

Safety of Uncrossmatched ABO-Compatible RBCs in Alloimmunized Patients with Bleeding: Data from Two Decades: Results of a Systematic Analysis in 6,109 Patients

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Keywords

Blood transfusion · Uncrossmatched · Trauma · Incompatibility · Hemorrhage

Abstract

Introduction: Uncrossmatched ABO-compatible red blood cells (RBCs) are generally recommended in patients with life-threatening massive bleeding. There is little data regarding RBC transfusion when patients are transfused against clinically significant alloantibodies because compatible RBCs are not immediately available. **Methods/Patients:** All patients reviewed in this study ($n = 6,109$) required emergency blood transfusion and were treated at the Charité – Universitätsmedizin Berlin between 2001 and 2015. Primary uncrossmatched O Rh(D)-positive or -negative RBC units were immediately transfused prior to complete regulatory serological testing including determination of ABO group, Rhesus antigens, antibody screening, and crossmatching. **Results:** Without any significant change in the protocol of emergency transfusion of RBCs, a total of 63,373 RBC units were transfused in 6,109 patients. Antibody screening was positive in 413 patients (6.8%), and 19 of these patients received RBC units against clinically significant alloantibodies. None of these patients appeared to have developed significant hemolysis, and only one patient with anti-D seems to have de-

veloped signs of insignificant hemolysis following the transfusion of three Rh(D)-positive units. One patient who had anti-Jk^a received unselected units and did not develop a hemolytic transfusion reaction. **Conclusion:** Transfusion of uncrossmatched ABO-compatible RBCs against alloantibodies is highly safe in patients with life-threatening hemorrhage.

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Introduction

The clinical significance of antibodies to red blood cells (RBCs) is reflected by the fact that the transfusion of correspondingly antigen-positive cells may result in severe hemolytic transfusion reaction (HTR) and even death [1–4]. Prior to the discovery of ABO blood groups by Landsteiner in 1900, blood transfusion was associated with acute HTR and mortality in 50% of transfused patients. On this, experiences in this field remained largely negligible for roughly one century following the first successfully performed direct blood transfusion in 1819 [5]. During the world wars and until the introduction of separated RBC concentrates in the sixties, acute HTRs were observed in many cases due to the isoagglutinins anti-A and/or anti-B in the used whole blood. Today, acute HTRs and related mortality are relatively rare (1:76,000 and 1:1.8

millions, respectively) and the incidence of delayed HTRs is $\leq 1:60,000$ [5]. To avoid HTRs, serological investigations including estimation of at least ABO blood group and Rhesus(D) antigen, antibody screening test, and cross-matching prior to RBC transfusions are recommended worldwide, even in countries with limited resources. The most relevant alloantibodies which may cause HTRs are directed against Rhesus, Kell, Kidd, Duffy, and less commonly against some other antigens [1, 2, 6]. In some instances, the clinical relevance of alloantibodies may remain unclear, and several tests have been described to characterize the clinical significance of such antibodies. These include the chromium-51 (^{51}Cr) and biotin label RBC survival assays [7, 8], phagocytosis of presensitized RBCs by monocytes, the antibody-dependent cellular cytotoxicity [9], and the so-called biological compatibility testing [10]. The gold standard for predicting the clinical significance of alloantibodies remains, however, the 1-h ^{51}Cr -labeled RBC survival of transfused cells as recommended by the International Committee for Standardization in Hematology [11]. Whatever the method used may be, the occurrence and significance of HTR cannot invariably be determined. The response to transfusion of incompatible RBCs is dependent on several factors including antibody concentration and class, capacity, and state of recipient's macrophages, complement activation, amount of transfused RBCs, and most importantly, as we think, whether the transfused cells remain in the circulation of affected patients or will be lost due to the uncontrolled hemorrhage. Though the latter point plays a key role in case of massive blood loss and blood transfusion, it has not yet been considerably evaluated. The vast majority, if not all, of recommendations stress the holding rather than transfusion of incompatible RBCs, even in emergency cases and life-threatening blood loss [12–17]. Based on our experience, detectable alloantibodies should not represent a contraindication in patients with massive bleeding as long as bleeding has not been stopped. In this study, we present the data of a large patient cohort and discuss relevant literature publications.

Patients and Methods

All patients presented here had massive bleeding and urgently required (massive) blood transfusion consisting of uncross-matched ABO-compatible RBCs and other blood products (Table 1). Blood collection, testing, and support was organized by the main staff of the local blood bank, and all the patients were treated at the same local university hospital (Charité – Universitätsmedizin Berlin, Germany). Blood group typing, antibody screening, and crossmatching were done by standard serological methods as described [18].

