortality, bleeding events or transfusion reactions as primary endpoints.

On the other hand, it has been shown that providing ABO-identical platelets might be associated with reduction in red blood cells (RBCs) transfusion requirements and improved outcomes in surgical trauma patients, in cardiac surgery patients as well as in patients with acute leukemia.[17-19]

Although ABO-identical platelets transfusion seems to be the most effective and safest therapeutic strategy, applying such a policy to all patients is not always feasible. The limited availability of ABO-identical platelets at the time of an urgent need and the limited shelf-life of platelets, as they expire 5 days after collection, are the main reasons.[15,20] Nevertheless, according to a recent publication providing ABO-identical PLTs, for a 4-year period, was feasible enough for almost all patients without significant cost increase or platelet wastage.[21]

Transfusion of Platelets with Major ABO-incompatibility

It has been shown that ABO major incompatibility is associated with lower rates of postransfusion corrected count increment (CCI) at 4 and 24 h compared to ABO-identical PLT transfusions. Patients receiving prophylactic PLTs transfusions with major ABO-incompatibility require transfusions at shorter intervals compared to ABO-identical platelets.[20,22,23] Studies performed in healthy volunteers individuals, transfused with radiolabelled platelets with major ABO-incompatibility, showed an accelerated destruction of platelets in the recipient.[24] In addition, platelet function alterations after *in vitro* exposure to anti-A/B have also been implicated, and more specifically platelets seem to be less functional as that was depicted with tests such as platelet function analyzer-100, aggregation, and thrombin generation.[25]

Despite reduced posttransfusion PLT count increments, as it has already been mentioned when assessing the clinical outcome, the transfusion of PLTs with major ABO-incompatibility is equally effective in preventing clinical bleeding compared to ABO-identical and PLTs with ABO-minor incompatibility. In addition, ABO compatibility has been shown to have no impact on the time of onset of bleeding episode (WHO grade 2[26] or higher) following transfusion.[22]

Another reason that leads to poor CCIs after transfusion of platelets with major ABO-incompatibility is the development of anti-HLA and antihuman platelet antigen (HPA)-antibodies. A study in 1990 showed that recipients of ABO-major incompatible platelets developed refractoriness to PLT transfusion at a higher rate than recipients of ABO-compatible PLTs (69% vs. 8%, respectively; P =.001). The authors support that transfusion of platelets with major ABO-incompatibility not only increases anti-A and anti-B titers but also stimulates recipients' immune system to produce other alloantibodies such as anti-HLA and anti-HPA that mainly contribute in the development of PLT refractoriness, which is discussed later.[2,27]

Transfusions of Platelets with Minor ABO-incompatibility

Transfusion of platelets with minor ABO-incompatibility (incompatible plasma) has also been associated with poorer platelet count increments, but the main concern is the subsequent development of hemolytic transfusion reaction (HTR) of the recipient. This is particularly associated with Group O donors and nonGroup O transfusion recipients.[15,27-30] The risk of developing an acute HTR after receiving platelets with minor incompatibility ranges from 1/2500 to 1/46176 with a reported estimated risk of approximately 1/9000 platelet transfusions.[31] Actually, the current risk of an HTR following platelet transfusion with minor ABO-incompatibility may be slightly higher due to the increasing use of single donor's platelets which contain 4-8 times more plasma than random donor's platelets.[32]

It should be noted that HTRs from platelet transfusions are likely under-recognized and underreported due to their subclinical course and the subsequent difficulty at diagnosis.[33] Patients receiving PLTs are often critically ill and is likely that symptoms and signs of hemolysis in these patients may not be attributed to PLT transfusion.[34]

Several countries in the western world have taken a proactive approach in order to prevent HTRs from minor ABO incompatible platelet transfusions. Although the implementation of such policies

definitely reduces severe HTRs related to PLT transfusions,[35] it is worth noticing that HTRs are still recorded. In the UK, platelet concentrates from group O platelet donors are characterized as "high-titers" or "nonhigh-titers" after the determination of their critical titers of anti-A and anti-B in plasma. The method in use consists of a 1:20 dilution of donor plasma of all donations tested against A2B cells on microplates. The "high-titer" platelets components are transfused exclusively only to Group O recipients, while "nonhigh-titer" are considered as safe to be transfused to nonGroup O recipients.[15]

In order to implement universally such an approach, there are still obstacles to overcome mainly regarding the choice of methodology and the definition of "titer threshold." Screening methodologies for the determination of anti-A, anti-B titers, that include tube tests, gel tests, and solid phase tests methods, vary worldwide, and that renders comparison of results among institutions extremely difficult. The lack of accredited screening methods is further complicated by the lack of a universal "dangerous-critical anti-A and B titers" threshold, beyond which there is a high risk for the development of an HTR, related to PLT transfusions.[34,36] It has been shown that critical anti-A or B titer is not sufficient to predict the risk of hemolysis related to the transfusion of ABO-incompatible plasma.[35] Possibly additional factors, donor and patient related, should be taken into consideration in order to identify high-risk recipients for HTR development.[34]

