Risk of Hemolytic Transfusion Reactions Following Emergency-Release RBC Transfusion

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Key Words: Transfusion; Emergency release; Hemolytic transfusion reaction

Abstract

Group O RBCs are typically issued for urgent transfusions to avoid ABO-incompatible hemolytic transfusion reactions (HTRs). Identification of other clinically significant alloantibodies requires an antibody detection test, and emergency release (ER) of RBCs before its completion carries a risk of non-ABO alloantibody-mediated HTRs.

We performed a retrospective review of 1,002 ER RBC transfusions involving 265 ER episodes (262 recipients) in a tertiary medical center, 2006-2008, to determine the risk of non-ABO alloantibody-mediated HTRs. A positive antibody detection test was found in 29 (10.9%) of 265 ER episodes, with clinically significant alloantibodies in 17 (6.4%) of 265 ER episodes. Fifteen antigen-incompatible RBC units were transfused to 7 recipients with clinically significant alloantibodies; 1 transfusion was followed by an HTR.

Based on our study, transfusion of ER RBCs before completion of routine blood bank testing carries a low risk of non-ABO alloantibody-mediated HTRs (1/265 [0.4% ER episodes]) and receipt of antigen-incompatible RBCs (7/265 [2.6% ER episodes]).

In patients who urgently require RBC transfusion, it is sometimes necessary to transfuse emergency-release (ER) RBCs before completion of routine blood bank testing. In these cases, group O RBCs are typically issued to avoid a hemolytic transfusion reaction (HTR) due to ABO incompatibility. Detection of alloantibodies to other clinically significant, non-ABO RBC antigens requires performance of an antibody detection test (antibody screen) and, if positive, subsequent antibody identification. Patients who receive ER RBCs before the completion of this testing remain at risk for non-ABO alloantibody-mediated HTRs.

Saverimuttu et al conducted a retrospective study to determine the prevalence of non-ABO alloantibodies in a broad demographic group of 15,966 patients in the trauma, emergency department, hematology-oncology, and antenatal settings to assess the predicted risk of uncrossmatched blood in patients in need of urgent transfusion. In this study population, the prevalence of clinically significant alloantibodies was 1.9%. In patients admitted to the emergency department, the prevalence was 2.2% among all age groups and 0.5% in patients younger than 30 years. Based on their data, the authors estimated that the rate of alloimmunization was likely 0.5% to 4.0% in the majority of patients admitted to the emergency department, resulting in an overall low predicted risk associated with urgent transfusion of uncrossmatched group O blood in this setting. The actual rate of alloimmunization among patients receiving ER RBCs was not examined in this study.

Transfusion of uncrossmatched blood has been well documented in the military setting. Unfortunately, the risk of non-ABO HTRs in this population of predominantly young healthy men cannot be easily applied to the civilian population, which varies widely in age and sex. Multiple published reports
Materials and Methods

A retrospective review of all ER RBC transfusions at Beth Israel Deaconess Medical Center, Boston, MA, a tertiary care center with 621 licensed beds and a level 1 trauma center, was performed during an approximately 2-year period from July 2006 to October 2008. Following institutional review board approval, recipients of transfused ER RBC units were identified through the hospital blood bank computer database. A transfusion was considered an “emergency-release” transfusion if the unit was issued before completion of an ABO type, antibody detection test, and, if applicable, antibody identification, antigen typing of the transfused unit, and/or crossmatch using an in-date sample. An in-date sample was defined as a specimen no more than 3 days old and acceptable for pretransfusion testing.

The requesting department and number and type of RBC units transfused to each recipient were recorded. In our institution, if no in-date blood bank sample is available, group O, Rh− RBCs are issued by ER to all females younger than 50 years. Group O, Rh+ RBCs are issued by ER to all men and women 50 years or older. If a patient has been ABO typed only once in our institution, group O RBCs are issued until the ABO type is confirmed on a second separate specimen. Patients with a known history of an alloantibody in our institution are provided with ER antigen-negative RBCs for evidence of unreported transfusion reactions and/or abnormal hemolytic parameters (elevated lactate dehydrogenase [LDH] and bilirubin levels and decreased haptoglobin level). Clinically significant alloantibodies were defined as those with specificities known to be associated with hemolytic disease of the newborn, hemolytic transfusion reactions, or a decrease in RBC survival, as stated in the American Association of Blood Banks Technical Manual.12 Follow-up time was determined for these recipients and was defined as the number of days from the time of transfusion to the last date hemolytic parameters were measured within the same hospital admission.