The protocol regarding support and transfusion is largely in agreement with national and international guidelines. When blood transfusion is required in emergencies, at least 4 of ten already

packed RBC units of blood group 0 will be immediately delivered and, if necessary, as soon as possible transfused independent of serological findings. While all females and if possible young males with ages ≤ 45 years receive initially Rh(D)-negative units, all other patients receive Rh(D)-positive units unless the blood group of affected patients is known or has been estimated. If patient's plasma contains alloantibodies these antibodies will be considered as soon as possible, but only if antigen-negative RBC units are available. In cases with massive hemorrhage, alloantibodies did not present an absolute contraindication for incompatible blood transfusion if antigen-negative RBC units are not available and as long as bleeding has not been stopped.

The retrospective data analysis was approved by the Institutional Ethical Board and the Institutional Data Protection Board.

Results

Between 2001 and 2015 a total of 6,109 injured patients received 63,373 uncrossmatched ABO-compatible RBC units. There was no clinical evidence for the occurrence of any severe acute or delayed HTR due to alloantibodies following transfusion. Antibody screening test was found to be positive in 413 patients (6.8%). Incompatible blood transfusion could be avoided in 394 patients by the replacement of the initially supplied units by new units lacking the corresponding antigens to the detected antibodies. The remaining 19 patients were transfused with serologically incompatible RBCs (antigens have been detected post transfusion) (Table 1). In 2001, 2003, 2004, 2008, 2013, and 2014 none of the transfused units was incompatible. In the other years incompatibility was related to alloantibodies which are known to cause HTR (Table 1). Only one of these patients (No. 8) who received three incompatible Rh(D)-positive units appeared to have developed an insignificant HTR, since total bilirubin was found to have been moderately increased (2.2 mg/dL, normal range is below 1 mg/dL) and haptoglobin was less than 4 mg/dL (normal range 30–200 mg/dL). The remaining 4 patients received blood transfusion against alloantibodies which usually do not cause HTR (patient Nos. 3, 4, 5, 18).

In addition, one patient (Table 1, No. 7) intentionally received Jk^a-incompatible RBC units because no Jk^a-negative units were available for him. It remained unknown how many incompatible units were transfused.

In summary, none of the 19 patients who received incompatible units has developed clinically significant acute or delayed HTR.

Discussion

The results obtained here reflect largely those of daily practice in most centers dealing with trauma patients and massive blood transfusion of uncrossmatched RBC units. Trauma is a leading cause of death worldwide and the vast

Table 1. Incompatible RBCs transfused at the Charité – Universitätsmedizin Berlin between 2001 and 2015

Year	Patient	Age, years	Gender	Antibodies	All transfused units, <i>N</i>	Incompatible transfused units, <i>N</i>	HTR	Reason for massive bleeding
2002	1	45	M	D	10	2	No	Unknown
	2	66	F	K, Wr ^a	2	2	No	Unknown
2005	3	58	F	Kn	2	2	No	Cholecystectomy
2006	4	65	M	M	4	10	No	Pancreatic tail resection
	5	72	M	Le ^a	4	1	No	Partial bypass rupture
	6	52	M	D	10	2	No	Liver cirrhosis
2007	7	57	F	Jk ^a	14	Unknown*	No	Retransplantation of liver
	8	49	F	D	6	3	Delayed and mild	Uterus myomatosis
2009	9	67	M	D	12	6	No	Gastrointestinal bleeding
	10	78	F	C, D	30	5 CD, 3 D	No	Heart and kidney failure
	11	50	M	Fy ^a	4	1	No	Infected arterial port
	12	48	F	D	10	1	No	Thermal ablation
	13	43	M	Jk ^a	10	1	No	Polytrauma
2010	14	67	F	E	12	8	No	Small bowel resection
	15	48	F	Jk ^a	31	5	No	Hemipelvectomy
2011	16	49	F	Jk ^a	20	20	No	Ileocecal resection
	17	56	M	Lu ^a	40	2	No	Ileocecal resection
2012	18	56	M	Kn	2	2	No	Pleural empyema
2015	19	40	M	D	10	1	No	Aortic valve replacement

HTR, hemolytic transfusion reaction. * The number of units are unknown; however, the frequency of Jk^a is 0.5. Therefore, statistically, at least some of the 14 transfused units should have been Jk^a-positive.

majority of patients with massive bleeding may die within a few hours without resuscitation with blood products [19–23]. Thus, the immediate supply of blood plays a key role in the management of such affected patients, as most hemorrhagic deaths occur within 3–6 h of patients' arrivals [24–26]. Pretransfusion compatibility testing of RBCs is obligatory to prevent HTRs. However, this procedure including ABO and at least Rh(D) typing, screening for alloantibodies, identification of the specificity of unexpected antibodies that are detected, and compatibility testing between recipient and donor RBCs, may require more than 50 min [27]. Meanwhile, many protocols and recommendations are available to avoid any delay in supporting transfusion of RBCs in emergency cases. Without exception all available protocols recommend the use of uncrossmatched RBCs, at least, until serological testing has been completed. The incidence of alloantibodies is low and the occurrence of severe HTR due to alloantibodies is largely negligible [28–34].