Another parameter that cannot be overlooked is the formation of ABH immunocomplexes following mainly the transfusion of platelets with minor ABO-incompatibility. It is well known that when transfusing minor ABO incompatible platelets, anti-A and anti-B antibodies derived from the donor plasma are diluted in recipient's total blood volume. Circulating portions of ABH antigens and ABH glycosylated complexes of the recipient recognize and inactivate the transfused anti-A and anti-B antibodies. The long-term fate as well as the clinical relevance of the resulting formation of these soluble ABH immunocomplexes is not yet known, but they could be possibly harmful for the recipient.[18,21]

Nowadays, many efforts could be considered as accepted practice in order to overcome the ABO barrier in platelet transfusions. Such practices include:[37]

a. Screening platelet donors for high titer ABO antibodies,[36]
b. Encourage instrument manufacturers to develop and validate automated anti-A and anti-B titer screening,[34]
c. Wash and resuspend platelets in saline,[15]
d. Reduce plasma volume of group O apheresis PLTs concentrates to 50 ml,[38] and
e. Replace plasma with additive solutions or AB plasma after washing, (with the limitations described for the existing soluble A and B circulating antigens in AB plasma).[39-41]

As a conclusion, it seems that the most effective and safest therapeutic strategy in platelet transfusions, that carries the lowest risk for the patient, is the one from an ABO-identical donor, which is though not always feasible. The implementation of protocols to overcome the ABO barrier in platelet transfusions is most likely to increase both the workload and the cost.

Taking into consideration all these available data, a practical costless approach to inventory management could be to:

a. Transfuse ABO-identical platelets whenever possible.
b. Evaluate the patient and identify high-risk cases (i.e., neonates, pediatric patients, hematopoietic stem cell transplant (HSCT), and organ transplant recipients) and implement ABO-identical platelets transfusion policy to these groups.
c. Alternatively to ABO-identical platelets use random donor platelet concentrates in cases with minor ABO-incompatibility that contain less plasma volume than single donor platelets.
d. Alternatively to ABO-identical platelets use single donor platelet concentrates from A2 donor that are considered universal platelets donors.

The role of Rhesus D incompatibility in Platelet Transfusions Practice

Human platelets do not express any antigens of the rhesus system. However, platelet concentrates contain the variable volume of contaminating RBCs, which may induce RhD alloimmunization when transfused in a RhD negative subject. Although the risk is low especially for the majority of thrombocytopenic patients who need long-term platelet transfusions (immunosuppressive therapy, malignancies), it could have a clinical impact in childbearing age women, when RhD alloimmunization can cause hemolytic disease of the fetus and newborn.

The incidence of anti-D alloimmunization after RhD-incompatible platelet transfusion ranges from 0% to 18.7%, which is significantly lower than the incidence of RhD alloimmunization after RBC incompatible transfusions.[42-46] It is worth noticing that the low incidence of anti-D alloimmunization following platelet transfusions reported recently (3.8%),[47] may be mainly due to the decrease in RBC contamination in PLT concentrates due to improved blood component processing and apheresis technology. Contaminating RBCs volume in apheresis platelets products is 50 times less than the volume of RBCs in a whole blood-derived PLT concentrate using the PLT-rich plasma method (0.00043 ml vs. 0.036 ml).[43,47,48]

Several studies have attempted to correlate anti-D alloimmunization after platelets transfusion with the total number of the platelets units transfused. It has been shown that neither the number of RhD positive pooled PLT concentrates nor the total number of PLT products had an impact on anti-D formation. Thus, cumulative RBC dose and PLT dose as well as repeated exposure to RhD antigen appear not to be related to a higher rate of anti-D alloimmunization.[49]