At the beginning of the study period, all antibody detection tests were performed with PEG-IAT (PEG, Gamma Biologicals, Houston, TX) and the ImmucorGamma 3-cell screen (Immucor, Norcross, GA) according to standard institutional procedure, with agglutination reactions read macroscopically in tube. The laboratory subsequently switched to solid phase technology (Capture and Galileo, ImmucorGamma, Norcross, GA) using a 2-cell screen for all testing in January 2008.

Results

In total, 1,002 ER RBC transfusions were analyzed during approximately 2 years, representing 2.8% of the total institutional RBC transfusions during that time. The analyzed ER RBCs were issued during 265 ER episodes to 262 recipients. Two recipients received ER RBC transfusions on multiple separate admissions. The majority of the recipients (218 [83.2%]) received 1 to 4 total ER RBC units ■Figure 1. An average of
3.8 units were transfused per recipient (median, 2 units; range, 0-31 units). As expected, the majority (169 [63.8%]) of ER episodes occurred in the department of emergency medicine. The remaining ER episodes occurred in the department of medicine (37 [14.0%]), department of surgery (non-operating room, 22 [8.3%]; operating room, 15 [5.7%]), department of emergency medicine/operating room (11 [4.2%]), department of obstetrics (5 [1.9%]), neonatal intensive care unit (4 [1.5%]), and genitourinary department (2 [0.8%]). The most common indication for ER RBC transfusion was trauma (84 [31.7%]), followed by gastrointestinal bleeding (80 [30.2%]).

The 262 ER recipients included 152 males (58.0%) and 110 females (42.0%), who ranged in age from 0 to 101 years (mean, 58 years; median, 60 years). In total, 93 (35.5%) of 262 recipients had died at the time of this retrospective review. Of all recipients, 52 (19.8%) died within 1 day of receipt of ER RBCs, and 73 (27.9%) died within 1 week.

A positive antibody detection test was found in 29 (10.9%) of 265 ER episodes. In the 29 episodes, ER RBCs were issued owing to a pending antibody detection test/identification in 19 (66%), a pending crossmatch or unit antigen typing in 5 (17%), and no sample in 4 (14%). The remaining ER episode involved a patient who received an initial ER RBC unit owing to no prior sample and subsequent ER units due to pending antibody detection test/identification. Of the 29 ER episodes associated with a positive antibody detection test, clinically significant alloantibodies were ultimately identified in 17 of these cases (6.4% of total ER episodes), with 3 patients having multiple alloantibodies.

Of the 17 recipients with clinically significant alloantibodies present on the current screen, 7 were retrospectively found to have received a total of 15 antigen-incompatible ER RBCs. In 6 of these 7 patients, no hemolytic reactions were reported to the blood bank. Furthermore, no unreported hemolytic reactions were noted on a review of these patients’ charts. However, review was limited in the majority of cases by confounding illness and lack of follow-up and/or measurement of hemolytic parameters. The follow-up time during which hemolysis parameters were monitored ranged from 0 to 9 days (median, 1 day) of

Of the 17 recipients with clinically significant alloantibodies, 11 antibodies (6 anti-D, 4 anti-E, and 1 anti-c) belonged to the Rhesus blood group; 4 anti-K, 4 anti-Jka, 1 anti-Jkb, and 1 anti-Fya. Three recipients had multiple antibodies. Recipients having multiple antibodies included 1 patient with anti-K and anti-E; 1 with anti-Jka and anti-K; and 1 with anti-c, anti-E, and anti-Jka. In addition, 6 warm autoantibodies, 2 clinically insignificant antibodies (anti-M and passive anti-D [RhoGAM]), and 4 inconclusive cases were identified.

In total, a historical ABO and Rh-type and antibody detection test was available in 110 (41.5%) of 265 ER episodes. Five ER episodes involved patients with a current negative antibody detection test who had a history of a clinically significant antibody in our institution. In these recipients, ER RBCs were issued owing to a pending antibody detection test (2 cases), a pending crossmatch or antigen typing (2 cases), and no active sample (1 case). None of these patients received antigen-incompatible ER RBC transfusions.

