

Clinical Outcomes of ABO-Incompatible RBC Transfusions

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Abstract

Factors that predict outcome after ABO-incompatible RBC transfusions are not well defined. We studied whether the volume of incompatible blood transfused would determine the signs and symptoms and survival outcome for ABO-incompatible RBC transfusions. We reviewed ABO-incompatible RBC transfusions from our institutions and our consultations for 35 years and from a survey of America's Blood Centers' members regarding causes, volume, signs, symptoms, and outcomes of ABO-incompatible RBC transfusions in their service areas from 1995 through 2005.

All ABO-incompatible transfusions were due to error; 26 (62%) of 42 occurred at the patient's bedside. Of 36 patients who received more than 50 mL of incompatible blood, 23 (64%) manifested signs or symptoms related to the incompatible transfusion, and 6 (17%) died. Only 3 (25%) of 12 patients who received 50 mL or less of incompatible blood had associated signs or symptoms, and none died. Hypotension, hemoglobinuria, and/or hemoglobinemia were the most frequent findings in survivors and patients who died.

ABO-incompatible RBC transfusion does not inevitably mean death or even occurrence of symptoms. Prompt recognition and discontinuation of the transfusion are critical because transfusing less ABO-incompatible blood may minimize signs and symptoms and may prevent death.

During the past 3 decades, there has been tremendous improvement in blood transfusion safety, largely owing to a decline in infectious hazards.¹ However, blood transfusion still has potential risks of morbidity and mortality. One of the greatest risks to transfusion recipients is from errors leading to transfusion of an incorrect blood component.^{1,2} ABO-incompatible RBC transfusions can be devastating and have accounted for as many as 51% of transfusion-related fatalities reported to the US Food and Drug Administration (FDA).³ Within the last 9 years, this figure has declined to an average of approximately 10% of all transfusion-related deaths (Leslie Holness, MD, FDA, written communication, October 21, 2005). Other data indicate that ABO-incompatible RBC transfusions occur in an estimated 1:38,000 to 1:100,000 transfusions and that the risk of receiving such an incompatible blood component and consequently dying is 1:1.5 million to 1:2 million.^{4,5}

The decline in the relative percentage of deaths associated with ABO-incompatible RBC transfusions has followed implementation of numerous safety measures such as barcode devices for patient and blood sample identification and procedures to verify the ABO type of the patient. However, despite these efforts, ABO-incompatible transfusions still occur. Efforts must continue to be made to identify the errors leading to ABO-incompatible transfusions in order to improve transfusion processes and safety. In the United Kingdom, the Serious Hazards of Transfusion scheme was established in 1996 as a confidential system for reporting adverse patient events associated with transfusion (it is not limited to deaths). This system has built an evidence base of transfusion risks that has been used to improve patient safety by informing policy decisions, improving standards of hospital transfusion

practice, supporting production of clinical guidelines, and educating clinical users of blood.⁶

In the United States, transfusion-related deaths must be reported to the FDA. However, the transfusion has to be recognized as “related” to the fatality (may be claimed not to be for various reasons, eg, possible lawsuit). Reporting of serious but nonfatal events and so-called near misses is not required but is encouraged through the FDA’s Adverse Event Reporting System.⁷ Determination of what constitutes a transfusion-related death is not always straightforward, particularly in seriously ill or anesthetized patients who receive an ABO-incompatible transfusion. The signs and symptoms of a hemolytic transfusion reaction may overlap with those of a patient’s underlying condition or may not be apparent owing to anesthesia. Determination of the clinical consequences of ABO-incompatible transfusions is further complicated by the fact that patients who have received ABO-incompatible blood do not always manifest overt signs and symptoms, nor is the hemolytic reaction uniformly fatal.

We sought to highlight the types of errors that lead to ABO-incompatible transfusions and the clinical sequelae of these by using case reports and a survey of America’s Blood Centers (ABC). We sought to verify whether the volume of incompatible blood would determine, or predict, the signs, symptoms, and survival outcome for ABO-incompatible RBC transfusions. A study by Binder et al⁸ found that there were no deaths in patients who received less than 50 mL of incompatible blood. In another report by Glasser,⁹ patients who received less than 80 mL of incompatible RBCs survived and manifested minimal signs and symptoms compared with patients who received a larger volume of incompatible blood, most of whom had symptoms and 50% died.

