Unmatched Type O RhD+ Red Blood Cells in Multiple Injured Patients

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Keywords

Non-cross-matched transfusions · Type O RhD+ supply ·
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Summary

Background: Immediate supply of red blood cell (RBC) concentrates is crucial in the initial treatment of exsanguinating patients in the emergency room. General shortage of RhD– RBCs has led to protocols in which patients with unknown blood groups are initially transfused with group O, RhD+ RBCs. Limited data are available regarding the safety of such an approach. **Methods:** Transfusion protocols for all multiple injured patients from the regional polytrauma database were retrospectively analyzed over a period of 5 years. Data on side effects were retrieved from the local safety update registry. Follow-up data were obtained from patients with identified RhD-incompatible transfusions. **Results:** In total, 823 patients were registered as multiple injured in the database. An immediate transfusion of 259 units (mean number of units 4, range 1–6) group O, RhD+ RBCs was initiated in 62 of them. 14 of these patients were RhD– and received 60 units of RhD-incompatible RBCs in the emergency room. In the later course RhD– patients received additional 185 incompatible transfusions (13; 1–31). The overall seroconversion rate was 50%. No adverse outcome due to incompatible transfusion was observed. **Conclusions:** Initial supply with group O, RhD+ RBCs in multiple injured patients appears to be safe. Significant numbers of RhD– units can be saved for use in other patients.

Introduction

Immediate supply with red blood cells (RBCs) is a mainstay of the initial treatment of multiple injured patients with hemorrhagic shock [1, 2]. Trauma centers are requested to ensure timely and sufficient blood supply, without significant delays. In many hospitals, distance between blood bank and emergency room (ER) precludes an initial, direct supply of ER patients from the main hospital stock [3]. Marburg University Hospital holds a sealed blood product container in a certified blood fridge in the ER in which, according to the established local protocol, 6 units of group O, RhD+ RBCs, 2,000 IU prothrombin complex concentrate and 2 g of fibrinogen are available for initiating the massive transfusion protocol (MTP). A clinical scoring system (Emergency Transfusion Score) is used to identify multiple injured patients who require MTP. Patient blood samples are taken before initiating the emergency transfusion, and regular blood group serology is performed on these samples. The decision to provide RhD+ (instead of RhD–) RBCs in the ER was initially based on the fact that 85% of all patients are expected to be RhD+; and 66% are expected to be male [4, 5], indicating that the majority of multiple injured patients is at low risk for RhD immunization and/or long-term effects associated with such an immunization (e.g., pregnancy). In addition, based on historical data, it was calculated that less than 50% of ER patients require immediate transfusions and that the additional safety which comes with a RhD– strategy would result in approximately 50 unnecessary RhD– transfusions (to RhD+ recipients) per year.

This approach is supported by data from the US demonstrating that blood supply with non-cross-matched units of RBCs is safe in trauma patients [6–12]. Transfusion with RhD+ RBCs does not increase the rate of hemolytic transfusion reactions disproportionately

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Table 1. Demographics of patients dependent on transfusion need after admission

	Total	Transfusion in ER (first D+ RBCU via box)	Transfusion in 48 h (first TX not in ER)	No transfusion	p [#]
Number of patients with PT, n (%)	823	62 (7.5)	78	485*	
Age in years, AM (SD)	41.5	50.1 (37.4)	48.4 (23.6)	40.7 (21.1)	0.001
Male, %	73.3	69.6	72.6	75.8	
ISS, AM (SD)	13.2	30.2 (13.7)	23.1 (11.4)	11.7 (9.2)	0.0001
RISC II, %	9.1	34.8	12	5.8	
Death, %	7.4	32.1	17.8	4.5	
Length of hospital stay in days, AM (SD)	10.6	29.5 (17.3)	19.8 (11.3)	9.7 (9.5)	0.0001
Patients with clotting factors, n	49	27	21	10	
Patients with further transfusions in 48 h, n	–	55 (798 RBCU)	n.a.	n.a.	
Total number of RBCU (range)	1,330	259 (1–6)	536 (1–32)	n.a.	

AM = Arithmetic mean; ER = emergency room; ISS = injury severity score; PT = polytrauma; RBCU = red blood cell units; RISC = revised injury severity classification; SD = standard deviation; TX = transfusion; n.a. = not applicable.
 *Missing cases without complete data.
[#]Comparison between the three groups (ANOVA).

[12]. Mortality and morbidity were unchanged in trauma patients after RhD+ transfusions [13, 14]. These data were recently confirmed by results obtained in a German study [15].

In addition, several studies could demonstrate that the risk of RhD alloimmunization is relatively low in real life, ranging from 6 to 30% [15–18], compared to the 80% seroconversion rate calculated from early studies with healthy volunteers [19, 20].

Since data from Germany are sparse, we retrospectively analyzed data from the Marburg Polytrauma Database (DGU Trauma Register) and related information from the local safety update registry and the laboratory information system for a 5-year period.