In the presented study alloantibodies were detected in 6.8% ($n = 413$), and 19 of these patients received incompatible RBCs. Only one of the 19 alloimmunized patients seems to have developed a delayed HTR. This patient received three Rh(D)-incompatible RBC units. Based on a detailed clinical observation, there was no evidence for a

significant HTR, i.e., hemoglobinuria or instability of patients' conditions which might be related to HTR. The question whether the documented laboratory parameters total bilirubin and haptoglobin may in fact be related to a mild HTR or rather to the underlying disease (surgery of uterus myomatosis) remains unclear. However, it must be emphasized that the interpretation of laboratory data in such emergency cases with massive bleeding are very difficult due to the following facts: (1) these patients usually receive different and large amounts of infusions leading to a dilution effect on many laboratory parameters, (2) many laboratory parameters are frequently estimated as long as patients' conditions are instable. These parameters usually reflect oxygenation, hemostasis, and coagulation. Specific laboratory parameters related to hemolysis will be investigated only in patients who are suspected to have hemolysis, i.e., hemoglobinuria, and circulatory instability due to transfusion.

The conclusion that the other patients did not appear to have developed hemolysis is based on the fact that treating physicians did not report HTR in a single patient, even in patient No. 8. The report of all transfusion reactions is obligatory according to the transfusion guidelines. From a clinical view, there was no evidence for the development

Table 2. Incompatible RBC transfusions described in the literature

Study (references)	Transfused patients with untested RBCs, <i>N</i>	Incompatible transfused patients, <i>N</i>	HTR
Schmidt et al., 1988 [35]	418	1 (anti-c) 1 (anti-Er ^a)	No No
Unkle et al., 1991 [36]	135	1 (anti-Jk ^b) 2 (anti-Le ^a) 1 (anti-Sd ^a) 3 (unknown)	Delayed and mild No No No
Meny, 2004 [37]	2	1 (anti-D) 1 (anti-Fy ^a , -S, -Le ^b)	Yes Yes
Murthi et al., 2008 [38]	1	1 (anti-Jk ^a)	Yes
Goodell et al., 2010 [39]	265	3 (anti-D) 1 (anti-Jk ^b) 1 (anti-K, anti-E) 1 (anti-E) 1 (anti-c, anti-E, anti-Jk ^a)	No No No No Yes
Mulay et al., 2013 [34]	1,444	7 (unknown)	No
Fiorellino et al., 2018 [40]	1	1 (anti-Fy ^a and anti-K)	Yes

of HTR or any relationship between transfusion and outcome. Ultimately, our results are confirmed by several previous reports (Table 2) [34–40]. Only a few of the latter patients have developed HTR. Unfortunately, it remains unknown whether these patients had massive bleeding during the incompatible transfusion.

There are three possible explanations for the finding that incompatible RBC transfusion may not result in significant HTR: (1) at least one part of the transfused incompatible RBCs will be lost due to the ongoing bleeding, (2) the concentration of alloantibodies may decrease by blood loss per se, and by capturing from the circulation by the transfused incompatible RBCs, which also disappear from the circulation, and (3) the immune system might somewhat be paralyzed by the trauma and/or hemorrhagic shock. Ultimately, several inflammatory cells and cytokines are involved in hemorrhagic shock [41, 42]. The phenomenon that incompatible RBC transfusion may not result in significant HTR, independent from minor incompatibilities due to the isoagglutinins anti-A and anti-B, could often be observed after whole blood transfusions in military settings [43–47]. In addition, only a few incompatible RBC transfusion in the presence of alloantibodies have yet been reported. In case of massive transfusion, only six of the previously published patients who received incompatible RBCs developed HTR (Table 2).

All these findings and the results of our study indicate that the presence of alloantibodies to RBCs should not result in any delay of supplying and/or transfusion of incompatible RBCs, in case of life-threatening bleeding.

However, this statement should remain an exception rather than a general recommendation in transfusion medicine to avoid risk of complications. In addition, further reports dealing with incompatible RBCs in multiple-injured patients will be helpful in the management of such affected patients.

Statement of Ethics

All research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The retrospective data analysis was approved by the Institutional Ethical Board and the Institutional Data Protection Board.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.R.: literature search, study design, data collection, data analysis, data interpretation, writing, critical revision. H.S.: data analysis, data interpretation, critical revision. S.E.B.: data collection. C.S.: critical revision. J.S.: critical revision. A.S.: literature search, study design, data interpretation, writing, critical revision.

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