Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma

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BACKGROUND: The increasing use of fresh blood group O whole blood in acute trauma medicine makes it important to reevaluate the issue of hemolytic reactions related to the transfusion of ABO-incompatible plasma.
STUDY DESIGN AND METHODS: This review summarizes and evaluates published articles and case reports concerning hemolytic reactions in connection with the transfusion of group O whole blood or blood products to nongroup O recipients.
RESULTS: In 1945-1986, 15 nonmilitary publications reported hemolytic transfusion reactions with group O blood/blood products. All patients recovered except for two fatalities. Late in World War II and during the Korean and Vietnam wars and onward in Iraq and Afghanistan only "low anti-A, anti-B titer" group O whole blood has been used as universal blood. In spite of a large number of units transfused, there are no reports of hemolytic reactions. Twenty-five publications report hemolytic reactions after transfusion of group O platelets to nongroup O recipients. In all patients but one, the titer of the implicated A- or B-antibody was >100 (saline) or >400 (antiglobulin) and all cases with an infused volume of incompatible plasma <200 mL were related to anti-A or anti-B antiglobulin titers >1000.
CONCLUSION: In emergency lifesaving resuscitation, the risk of hemolytic transfusion reactions from transfusion of group O blood to nongroup O recipients constitutes risk that is outweighed by the benefits. A low titer of anti-A/B will minimize the risk for a hemolytic reaction, particularly if the screening is repeated after an immunization episode, e.g., blood transfusion, vaccination, or pregnancy.

INTRODUCTION

In far-forward areas where neither a large pool of whole blood nor rapid ABO typing of donors was available, military providers used fresh whole blood of group O for patients with life-threatening bleedings.[1-4]

The aim of this review is to provide a background for a risk evaluation of the use of whole blood from group O donors as "universal blood" for transfusion in emergency cases where there is no availability of blood components. The review summarizes and evaluates published reports on the risks of a hemolytic transfusion reaction in the recipient following a transfusion of a product containing ABO-incompatible plasma.

Recognizing the possibility of a hemolytic reaction, the transfusion of group O whole blood to patients other than group O was limited to two units in civilian setting. This was done to restrict the volume of transfused ABO-incompatible plasma. Whole blood transfusions were practically abolished with the introduction of blood components (RBCs, plasma, and platelet concentrates). The group O RBC packs contained only about 10 mL of plasma and thus carried much less risk for a hemolytic reaction when transfused to a nongroup O recipient and became used as a "universal" unit.

With the present introduction of fresh whole blood as a therapeutic tool in acute trauma care, the old problems connected to the transfusion of ABO-incompatible plasma need to be reevaluated.

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Immunology

Since Landsteiner first described the RBC blood groups A and B, the blood groups in humans have been separated into 30 different blood group systems. By definition, a blood group substance is able to function as an antigen and stimulate the production of the corresponding antibody in an individual lacking that blood group. Most of the blood groups are part of a RBC membrane protein and must be injected or infused in order to cause an immunization. The blood groups based on carbohydrate chains on the other hand have their antigenic substances also occurring in several other species like bacteria or plant seeds. Antibody production may take place without any human intervention, and the corresponding antibodies are often referred to as "natural antibodies."[5]

A hemolytic transfusion reaction can be characterized as immediate intravascular hemolytic transfusion reaction (IHTR) and delayed hemolytic transfusion reaction (DHTR). The former is caused by antibodies already existing in the circulation and able to mediate the binding of complement to the transfused RBCs. This results in the formation of the complement membrane attack complex and a production of pores through the cell membrane resulting in subsequent lysis of the cell. The DHTR on the other hand is the result of an immune response provoked by the transfusion and leading to an antibody production where adverse clinical symptoms will be noticeable after 2-3 weeks.

Antibodies bound to the RBC membrane, including those that are noncomplement activating, will mediate an extravascular destruction of the cell through erythrophagocytosis in the reticulo-endothelial system. In addition, activated cytotoxic monocytes have been described to cause an extracellular lysis of the antibody-coated RBCs.[6] This may explain the clinical signs of hemoglobinemia seen in hemolytic reactions without the presence of a complement-activating antibody. Antibodies causing a macroscopic agglutination in vitro are in earlier publications often referred to as hemagglutinins.