Materials and Methods

We performed a retrospective review of ABO-incompatible RBC transfusions from our institutions during the past 35 years, from our consultations, and from a survey of ABC members. The following information was obtained from the survey: (1) the number of ABO-incompatible RBC transfusions that occurred from 1995 through 2000 in the hospitals each center serviced, and (2) the volume of RBCs transfused, patient signs or symptoms of hemolysis (disseminated intravascular coagulopathy [DIC], renal failure, and/or shock), patient outcome, and cause of the ABO-incompatible RBC transfusion. For statistical comparisons, a 2-sample test of proportion was done using Stata software (StataCorp, College Station, TX).

We also sought information from the FDA on the number and causes of transfusion-related deaths reported from 1995 through 2006. In addition to the data on transfusion-related

deaths, we received information on “near-miss” (“near-hit,” actually) events reported to the FDA from 2001 through 2005.

Results

Case Reports

Case 1

A 60-year-old man with blood type O and coronary artery disease received 4 U of packed RBCs following laceration of the left ventricle during a third cardiac bypass surgery. The laceration was repaired; however, persistent hypotension, uncontrolled bleeding, a drop in hematocrit, and hemoglobinuria developed when the patient was being weaned from cardiac bypass. Renal failure and DIC ensued, and the patient died. Investigation revealed that 3 of the 4 RBC units, which were taken from an operating room blood refrigerator, were blood type A, intended (and labeled) for another patient with a similar name.

Case 2

A 36-year-old woman with blood type O, a trauma victim with hemoperitoneum, received 7 U of packed RBCs in the operating room. During infusion of the seventh unit, the patient became hypotensive; despite this, the transfusion was completed. Investigation revealed that 6 of the 7 units were blood type O but the seventh unit was blood type A and labeled for another patient. The patient did well with no further sequelae.

Case 3

A 53-year-old woman with blood type O and a history of autoimmune hepatitis, diabetes mellitus, systemic lupus erythematosus, and Sjögren syndrome was admitted because of congestive heart failure. Two units of packed RBCs were ordered for anemia (hemoglobin level, 7.9 g/dL [79 g/L]). Following administration of the first 40 to 50 mL of blood, the patient complained of severe back pain, which decreased when the transfusion was stopped. The transfusion was resumed, however, and all 360 mL was infused. After transfusion of this unit, the patient had decreased urine output, urine described as “tea color,” an increase in systolic blood pressure, and a temperature of 38.9°C. Nevertheless, a second unit of packed RBCs was transfused. Near the end of the second transfusion, it was found that both of the transfused units were of the wrong type (type A). The patient died 5 days later.

Case 4

An 81-year-old man with blood type A and a history of cirrhosis received 1 U of type B packed RBCs while undergoing

aortic valve replacement and triple coronary artery bypass surgery. The postoperative course was complicated by bleeding from the chest tube, aortotomy incision, and bleeding esophageal varices. He received several more transfusions of compatible blood, but died 12 days after the initial cardiac surgery. His death was attributed to aortic valve disease, gastrointestinal bleeding, and terminal hepatitis.

Case 5

An 80-year-old man with blood type O received multiple units of packed RBCs during surgery to repair a bleeding gastric ulcer. Hemoglobinuria and hemoglobinemia subsequently developed; the latter was still present in a blood sample drawn 6 hours later. He died perioperatively secondary to shock. The blood type of the transfused components could not be confirmed owing to missing paperwork. However, the eluate of a posttransfusion blood sample contained anti-A, verifying that he had received type A blood.

Case 6

A 78-year-old man with blood type O and anemia received 1 U of type B packed RBCs intended for another patient on the same ward with an identical surname. The patient developed no symptoms and no complications. His anti-B titer was very low, and type B RBCs were present for days in his circulation.

Case 7

A 65-year-old man with blood type O received 2 U of type A packed RBCs following cardiac bypass surgery. Hemoglobinuria, marked hemoglobinemia, and renal failure developed. Investigation revealed that the 2 U of packed RBCs were intended for another patient with the same surname (but slightly different spelling) who was also in the surgical intensive care unit. The patient did well following 2.5 weeks of renal dialysis.

Case 8

A 32-year-old man with blood type O, a trauma victim, developed unexplained hypotension at the end of surgery. The patient was found to have received two thirds of a unit of type A blood, which was intended for another surgical patient. Hemoglobinemia was present immediately after the transfusion but resolved within 6 hours. The patient had no apparent complications. Despite his young age, his anti-A titer was low and anti-A was absent in the posttransfusion specimen. Type A RBCs survived for days in his circulation.