Material and Methods

Study Population

We collected data from all multiple injured patients who received their first treatment in the ER between January 1, 2010 and December 31, 2014. Patients were identified in the Marburg Polytrauma Database. Transfusion history and serological results were traced back from the laboratory information system (Swisslab/Roche, Berlin, Germany). Information on additional side effects were collected from the safety update registry installed under European directive 2010/84/EU.

Data Collection

We collected age, sex, ISS (injury severity score), length of hospital stay, death, RISC II (revised injury severity classification), transfusion history, blood group in transfused patients, antibody screen, and side effects. In case of RhD-incompatible transfusion, subsequent data for serology, hemolysis, and side effects were collected.

Serological Investigation

Blood group typing and antibody search were performed via solid-phase (SP) automated technology on Galileo instruments (Immucor, Rödermark, Germany). Serological follow-up of patients with RhD-incompatible transfusions included antibody screen via SP and column agglutination (CA; indirect antiglobulin test and enzyme test; BioRad, Dreieich, Germany). In case of suspected hemolytic transfusion reaction, a direct antiglobulin test (DAT) was performed by CA (BioRad). All DAT IgG-positives were further analyzed after acid elution.

Statistical Analysis

Descriptive statistics were performed using MS Excel 2010 (Microsoft Corp, Redmond, WA, USA). Descriptive data are given as mean and range or standard deviation (SD). Comparison between the groups was performed by ANOVA; $p < 0.05$ was considered to indicate significance.

Results

Patient Cohort and Transfusion Events

During the 5-year period, 823 multiple injured patients were treated in the ER. Their mean age was 42 years (range 2–89 years), 73% were male, the mean ISS was 13.2, and the mean RISC II was 9.1%. Mean trauma scores indicate that severity of injury in our trauma center showed average values when compared with data from Germany. Mean length of hospital stay was 10.6 (± 12) days, and 61 trauma patients (7.4%) died in hospital.

The majority of patients in ER remained untransfused within the first 48 h ($n = 683$; 83%), whereas 62 patients (7.5%) received RBC units from the sealed blood product container in ER immediately and 78 (9.5%) were transfused within 48 h, but not immediately in the ER. The demographics of all three groups are summarized in table 1. Most of the patients ($n = 55$; 89%) with immediate transfusions in the ER required additional transfusion support during the next 48 h (on average 14.5 units; range 1–80 units). Nearly half of them were also infused with coagulation factors ($n = 27$; 44%). Further details for the 62 patients with immediate transfusions are summarized in table 2.

Pre-Transfusion Antibody Status

Antibody screen performed on the initial blood sample taken in ER was negative in 138/140 patients who received transfusions within 48 h. One male patient of blood group A RhD+ had a warm-reactive antibody of unknown specificity; and a female patient of blood group O RhD– was diagnosed with anti-D. Both antibody-positive patients did not require immediate transfusions in ER and received compatible RBC units in the due course.

Table 2. Characteristics of RhD– patients supplied with RhD+ RBCU and their immunohematological follow-up

	2010–2014
Total number of patients with PT	823
Total patients with TX	140
Total RBCU to all patients with TX	1,330
total patients with RBCU out of box	62
Total RBCU to patients with TX out of box	259
Total D– patients (of patients with TX)	33* (21%)
Number of D+ RBCU to D– patients (AM; range)	245 (13; 1–31)
Number of D+ RBCU to D– patients through box	60
Number of D– RBCU to D– patients (AM; range)	82 (7; 2–11)
Number of D– patients receiving D+ RBCU	18
Through box in ER	14 (22%)
Later on	4
Patients with additionally substitution	10
Anti-D in follow-up	9
Nonresponder (ABS negative after 1 year)	3
Death in hospital or during follow-up	3
No follow-up (no ABS after 120 days)	3
Hemolytic transfusion reaction	0
D– female in childbearing age with D+ RBCU	3
Patients with positive ABS before TX (1× no specificity, 1× anti-D)	2
ABS = Antibody screening; AM = arithmetic mean; PT = polytrauma; RBCU = red blood cell units; TX = transfusion.	
*Two with unknown blood group, one of them with incomplete transfusion data.	

Transfusions in RhD– Multiple Injured Patients

In total, 31/140 patients (21.5%) with transfusions within the first 48 h were typed RhD–. 13 patients received RhD– units throughout. 18 patients received RhD+ units: 14 were directly transfused from the sealed blood product container in the ER, and 4 were switched from an initial RhD– transfusion to RhD+ transfusions, after MTP was initiated. The mean number of all RBC units (including type RhD+ and RhD–) in incompatible transfused patients was 14.5 (range 1–37), and the mean number of RBC units in compatible transfused patients was 6.8 (range 2–11). Table 2 summarizes data from the RhD– patients only and the total number of transfused RhD+ and RhD– RBCU.