In most cases, the antibodies responsible for an IHTR belong to the immunoglobulin (Ig)M class and have a heterogenic background like immune stimulation by substances from intestinal bacteria[7] or deliberate immunization with vaccines. Because of their size and ability to bind 10 antigens per molecule, the complement activation cycle can be initiated by a single membrane-bound IgM antibody.

In contrast, the initiation of a complement activation by the much smaller "immune" antibodies of the antiglobulin (IgG) class requires a minimum of two closely membrane-bound antibodies. Because of this lower complement-activating reactivity, the IgG class antibodies responsible for an IHTR usually need to be present in a higher concentration than the corresponding IgM antibody.

The antigens of the ABO system belong to the carbohydrate type, and the ABO system is by far the clinically most important blood group system. The antibodies anti-A and anti-B are naturally occurring antibodies of the IgM class and are present in practically all humans who lack the corresponding antigen. These antibodies will react immediately with a transfused antigen positive cell and in most cases result in an intravascular lysis of the cell. Elevated titers of ABO reactive antibodies are reported after immunization with several routinely used vaccines, e.g., tetanus toxoid, T.A.B. (typhoid, paratyphoid A, paratyphoid B) vaccine, diphtheria, and blood group A-like substances have been found in vaccines against meningococcus, hemophilus influenzae, influenzae virus A/B, and plague.[8-15] This active immunization will stimulate the production of antibodies of both IgM and IgG classes. In a recent report, Daniel-Johnson and colleagues[16] describe a very high titer of anti-B in a group A platelet donor after stimulation by a commercial probiotic containing several strains of lactobacilli and bifidobacteria.

Quantification of anti-A and anti-B

Of all laboratory methods, the quantification of the reactivity for a specific blood group antibody is probably one of the most difficult to standardize. Titration of anti-A and anti-B has for a long time been used to select safe universal blood group O donors.[17-19] The optimal technique is still discussed, and no technique has so far got universal acceptance.[20-23]

Transfusion of group O whole blood to nongroup O recipients

In 1911, Ottenberg[24] proposed that persons of blood group O could serve as "universal donors." In his opinion, the naturally occurring A- and B-agglutinins in a blood unit would be too diluted by the transfusion to damage the RBCs in recipients belonging to the blood groups A, B, or AB. The use of O as universal blood group for transfusion was widely accepted and practiced during World War II.

In 1942, Aubert and colleagues[25,26] reported a more systematic investigation of the physiological effects when plasma containing A-agglutinins was transfused to recipients of blood group A. They found varying degrees of hemoglobinemia, intravascular agglutination, hyperbilirubinemia, and a subsequent reduction of the number of RBCs. The lowest antibody titer showing RBC hemolysis was 512, and these high titers were found in about 40% of their tested group O donors.

In 1945, Gasser[27] described hemolysis and osmotic fragility after the transfusion of group O plasma to three children of groups A and AB. The children, weighing 3.3-4.5 kg, received 50-90 mL of plasma and became icteric within a few hours. In two of the cases, plasma from the same donor had been given the day before without any

clinical reactions. Possibly the antibodies from the first transfusion bound most of the soluble blood group substance and thus lowered the capacity for the patient to neutralize the antibodies in the second plasma. The same year Alberton[28] reported a fatal IHTR after transfusion of only 100 mL of a supposedly "safe" group B plasma/saline mixture to a group A patient. Investigation of the donor plasma showed an agglutination titer of 4096.

Tisdall and colleagues[29] reported in 1946 that 23% of their group O donors had anti-A or anti-B titers of above 640. The transfusion of 250 mL of this plasma was frequently associated with hemoglobinemia and bilirubinemia. In further studies by the same group,[30] group A volunteers were transfused with plasma from B donors immunized by the injection of group A substance, and they could show that as little as 25 mL of plasma with an anti-A titer of 2500 induced hemoglobinuria in the recipient. The addition of the specific blood group A substance to the plasma prevented the hemolysis, and 250 mL of the treated plasma could be transfused without clinical symptoms.