ABC Survey Results

Of 77 ABC blood centers, 18 responded to our survey. Ten were unaware of any ABO incompatible RBC transfusions in hospitals that they served. The remaining 8 centers

reported a total of 42 ABO-incompatible RBC transfusions administered to 40 patients owing to a variety of errors. Bedside errors, including clerical errors and absent or incorrect verification of patient identification, were most frequent (26/42 errors [62%]) followed by analytic (laboratory) errors, ie, wrong sample tested or wrong blood issued (12/42 [29%]), followed by preanalytic errors in sample collection or labeling (4/42 [10%]).

Combined data from the ABC survey and our 8 cases comparing volume of incompatible RBC transfusions with outcome and symptoms are provided in **Table 1**. Of the 36 patients who received more than 50 mL of incompatible blood, 64% (23/36) manifested signs or symptoms related to the incompatible transfusion, and 17% (6/36) died. In contrast, only 25% (3/12) of the patients who received 50 mL or less of incompatible blood had associated signs or symptoms, and none died. The frequency of signs and symptoms was statistically higher in the patients who received more than 50 mL compared with patients who received 50 mL or less of incompatible blood ($P = .02$; t test). The patients who received more than 50 mL of incompatible blood were also more likely to die, although this did not reach statistical significance ($P = .13$; t test). Signs or symptoms in survivors and patients who died included the following (in descending order of frequency): acute hemolytic transfusion reaction (mild to moderate hypotension, hemoglobinuria, and/or hemoglobinemia), decline in renal function or renal failure, and shock. DIC occurred only in patients who died but was the least frequent of the signs and symptoms observed.

FDA Data

Figure 1 shows the percentage of transfusion-related deaths from ABO hemolytic reactions for the 1995-2006 period reported to the FDA. There is a progressive decline in the percentage of reported deaths due to ABO-incompatible transfusions. This decline in percentage was paralleled by a decline in the absolute number of transfusion-related deaths due to ABO-incompatible RBC transfusions from 15 in 1996 to 3 in 2006.

Table 1
Volume of ABO-Incompatible RBCs Transfused vs Outcome and Symptoms for 48 Patients

	≤50 mL	>50 mL
No. of patients	12	36
Survived	12	30
Died	0	6
No. of patients without signs or symptoms	9	13
No. of patients with signs or symptoms	3	23
Acute hemolytic transfusion reaction	3	16
Renal failure	0	10
Shock	1	3
Disseminated intravascular coagulopathy	0	3

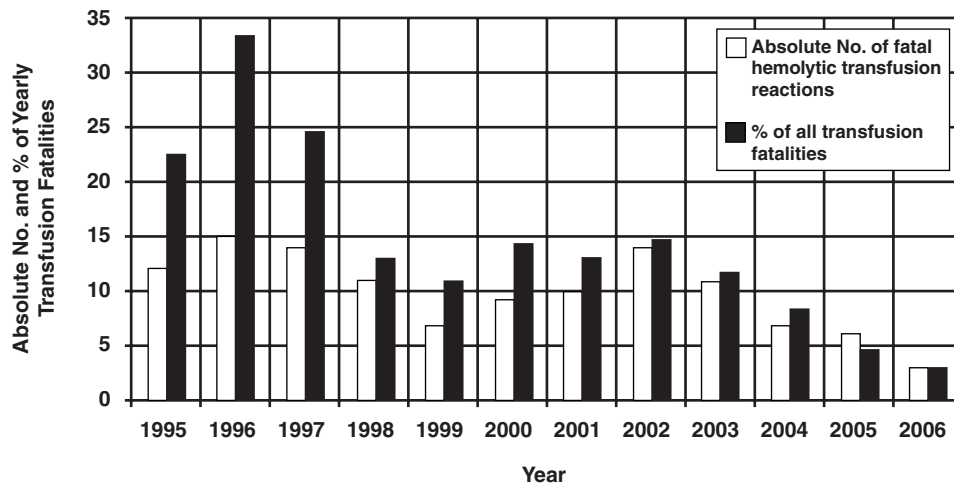


Figure 1 Percentages and absolute numbers of transfusion-related deaths from ABO hemolytic reactions, 1995-2006, reported to the US Food and Drug Administration.