On the other hand, factors that have been reported to play a protective role and prevent anti-D alloimmunization include ABO-incompatibility, patient's immunosuppression, and leukoreduction. ABO-incompatibility is reported to reduce the rate of anti-D alloimmunization in normal volunteers and pregnant women. The protective effect of ABO-incompatibility is attributed to the destruction of RBCs (due to ABO-incompatibility) before the RhD antigen is recognized by the recipient.[49] Immunosuppression (disease or treatment related) has also been implicated as a factor with a protective effect in alloimmunization, with the limitation that almost all studies referred to immunocompromised patients receiving platelet transfusions.[50] The risk of alloimmunization does not seem to be associated with either disease stage or patients' age.[51] Leukoreduction of blood components, including

platelet concentrates, may have an additional protective role in alloimmunization. Actually, alloimmunization rates have been reported to decrease after the implementation of universal leukoreduction.[52] The lower alloimmunization rate is suggested to be secondary to a change in T-cell response to foreign antigens resulting by changes in cytokines.[53] Febrile non-HTR (FNHTR), secondary to platelet transfusions, leading to cytokine release, have been associated with increased alloimmunization (8% vs. 3%, $P = 0.026$). Leukoreduction decreases the likelihood of FNHTR and potentially subsequent antibody formation.[54] Although the idea of inflammation-altering immune response is intriguing, more human data are needed to document its association with alloimmunization.

In conclusion, nowadays, data suggest a low rate of anti-D alloimmunization related to platelet transfusion. Thus, transfusion practices could allow the transfusion of RhD positive PLT units to RhD negative patients, with the exception of females of childbearing age. The prevention of anti-D alloimmunization can be achieved using Rh immune globulin (RhIG). For RhD mismatched PLT transfusions, the lowest dose of standard preparations of RhIG (e.g., 125 or 300 mg) should be sufficient to prevent alloimmunization given the small RhD positive RBC volumes involved. Such a treatment does not affect the survival of transfused platelets since the platelets do not express Rh antigens.[55] If the lower risk of anti-D formation with apheresis PLTs components is confirmed in future studies, a practice of transfusing platelets irrespective of RhD typing could be feasible for all categories of patients.[47,56]

The Role of Human Leukocyte Antigen in Platelet Transfusions

Platelets express on their surface antigens of the major histocompatibility system (HLA) class I (A, B, C) while they do not express HLA class II antigens.[57] Their action is well-defined in white cells while in other cell types such as platelets it is not sufficiently specified. The expression of HLA-A and B antigens on platelets is stronger than HLA-C. Although platelets are capable to synthesize HLA class I antigens (endogenous synthesis),[58] *in vitro* studies have shown that 2/3 of these molecules is a result of adsorption of plasma soluble HLA antigens derived from the proteolytic excision from the membranes of somatic cells.[59] It also seems that the majority of HLA antigens on the surface of platelets consist mainly of heavy chains with only a minimal amount of B macroglobulin and most of the HLA molecules on platelets are structurally modified (denatured) and have the ability to detach from their surface especially during platelet storage. Still these molecules retain the ability to induce the development of alloantibodies.[60] HLA class II is mainly expressed by professional antigen-presenting cells (APCs) (i.e., macrophages, B cells, dendritic cells).[61] The HLA class II antigens (-DR, -DQ, and -DP) participate in the antigen presentation of external pathogens to $CD4^+$ T lymphocytes promoting humoral and cellular immunity.[62]

The HLA antigens of the donor are recognized by the immune system of the recipient either directly or indirectly. Directly, APCs of the donor, expressing HLA II antigens are recognized and they activate the recipient's T-cells. Indirectly, HLA I antigens of the donor are recognized by the APCs of the recipient. Splenic macrophages and dendritic cells of the recipient phagocytose or pinocytose, respectively, the antigens and in turn activate the recipient's T-cells.[63]

The Role of Human Leukocyte Antigen in Platelet Transfusion Refractoriness

Platelet refractoriness is defined as the failure to achieve an acceptable increment in platelet count following platelet transfusion at least on two occasions. Platelet count must be measured within 1 h after transfusion.[64] Alternatively, the CCI can be calculated. CCI of 5500-7000 or above is considered an adequate response. Refractoriness in platelet transfusions has been documented in 30-50% of patients who undergo regular platelet transfusions and both immune and nonimmune mechanisms are implicated in the pathogenesis of this phenomenon. The nonimmune mechanism includes, diseases of the recipient such as fever, splenomegaly, DIC, bleeding, or drugs (amphotericin B, ciprofloxacin). The immune mechanisms include the destruction of platelets by recipient's antibodies. Most of the patients with platelet transfusion refractoriness are sensitized against HLA antigens, but anti-HPA antibodies have also been documented. High titers of natural ABO antibodies, as it has been already described, can also underlie platelet refractoriness.[65,66]

Patients confirmed with immune platelet transfusion refractoriness could be investigated for the presence of HLA specific antibodies. Most common methods used for this identification are the panel reactive antibody, an assay based on lymphocytotoxicity or the enzyme-immunoassay-based method and the antigen specificity prediction method (ASP).

