Type and screen policy in the blood bank: Is AHG cross-match still required? A study at a multispecialty corporate hospital in India

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Abstract:

Background: Antibodies against only about 25–28 blood group antigens are known to cause hemolytic reactions (HTRs), and red cell antibody screening should detect such clinically significant antibodies. An extension of the antibody screening test is the 'type and screen' done to detect clinically significant antibodies, omiting the anti-human globulin (AHG) cross-match. **Aim:** The aim of this study was to find out if the type and screen procedure is a safe method for pre-transfusion testing when compared to the AHG cross-match currently in use in India. **Materials and Methods:** We evaluated data from 45373 patients for whom a total of 61668 units of packed red blood cells (PRBC) were cross-matched in the AHG phase using DiaMed® ID cards. An antibody screen was carried out in all the patients using the DiaMed® ID-DiaCell I+II+III. The AHG cross-match was also carried out for all recipients, irrespective of the result of the antibody screen. The results were compared to see if there were any cases where the antibody screening was negative but the AHG cross-match showed incompatibility. **Results:** Not a single case was found where the antibody screen was negative and AHG cross-match showed incompatibility. In 68 cases the antibody screening was positive. Out of the 68 cases, AHG cross-match was incompatible with at least one unit of PRBC in 41 cases. **Conclusion:** The screening cell panel adequately detected the clinically significant antibodies in the Indian population in our study. The type and screen policy can be safe, efficient, cost-effective, and beneficial to the transfusion service in India.

Key words:

Anti-human globulin cross-match, alloantibodies, type and screen

Introduction

It is the responsibility of transfusion medics to ensure that transfused blood is as safe as possible. Due examinations and tests must be carried out on donors and donated blood, respectively. Besides the risk of transfusion transmitted infections (TTI), there is also the possibility of transfusion-associated hemolysis, the risk of which must be reduced as far as possible before a component of blood is issued by the blood bank. Thus, certain pre-transfusion tests have to be carried out to ensure that the transfused blood components have adequate survival when transfused and do not cause harm to the recipient.

The concept of safe transfusion from a red cell serology point of view, which we are familiar with today, was heralded by the discovery of the ABO blood groups by Karl Landsteiner in 1901.[1] Since then a large number of red cell antigens have been discovered, for example, the Rh antigen in 1940[2] and the Kell antigen in 1946.

Blood groups are antigens and, by definition, a molecule cannot be an antigen unless it is recognised by an antibody. Thus, all blood group specificities are defined by antibodies. Most adults have antibodies to A or B antigens, or to both; that is, they have 'naturally occurring' antibodies to those ABO antigens that they lack. For most other blood groups, the corresponding antibodies are not 'naturally occurring.' As of now, according to the International Society of Blood Transfusion (ISBT), there are about 300 blood group antigens.[3]

Blood group antibodies are usually IgM or IgG, although some may be IgA. 'Naturally occurring' antibodies are usually predominantly IgM, whereas 'immune' antibodies are predominantly IgG. However, not all antigens lead to the formation of clinically significant antibodies. Only about 25–28 antigens out of the known 300 are known to cause hemolytic transfusion reactions (HTR). At their worst, HTRs give rise to disseminated intravascular coagulation, renal failure, and death. At their mildest, they reduce the efficacy of the transfusion. The antibodies which cause HTR are termed as clinically significant. Thus, pre-transfusion tests should be such that all the clinically significant antibodies can be ruled out.

In the majority of the blood banks, the conventional method of pre-transfusion testing involves

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determining the ABO and Rh types of the donor and the recipient, and performing a major cross-match (testing the recipient's serum/plasma against the donor's red blood cells). The pre-transfusion testing should consist of an AHG (Coombs phase) cross-match. The reason for doing an AHG cross-match is to detect red cell antibodies, most of which are non-agglutinating (incomplete) IgG antibodies, although some antibodies are IgM.