Figure 2 shows the number of near-hit transfusion events and their causes reported to the FDA during the 2001-2005 period. These near-hit events represent serious but non-fatal transfusion errors leading to the issuing of an incorrect blood component; however, it is not known whether the unit was transfused. The most frequent types of errors that did not (apparently) result in an ABO-incompatible transfusion are summarized in Figure 2. Labeling errors were most frequent, followed by selection of an incorrect blood component (as can occur in operating room refrigerators containing blood for more than 1 patient).

Discussion

Mistransfusion of blood remains a serious hazard of transfusion worldwide,¹⁰ occurring at an estimated rate of 1:13,000 to 1:19,000 units according to passive reporting systems.^{1,11} The vast majority of mistransfusions occur as a result of potentially avoidable system failures throughout the transfusion chain.⁶

The most frequent error leading to transfusion of ABO-incompatible blood is failure of the final patient identification check at the bedside, leading to transfusion of properly labeled blood to a recipient other than the one intended.^{4,6,10,12} In a recent report from Ireland's hemovigilance system, more than half of all adverse reactions to blood transfusion were caused by the patient being given the wrong blood component.¹³ The relative distribution of errors in our cases and survey results are similar to those in other reports, with failures in pretransfusion verification of patient identification comprising a majority of all errors, followed by laboratory errors, and errors in sample collection and labeling. Although laboratory errors were higher than those reported by Honig and Bove,¹⁴ increased

awareness of the necessity to detect and report any errors that could potentially result in an ABO-incompatible transfusion may, in part, account for the higher figure.

Signs and symptoms associated with ABO-incompatible transfusions generally include fever, back pain, hemoglobinuria, hemoglobinemia, renal failure, DIC, hypotension, and shock. However, in anesthetized patients, the only change may be in vital signs or diffuse, unexplained bleeding. We found that symptoms related to acute hemolysis (mild to moderate hypotension, hemoglobinuria, and/or hemoglobinemia) were most frequent, followed by a decline in renal function or renal

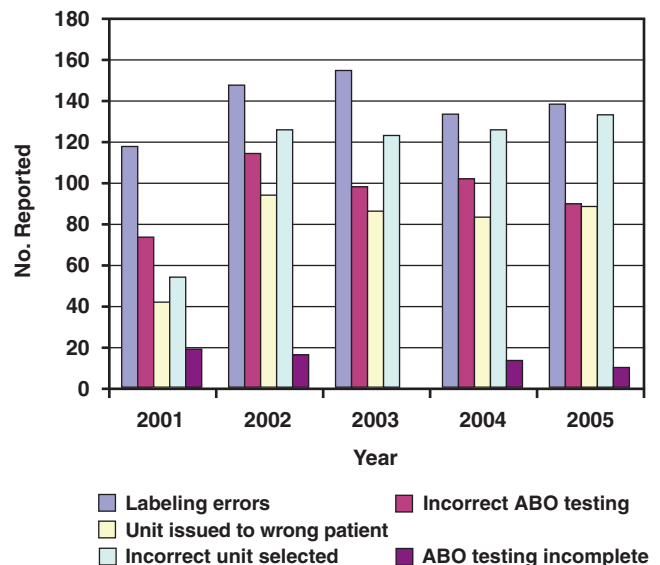


Figure 2 Number of "near hit" transfusion events and their causes reported to the US Food and Drug Administration, 2001-2005. In all cases, a unit was issued, but whether the unit was transfused is not known.

failure and shock. DIC was the least frequent manifestation, but it only occurred in patients who died.

Signs and symptoms of ABO incompatibility are not always detected or noticed. In nearly half of the cases we reported, there were no associated signs or symptoms noted with the ABO-incompatible transfusion. Awareness of error detection methods may help identify the cases that otherwise would have been undetected because patients were free of symptoms. Furthermore, signs and symptoms can be nonspecific, especially in patients with coexisting morbidities. Postoperative bleeding, hypotension, and even DIC in a post-surgical patient, for example, could be attributed to complications of surgery and blood loss rather than to a hemolytic transfusion reaction, unless the index of suspicion is high enough to warrant a thorough investigation and transfusion reaction workup.

The outcome of ABO-incompatible transfusions is often not fatal. Linden et al⁴ reported that death occurred in only 5.5% of cases. In our study, 14% of cases were fatal. In the study by Glasser,⁹ the death rate was as high as 30%. Our results are thus within the range of other reported series. Coexisting morbidities may affect the outcome. For example, in our 8 case reports, 4 of 5 patients with significant coexisting morbidities died vs 0 of 3 without serious coexisting morbidities.