Two main transfusion approaches are currently implemented for patients with platelet refractoriness due to HLA alloimmunization: Either transfusion with cross-matched platelets or transfusion with HLA-matched platelets. Additional alternative measures with varying efficacy include transfusion of ABO-compatible platelets in high doses, gamma globulin IV (IVIG), and plasmapheresis. Recently, transfusion of platelets treated with specific acid dilutions to an alloimmunized patient had encouraging results.[67]

Platelet cross-match transfusion practice is mainly carried out by solid phase technique (the solid-phase red cell adherence test). On the other hand, the practice of transfusing HLA-matched platelets from HLA-identical donors (related or unrelated) has been applied since 1969, leading to a laboratory response in 44-96% of patients. Given the genetic variability of the HLA system, it soon became obvious that we should have a very large pool of platelet donors in order to meet the need for every patient with resistance to platelet transfusion.[68] In order to overcome this problem over the last years many methods have been developed and applied, including; (a) the method of (permissive mismatching), that exploits the fact that among HLA antigens there are HLA-A and HLA-B antigens groups with serological cross-reaction (serologically cross-reactive groups).[69] These groups share common "public" epitopes and thus patients exposed to epitopes common with their own do not develop antibodies. This approach is not useful for patients with antibodies to specific (personalized) epitopes, (b) The method of "ASP" or "antigen negative approach" which involves the accurate determination of the specificity of HLA antibodies and the provision of PLTs negative for HLA antigens against which the patient had created alloantibodies.[70] The HLA-matched platelet approach is facilitated by software programs, such as the "HLA matchmaker" and the epitope-based matching.[71,72]

The main drawbacks of the methods available are that HLA-matched platelets are an expensive approach and frequently unavailable and on the other hand since platelets have a shelf life of 5 days, platelet cross-match, although less expensive has to be frequently repeated.[73]

It is quite clear that selecting the method with which we approach and manage platelet refractoriness depends on the available techniques and their cost and thus practices vary considerably among institutions and countries. Although in the literature, there are studies describing the effectiveness of each transfusion practice alone, there are not many studies directly comparing these two approaches. One study concluded that although HLA-compatible platelets provide the optimal support for refractory patients, cross-match-selected platelets can serve as an acceptable alternative approach,[74] while another recent study[75] has shown that the use of cross-match-compatible or HLA-matched units did not provide better increments in PLT count when compared to random nonselected units.

The other parameter that should be taken into account is the cost effectiveness of these approaches. Only one study with economic analysis showed that the HLA-matched single-donor platelets were relatively cost-inefficient in comparison to the crossmatch-compatible platelets.[76]

What is more important in determining the superiority of the available methods is accessing not only the laboratory outcome (reduction in HLA alloimmunization, improvement in PLT count increment) but also the clinical outcome (i.e., reduction in PLT utilization; in mortality; reduction in frequency or severity of hemorrhage). Two recent reviews have tried to answer the question of the efficacy of (a) cross-matched platelets and (b) HLA-matched platelet transfusions. Both reviews concluded that data on the clinical outcome are scarce and that fact warrants the need of future prospective studies addressing the impact of both approaches on clinical outcomes.[77,78]

In terms of prevention, it has become clear over the past years that the basis of HLA alloimmunization after platelet transfusion is not the HLA I that platelets harbor but rather the HLA II expressed on the white cells that circulate in the transfused product.[79] There are many controlled trials in the literature that have shown that leukoreduction can prevent HLA alloimmunization.[80] TRAP study clearly showed that the use of leukoreduced or UVB-irradiated pooled random platelets concentrates led to a reduction of the incidence of alloimmunization and alloimmune refractoriness when compared with untreated pool random donor platelet concentrates.[81]

Conclusions

ABO-identical platelet transfusion seems to be the best, safest, and most effective approach in platelet transfusion practice and should be implemented when possible. The identification of high-risk patients (i.e., neonates, pediatric patients, HSCT, and organ transplant recipients) and the implementation of rigorous ABO-identical platelets transfusion policy to these groups could also contribute to better results. In cases of minor ABO-incompatibility, random donor platelet concentrates or single donor platelet concentrates from A2 "universal" PLT donors could be alternative approaches.

Transfusion of RhD positive platelets to RhD negative recipients is a safe practice except women of reproductive age (<50 years old). In this case, prophylactic administration of anti-D globulin should be applied.

The development of anti-HLA antibodies is the most frequent reason of immune platelet refractoriness. The choice of leukoreduced products for thrombocytopenic patients requiring long-term platelet support can be an effective measure of reducing the incidence of both anti-D and anti-HLA alloimmunization. When poor CCIs are encountered, administration of ABO-identical platelets can be the initial approach. Administration of cross-matched platelets or HLA-matched depends on the accessibility to such methods by individual blood bank services, but data are still lacking for the efficacy of both practices in terms of clinical outcome.

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