<table>
<thead>
<tr>
<th>Antibody Detection Test Results</th>
<th>ER Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>29</td>
</tr>
<tr>
<td>Negative</td>
<td>236</td>
</tr>
</tbody>
</table>

**Figure 2** Antibody identification results for emergency-release (ER) episodes. A clinically significant alloantibody was detected in 17 (6.4%) of 265 ER transfusion episodes. Antibody specificities detected were as follows: 11 antibodies (6 anti-D, 4 anti-E, and 1 anti-c) belonged to the Rhesus blood group; 4 anti-K, 4 anti-Jka, 1 anti-Jkb, and 1 anti-Fya. Three recipients had multiple antibodies. Recipients having multiple antibodies included 1 patient with anti-K and anti-E; 1 with anti-Jka and anti-K; and 1 with anti-c, anti-E, and anti-Jka. In addition, 6 warm autoantibodies, 2 clinically insignificant antibodies (anti-M and passive anti-D [RhoGAM]), and 4 inconclusive cases were identified.

**Table 1** Summary of Transfused ER RBCs

<table>
<thead>
<tr>
<th>ER Units</th>
<th>ER Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compatible</td>
<td>987 (98.5)</td>
</tr>
<tr>
<td>Incompatible, no HTR</td>
<td>14 (1.4)</td>
</tr>
<tr>
<td>Incompatible, alloantibody-mediated HTR</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1,002</td>
</tr>
</tbody>
</table>

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the hospital admission (Table 2). In addition, one of the recipients died on hospital day 1. As such, delayed HTRs could not be excluded with certainty.

In the remaining patient, transfusion of 1 incompatible unit was followed by a clinically apparent alloantibody-mediated HTR. In this case, the patient was a 68-year-old man with a group O, Rh D-positive blood type admitted with recurrent gastrointestinal bleeding who had a history of multiple recent RBC transfusions. An antibody detection test performed 4 days before this admission was negative. On arrival at the hospital, he received 1 uncrossmatched group O, Rh D-positive ER RBC transfusion followed by 4 additional (non-ER) RBCs compatible by IgG crossmatch on the day of admission. No acute reactions were reported. The result of the pretransfusion antibody detection test and identification at the time of transfusion of the ER unit was pending, but on completion revealed the presence of anti-c, Jk$, and E. A pretransfusion direct antiglobulin test was positive with both anti-IgG and C3 reagents, and an eluate demonstrated anti-c, anti-E, and anti-Jk$ antibodies. The transfused ER RBC unit was retrospectively found to be c antigen–positive and E antigen–negative. Jk$ antigen typing could not be performed owing to an insufficient sample. Approximately 36 hours following the ER episode, samples for hemolysis parameters were obtained and demonstrated a LDH level of 1,057 U/L (17.7 μkat/L), total bilirubin level of 2.2 mg/dL (37.6 μmol/L), and haptoglobin concentration of less than 20 mg/dL (200 mg/L), up from a baseline LDH level of 110 U/L (1.8 μkat/L) and total bilirubin level of 0.6 mg/dL (10.3 μmol/L) a week before the ER transfusion. Based on the results of the pretransfusion eluate, destruction of incompatible RBCs from transfusions before this admission may have contributed to the observed delayed hemolysis in this patient.

**Discussion**

Urgent transfusion of ER RBCs is necessary and lifesaving for patients with severe hemorrhage or with life-threatening anemia. In these circumstances, the risks of ER transfusion are clearly outweighed by the benefits of rapid restoration of adequate RBC volume. Less often, ER RBCs are requested for patients who do not require a rapid intervention. In these cases, ER RBCs may be requested as a matter of convenience, because of poor understanding of the ramifications of the request, or because of a clinician’s impatience with the time needed for complete blood bank testing. In the latter circumstances, it is helpful to quantify risk to counsel the requesting clinician and avoid unnecessary patient harm. This study aimed to quantify the risk of incompatible RBC transfusion and HTRs following ER RBC transfusion in a diverse patient population admitted to a large tertiary care center. In total, 1,002 ER RBC transfusions involving 265 ER episodes (262 recipients) were evaluated. As expected, ER RBC units were largely used by the department of emergency medicine.