We also studied whether the volume of ABO-incompatible blood transfused determined outcome and the presence of signs and symptoms. We found that patients who received more than 50 mL of ABO-incompatible blood were more likely to manifest signs or symptoms of a transfusion reaction and that deaths only occurred in patients who received more than 50 mL of incompatible blood, although this finding did not reach statistical significance. We speculate that additional clinical factors such as the rate of infusion, patient age, comorbid conditions, and isoagglutinin titer, as well as rapidity of appropriate treatment, may affect signs, symptoms, and outcome, although our study was not designed to specifically evaluate these factors.

Fortunately, reported deaths due to ABO-incompatible RBC transfusions have declined in recent years in the United States. The decline is likely multifactorial, reflecting a true decline in the incidence of ABO-incompatible transfusions and a relative increase in the incidence or reporting of other transfusion-associated deaths plus prompt recognition and treatment of hemolytic reactions. Awareness of staff at the bedside and laboratory of the potential for errors is one of the most effective tools for detecting and preventing transfusion errors. Taswell et al¹⁵ used a quality control exercise in which deliberate errors on fictitious patients were introduced to test the proficiency of clerical, nursing, and laboratory personnel. During a 15-month period, there was a decrease in the introduced errors missed from 13% to 7.7% and an increase in the number of true errors detected.¹⁵

With an increased awareness of the root causes of transfusion errors, hospitals have taken steps to address them, such as requiring 2 pretransfusion samples to confirm a patient's initial ABO blood type result (independent of the American Association of Blood Banks standard requiring 2 determinations of the recipient's ABO type if using computer cross-matching). In theory, requiring a second sample to confirm the ABO blood type could significantly reduce ABO-incompatible transfusion because the vast majority of errors are due to sample collection and labeling and bedside errors.

A reduction in the use of stationary refrigerators in the operating room is reported to have reduced some transfusion errors.¹⁶ Some hospitals dispense only type O RBCs for bleeding patients in the emergency department. It is, however, difficult to assess the true success of measures introduced to reduce errors because near-hit events and cases in which the patient survives an ABO-incompatible transfusion may not be reported. Various devices have also been introduced to minimize errors in sample collection and transfusion to the intended recipient and have prevented some errors. These are summarized in a recent review.¹⁷ However, it is difficult to know whether actual use of these devices is widespread and their effectiveness in preventing ABO-incompatible transfusions.

Quality improvement dictates that analysis of adverse sentinel events such as ABO-incompatible transfusions be performed. When such an event has been identified, corrective measures should be instituted to prevent recurrences. In our case 5, operating room personnel had not signed transfusion records to ensure that the patient and blood component identifications matched. It became hospital policy that 2 people follow this protocol in all cases of transfusion of blood components. In case 6, in which 2 patients had the same surname, the subsequent policy was for blood bank personnel to attach name alerts to such cases; if the patients were on the same ward, the manager was notified. In case 7, all identification had been removed from the patient. Subsequently, a policy requiring patients to have an arm band and an ankle band was instituted. In case 8, a completely unrelated blood unit was taken from the common operating room blood refrigerator and transfused. The common operating room refrigerator was removed, and portable refrigerators for use in a single operating room were acquired and used.

If an ABO-incompatible transfusion occurs or is suspected, the transfusion should be stopped immediately, the venous line should be kept open with normal saline, and supportive care administered as needed. Transfusing fewer ABO-incompatible RBCs may minimize signs and symptoms and possibly prevent death. Therefore, close surveillance of the patient's vital signs for the first 30 minutes of transfusion should help identify most incompatible transfusions early. In an audit in the United Kingdom, 34% of the transfusions were not monitored during the first 30 minutes, and, in 15% of the

total cases studied, no record was made of the vital signs during the transfusion.¹⁸

Treatment may include intravenous fluids to combat hypotension and shock, diuresis to promote urine output and improve renal blood flow (eg, with furosemide), and vasopressive medication.¹⁹ The use of heparin has been suggested by some to combat DIC; however, this practice remains controversial.^{19,20} Vital signs and urine output should be closely monitored. Management of respiratory distress includes oxygen administration, and, if necessary, intubation and mechanical ventilation.¹⁹ The correct identity of the patient and the blood product should be verified and the blood bank alerted to the possibility of a hemolytic transfusion reaction. Until the patient's blood type is verified, type O RBCs should be given to patients still needing a transfusion. In our survey, we did not ask about therapeutic interventions, so we do not know what role these may have had in reducing morbidity and mortality of ABO-incompatible RBC transfusions.

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