Over the last 3–4 decades, pre-transfusion tests have undergone substantial revision. In the early 1960s, many blood banks carried out minor cross-match in addition to major cross-match. It was only in the mid 1970s that the minor cross-match was abandoned, as antibody screening of donor blood became routine.[4] The standards of most national bodies stipulate that blood from donors with a history of prior transfusion or pregnancy be tested for red blood cell (RBC) alloantibodies; however, most blood banks test all donor blood for RBC alloantibodies because of the difficulty in determining donors' past histories.

In the late 1970s and early 1980s, the need for doing the major cross-match was also questioned.[5] In fact, as early as 1964, Groves-Rasmuessen had proposed it be abandoned. It was suggested that the AHG phase of the cross-match added little extra value for improving patient safety when the antibody screen was negative. The basis of this argument was that if the serum or plasma of the recipient is tested in the AHG phase with red cells of two to three un-pooled O group RBCS, the clinically significant RBC alloantibodies can be either detected or ruled out. It is important that the reagent red cells are selected in such a manner that they express the antigens associated with most clinically relevant antibodies. Reagent cells licensed by the Food and Drug Administration (FDA) in the US for this purpose are required to express the following antigens: D, C, E, c, e, M, N, S, s, P1, Le^a, Le^b, K, k, Fy^a, Fy^b, Jk^a, and Jk^b.[6] There are no requirements for other antigens, such as Lu^a, V, or Cw. Some weakly reactive antibodies react only with screening red cells from donors who are homozygous for the genes controlling expression of these antigens, a serologic phenomenon called dosage. Antibodies in the Rh, Duffy, and Kidd systems are the ones that most commonly manifest the dosage phenomenon. If the AHG cross-match is carried out between a recipient and a donor, and the donor RBC carries Rh, Duffy, or Kidd antigens in a heterozygous dose, the AHG cross-match may be compatible but, despite this, there will be a hemolytic transfusion reaction. Thus, by providing the important RBC antigens in a homozygous dose, antibody screening cells increase the probability of detection of clinically significant antibodies.

If the antibody screen is negative and the patient has no past history of unexpected antibodies, the presence of an IgG antibody is highly unlikely. It can be predicted that all the ABO-compatible RBC units would then be compatible in an AHG cross-match. ABO and Rh compatible blood can be selected from the stock and issued in less than 10 minutes without carrying out an AHG cross-match (only immediate-spin cross-match is carried out). This is the type and screen method of issuing blood.

On the other hand, if the antibody screen is positive, as will be the case in approximately 1% of patients, the antibody can be identified using a cell panel and antigen negative blood be provided. This would usually take a couple of hours, unless there are multiple antibodies or antibodies against high-frequency antigens.

Performing antibody screening tests before or instead of a cross-match permits early recognition and identification of clinically significant antibodies and makes the decision about immediate-spin cross-match easier. When the recipient has no clinically significant red cell antibodies and no history of such antibodies, it is extremely rare for the AHG cross-match to be incompatible or to detect a clinically significant unexpected antibody. At the same time, pre-cross-match detection of antibodies allows more time to screen for donor units that lack the relevant antigen, facilitating the timely provision of blood for transfusion. The transfusion service may even adopt the computer cross-match eventually.[7] The type and screen method is extremely useful where the chance that the patient will be transfused is low. If the status of the patient changes and transfusion is required, blood can be released by the blood bank within 10–15 minutes. For patients who currently have, or have previously had, a clinically significant antibody, the cross-match method must include AHG testing as well ABO incompatibility testing.

Even though well accepted and practiced in many countries, there has been criticism of the type and screen policy in some countries because of the following reasons:

- Antibodies might be missed if the screening cells have only a single dose or weak expression of the corresponding antigen.
- Antibodies might be missed if the corresponding antigens are not present on the screening cells.
- Some antigens could be present in Asian/Indian populations, while being absent in Caucasians who may be the source of the reagent red cells used for antibody screening. A good example of this would be the Mi(a) antigen.[8]

The type and screen policy was well studied in North America and other countries before being implemented. One study in the US involved a series of more than 32000 recipients,[5] whereas another study in Canada studied close to 10000 recipients.[9]

We carried out this study to test the hypothesis that the type and screen procedure is a safe method for pre-transfusion testing when compared to the AHG cross-match that is currently in use in India. We also wanted to study if the commercially available screening cell panels manufactured using red cells from Caucasian donors are safe for use in India. Another objective was to study the distribution of the different types of alloantibodies in Indian population.