In our study, clinically significant alloantibodies were detected in 6.4% of ER episodes. We found that 1 ER RBC transfusion episode (1/265 [0.4% ER episodes]) was followed by an HTR. However, about 20% of recipients died within 24 hours of transfusion, which included 8 recipients in which an antibody detection test was not completed. Given the number of deaths precluding adequate testing and clinical follow-up, it is possible that the actual number of incompatible ER RBC transfusions and HTRs may have been higher. These data are in contrast with data from multiple studies evaluating the use of uncrossmatched blood in emergency situations, which reported no hemolytic transfusion reactions in cohorts ranging from 49 to 449 patients but lacked details on the results of admission antibody detection tests. In contrast, a 1991 study by Unkle et al of 135 patients who received uncrossmatch blood reported that no patient had an immediate HTR. One patient was noted to have a delayed HTR due to anti-Jk$ within 10 days of transfusion, but this antibody was not detectable on the initial antibody detection test. In addition, the authors reported that 6 patients had antibodies upon admission (4.4%), which included 2 patients with anti-Le$, 1 patient with anti-Sd$, and 3 patients with a positive direct antiglobulin test (no further information given).

**Table 2**

Summary of Data for Recipients of Incompatible ER RBCs

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ER Indication</th>
<th>Patient ABO/Rh</th>
<th>Antibody Specificity</th>
<th>No. of Transfused ER Units</th>
<th>No. Transfused Incompatible Units</th>
<th>Follow-up Time (d)</th>
<th>Observed HTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GI hemorrhage</td>
<td>A/ negative</td>
<td>D</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>GI hemorrhage</td>
<td>O/ positive</td>
<td>K, E</td>
<td>1</td>
<td>1 (E+)</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Postoperative hemorrhage</td>
<td>A/positive</td>
<td>D</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>GI hemorrhage</td>
<td>B/ positive</td>
<td>E</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Hemorrhage due to trauma</td>
<td>A/ negative</td>
<td>D</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>GI hemorrhage</td>
<td>O/ positive</td>
<td>c, E, Jk$</td>
<td>1</td>
<td>1 (c+, Jk$ ?!)</td>
<td>9</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>GI hemorrhage</td>
<td>O/ positive</td>
<td>Jk$</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>No</td>
</tr>
</tbody>
</table>

ER, emergency-release; GI, gastrointestinal; HTR, hemolytic transfusion reaction.
* Follow-up time defined as days from transfusion to last date of measured hemolysis parameters (lactate dehydrogenase, haptoglobin, and bilirubin) for hospital admission.
† Testing for Jk$ antigen not completed owing to insufficient sample.
The higher prevalence of antigen-incompatible transfusions vs clinically apparent HTRs (Table 1) observed in our study raises the possibility that the actual risk of HTRs after receipt of ER RBCs is underestimated. The observed lower incidence of HTRs may be a result of underrecognition of delayed HTRs owing to lack of clinical follow-up and monitoring of hemolysis parameters, early death of recipients precluding clinical follow-up, or difficulty in recognizing clinical symptoms or laboratory signs of HTRs owing to confounding illness.

Our study has several limitations. First, all data were collected retrospectively, and analysis of cases in which patients received antigen-incompatible transfusion was limited by what could be ascertained from clinical notes and laboratory results. A prospective study would allow more careful monitoring of patients for delayed HTRs. In addition, in 8 cases, in-date type and screen results were not available owing to the rapidity of the patients’ deaths, and this may contribute to underestimation of risk. Finally, transfusion and pregnancy history could not be obtained for all recipients. It is well established that prior pregnancy and transfusion confer a higher rate of alloimmunization, and such information would be useful for comparing our patient population with that of other institutions.12

Our study demonstrates that transfusion of ER RBCs before completion of routine blood bank testing carries a low but real risk of receipt of antigen-incompatible RBCs (1.5% of ER units or 2.6% of ER episodes) and non-ABO alloantibody-mediated HTRs (0.1% of ER units or 0.4% ER episodes). This overall risk is low, posing an acceptable risk in the urgent transfusion setting. This information may be valuable to clinicians when weighing the risks and benefits of ER RBC transfusion.

REFERENCES