Seroconversion after RhD-Incompatible Transfusions

Out of 18 patients with RhD-incompatible transfusions, 9 developed anti-D (50%), three of whom also formed other antibody entities (anti-C, anti-E, and anti-K). The first follow-up investigation after the transfusion event was between day 3 and day 39, all without evidence for the presence of antibodies. The earliest seroconversion was detected at day 66; all other antibodies were detected at least 6 months after the incompatible transfusion event. No antibody formation was observed in 3 patients (follow-up period > 140 days), indicating non-responder status. Three patients died in hospital (between day 1 and day 37), and 3 patients were lost on follow-up on day 5, 41, and 73 after the first incompatible transfusion, all with no signs of seroconversion up to then. No signs of hemolysis were evident in any of the patients (table 2).

Patients of Childbearing Age

Three out of the 18 patients were female and of childbearing age (<40 years), with one of them being pregnant in week 31 of gestation. One patient received 2 units of incompatible RBCs, with no antibody formation (day 153). The other 2 patients went on MTP and both developed anti-D later. Fetal loss occurred within 48 h after the accident.

Discussion

In many tertiary care hospitals, the demand for blood group O, RhD– units is larger than the supply made available by blood establishments. These units are specifically required for intrauterine transfusions, the transfusion of newborns, and patients with pre-formed antibodies [21]. Because of their almost universal compatibility, blood group O, RhD– units are also often used in emergency transfusions in which the patient's blood group is unknown. RhD– transfusions are usually a precautionary measure in order to avoid anti-D immunization. In fact, this will turn out as unnecessary in most cases. It has been pointed out previously that the shortage of blood group O, RhD– RBC units even worsened, despite the overall decrease in RBC usage and the implementation of patient blood management strategies in many hospitals [21].

In this study, 62 multiple injured patients with a need for immediate transfusion received 259 RBC units via the sealed box in ER, 199 of which were given to RhD+ patients. Accordingly, the overall number of saved RhD– units was 259, and the overall number of correctly saved RhD– units was 199 (77%). Vice versa, an RhD– transfusion strategy would have led to a waste of 199 RBS units over 5 years (40/year). These data match the study results of Newman et al. [22], who calculated a 72% rate of unnecessary RhD– RBC transfusions. The demand for blood group O, RhD– units in our hospital is between 800 and 900 per year, 6% of which can be saved with this strategy. If we include the RhD+ RBCU, given to the RhD– patients in the later course (n = 185) but not via the sealed box in ER, the number of saved RBCU per year even raises to 77/year (8.5%). This rate may appear low, but is significant with respect to the shortage in blood group O, RhD– supply.

The exposure rate (RhD– patients transfused with RhD+ RBC units) was 54% in our study, which was comparable to the 46% reported by Meyer et al. [14], and somewhat higher than the 20% reported by Selleng et al. [15]. Other studies [3, 8, 9, 11] reported well lower exposure rates (6–7%), partially, because a limited number of RhD– units was also available in the ER [3, 8, 9]. The British Guidelines recommend to use no more than 2 units of RBCs for patients with unknown blood group [23] and to switch to RhD+ units in men, women of not childbearing age, and in MTPs, a recommendation that was implemented in many trauma centers [24]. In our cohort, however, only 2 patients required no more than 2 units of RBCs. Accordingly, the calculated exposure rate would only be marginally lower following this strategy (from 54% to 48%), but the unnecessary use of RhD– units would remain high (143 units). The German Guidelines are less specific when stating

that RhD-incompatible transfusions are sometimes unavoidable but should, whenever possible, be restricted to MTP and not be given to women of childbearing age at all [25].

The seroconversion rate in RhD- recipients of RhD+ RBCs was 50% in this study. We included all patients who died in the clinical course or who were lost to follow-up, because we believe that this represents the effective, observed conversion rate. It should be noted that this rate is comparable to the 45% reported by Selleng et al. [15], who did not include patients lost by death, but did include 'potential' seroconverters. We believe that our relatively long follow-up period affects the seroconversion rate significantly. Most other studies reported seroconversion rates between 9.5 and 33% with mean follow-up periods of 14–74 days [9, 11, 12, 14]. Since most multiple injured patients are not immunosuppressed per se, anti-D formation is to be expected more often than in patients with bone marrow transplants or sepsis [26–29].

In our study, immunization against RhD did not depend on the number of transfused units. Findings from others point in the same direction [15–17]. Interestingly, a strategy according to the British Guidelines would not have affected the number of seroconverters.

Apparently, transfusing RhD+ blood exposes patients with preformed anti-D to higher risk. Unfortunately, literature on incompat-

ible emergency transfusions is sparse. The authors identified one case where the incompatible transfusion in an emergency setting was due to a preformed anti-c antibody [12]. This example demonstrates that RhD- transfusions are not 'universally' compatible. A second case describes boosting of preformed, undetectable anti-Jk(a) antibodies [11]. No general conclusion can be drawn from these data.

Given the fact that restricted supply with blood group O, RhD- units is unlikely to change in near future, we believe that supplying multiple injured, exsanguinated patients with blood group O, RhD+ units is an acceptable strategy. Whether this procedure leads to reduced numbers of RhD-incompatible transfusions for patients in elective or semi-urgent settings is currently being evaluated.

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Disclosure Statement

The authors have no potential conflicts of interest to declare.

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