Materials and Methods

The study was carried out in the Transfusion Medicine department of the Max Super Speciality Hospital (A unit of Devki Devi Foundation), Saket, New Delhi. All patients who required blood transfusion were subjected to antibody screening. The antibody screening for patients was carried out by using a 3-cell screening panel (DiaMed™ DiaCell-ID I+II+III). The antibody screening was carried out on the DiaMed® ID System Gel cards.

The DiaMed® ID system utilizes a Sephacryl™ S-200 Gel to capture agglutinates in a semisolid medium. This allows better visualization of agglutination as compared to the traditional tube techniques. For patients with positive antibody screens, antibody identification was performed using the DiaMed® ID-DiaPanel

(11 cells) and, if required, the DiaMed® ID extended-panel (six cells) on the DiaMed® ID-System Gel cards. When specific antibodies were identified, antigen-negative units were selected for the AHG cross-match. It is generally considered more effective to perform an antibody identification test by both AHG and enzyme test procedures to detect weaker antibodies. All patients underwent the AHG cross-match in the DiaMed® ID System Gel cards, even if the antibody screen was negative.

Results

We evaluated data from 45373 patients (from November 2006 to March 2010) for whom a total of 61668 units of packed red blood cells (PRBC) were cross-matched in the Coombs phase. No distinction was made between first-time recipients and multiple-transfused patients. The data is presented in Table 1.

Among the 68 patients who were antibody screen positive, the prevalence of the alloantibodies is shown in Table 2. We could get a clear history of blood transfusion/pregnancy from only 55 of these 68 persons. Out of these 55 subjects, 23 were females with a history of two or more pregnancies and the remaining 32 had received transfusion in the past.

AHG cross-match after antibody screening was negative

The AHG cross-match was carried out in all cases, irrespective of the result of the antibody screen. However, from this study's point of view, the AHG cross-match in antibody-negative units was the most important issue. Table 3 gives the breakup of the PRBCs cross-matched, with all the patients undergoing antibody screening.

AHG cross-match after antibody screening was positive

Out the 68 cases where the antibody screen was positive, the AHG cross-match was incompatible with at least one unit of PRBC in 41 cases. In 22 cases, we were able to find a compatible PRBC unit that was negative for the antigen against which an alloantibody was detected. In 19 cases, the antibody screen was positive, but

we were able to find a compatible unit after cross-matching with 8–10 randomly chosen PRBC units. However, at least one or more unit was found to be incompatible during the cross-match in these 19 cases. In the 9 cases with PAN-positive reactions with screening and identification panel, no compatible unit could be found after AHG cross-match. The AHG cross-match was carried out with 13–15 units of PRBC on an average, but not a single compatible unit could be found.

A total of 363 units were cross-matched in patients whose antibody screen was positive.

Discussion

The rational of pre-transfusion testing has undergone frequent changes over the last 3–4 decades. The type and screen policy is currently practiced as a pre-transfusion procedure in North America and in European countries, but its use and importance is currently a matter of deliberation in many South Asian countries.

Among the most common risks associated with RBC transfusion is the development of RBC alloantibodies. The incidence of RBC alloimmunization is not insignificant, ranging from 1% to as high as 35% in some patient populations.[10,11] However, in our study the rate of alloimmunization was significantly lower at 0.15%.

In the clinical setting, RBC alloimmunization and transfusing RBCs with corresponding antigens can result in delays in patient care, hemolytic transfusion reactions, and hemolytic disease of the fetus and newborn. Examination of the distribution of the different types of alloantibodies showed that the most common antibody was anti-D (32.3%; 22/68) followed by anti-M (13.2%; 9/68). The anti-M was reactive at room temperature in four out of the nine cases. The third most common antibody was anti-C (8.8%; 6/68). This is in contrast to the findings of studies from Western countries, where the frequency of Kell antibodies is quite high.[11,12]

The most important outcome of this study was that not a single case was found where the antibody screen was negative but the AHG cross-match was incompatible. This goes to show that the antibody screening (with the DiaMed® ID-DiaCell I+II+III 3-cell screening panel) picked up all the clinically significant antibodies. In the 45305 cases where the antibody screen was negative, the AHG cross-match was found to be compatible. This further suggests that if in these cases the AHG cross-match had been omitted and the blood issued on the basis of an abbreviated immediate-spin cross-match or an electronic cross-match, there would have been no cross-match

Table 1: Patients undergoing antibody screening

Total number of patients	Antibody screen negative	Antibody screen positive	Prevalence of RBC antibodies
45373	45305	68	0.15%

Table 2: Prevalence of the red cell alloantibodies

Total number of cases where antibody screen was positive	68
Anti-D	22
Anti-M	9
Anti-C	6
Anti-C + Anti-E	3
Anti-D + Anti-C	2
Anti-E	2
Anti-Jk^b	2
Anti-S	2
Anti-Le^a	2
Anti-M + undetermined antibody	2
Anti-c + undetermined antibody	2
Weak/Developing/Undetermined antibody	2
Anti-K	1
Anti-Cw	1
Anti-N	1
DAT-positive/PAN-positive	9

Table 3: PRBCs cross-matched for the 45373 patients

Total number of patients who underwent antibody screen	45373
Patients in whom the antibody screen was negative	45305
Total number of units cross-matched	61668
Number of units cross-matched in patients with positive antibody screen	363
Number of units cross-matched in patients with negative antibody screen	61305
Patients for whom only one unit was cross-matched and reserved	35094
Patients for who more than one unit was cross-matched and reserved	10211
Units where the AHG was incompatible when antibody screen was negative	0

that would have shown incompatibility in the AHG phase *in vitro*.

The DiaMed® ID-DiaCell I+II+III 3-cell screening panel is manufactured in Switzerland and consists of red cells from donors of mainly Caucasian descent. These screening cells detected all the clinically significant antibodies. The fact that there was no case of the AHG cross-match being incompatible after the negative antibody screening suggests that this screening panel is suitable for the Indian population. There are certain antigens that are predominantly found in the Asian population. One such antigen is the Mi I11 phenotype of the Miltenberger subsystem (or GP Mur). It is relatively common in Southeast Asia, especially along the south-east coast of China and Taiwan.[13] There is a possibility that such antigens may also be present in the Indian population. Since the screening cells are made from donors of mainly Caucasian descent, they will be lacking such antigens and in that case the antibodies, if present, will not be picked up during the antibody screening. This may be a hindrance in implementing type and screen in countries such as India. Other studies in this part of the world have used indigenously prepared panels and commercially available panels.[14,15] In this study, with more than 40000 patients, we did not find any case where an antibody was missed due to the use of a non-indigenous cell panel, with a AHG cross-match later demonstrating incompatibility.

The benefits of omitting the conventional AHG cross-match include decreased workload, reduced reagent costs, timely recognition of significant antibodies, and more effective use of blood inventory. Units of blood do not have to be reserved for a particular recipient and thus the turnover of blood components is more efficient. The type and screen policy is also ideal for a blood bank planning to start automation or semi-automation, as batch testing can be done (i.e., antibody screening of all potential recipients can be done at the same time). The technical staff will not have to carry out an AHG cross-match every 10–15 minutes and will therefore have more time to devote to other areas such as donor recruitment and well-being. Eventually, with validated software and checking points, a protocol for computer cross-match could also be established with the confidence gained in the type and screen policy.

Conclusion

This study demonstrated that the type and screen method achieves the expected safety level of 100%. A type and screen policy with an abbreviated immediate-spin cross-match can give the same safety and results as the AHG cross-match.

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