The same year Loutit and Mollison[31] investigated the clinical importance of agglutination by in vitro mixing group A RBCs with a potent anti-A and then injecting the agglutinated RBCs back into the donor. Although the cells had been heavily agglutinated, the survival was approximately normal. These findings were later confirmed by Jandl and colleagues[32] measuring the in vivo survival of agglutinated B-cells. They found that even if, in one experiment, 26% of the transfused agglutinated RBCs immediately disappeared from the circulation, most of them reappeared and now showed a normal survival.

In 1950, Ervin and colleagues[33,34] studied four cases where the transfusion of group O blood or plasma to patients of group A had resulted in a severe hemolytic reaction. They could demonstrate that in all cases the transfused plasma contained an anti-A, which was not inhibited by the addition of group A substance, and the plasma also showed a higher IgG titer than the saline titer. The transfusion of 250 mL of O plasma with a saline agglutinin titer of 640 to a group A volunteer patient was tolerated without any signs of hemolysis. A second transfusion to the same patient of a plasma with a saline agglutinin titer of 1280 resulted in a severe IHTR. In both cases, the plasma had been treated with AB-substance to neutralize the antibodies, and it was suggested that the second plasma contained a potent antibody of IgG type not inhibited by the added AB-substance. In 1953, Stevens and Finch[35] reported a severe IHTR with acute renal failure in a group A volunteer after the transfusion of 350 mL group O blood with a saline anti-A titer of 32-64. The recipient recovered, and questioning of the donor revealed that he had received tetanus antitoxin 7 months before the donation. Crawford and colleagues[8] showed that even if potent immune anti-A in the majority of cases were found in plasma containing high titer saline agglutinins, it was possible to find plasmas with a low titer of saline agglutinins and still containing a high titer of immune anti-A. This was also shown by Grove-Rasmussen and colleagues,[10] who described two cases where an immune anti-A caused severe hemolysis and renal failure. In one case, the patient was group A_2 and had a fatal transfusion reaction with renal failure after receiving one unit of group O blood with an immune anti-A titer of 256. The other patient, who was group A_1 and secretor, recovered in spite of receiving a group O unit with anti-A immune titer of 1024. A higher amount of circulating group A substance in the second case was put forward as a possible explanation of the difference in outcome.

The transfusion of 500 mL group O blood with a saline titer of 1024 (about 25% of the patient's blood volume) to a group A_2 patient resulted in a severe hemolytic reaction. The patient received a second transfusion with washed O cells without clinical symptoms and was fully recovered when discharged from the hospital.[36]

Bull and colleagues[37] described a case where nearly two bottles (about 800 mL) of group O blood were transfused to a patient resulting in a severe IHTR with seizures, low blood pressure, and later dark brown urine containing oxyhemoglobin. The patient was treated conservatively and recovered rapidly. The first blood bottle was shown to have an exceptionally high titer of anti-A that was strongly hemolytic even after neutralization with group A substance. In 1978, Inwood[38] described a case where 95 mL plasma in a unit of group O RBCs transfused to an adult group A leukemia patient resulted in a severe IHTR. The saline agglutination titer was not reported, but the IgG titer of the plasma was 8192 for anti-A and 512 for anti-B. In spite of the severe reaction and high titers, the patient had an uneventful recovery.

Barjas-Castro and colleagues[39] reported a severe hemolytic reaction after transfusion of 270 mL of a group O RBC unit (55 mL plasma) to a group A patient. The transfused plasma had a saline titer >100 and an IgG titer of 1024. The patient was a 38-year-old male with a non-Hodgkin lymphoma associated with a human T-lymphotropic virus type 1 infection.

In 1986, Schwab and colleagues[40] evaluated the use of untitered group O RBC packs for immediate transfusions to trauma patients. The cell packs contained 40-50 mL of plasma and were reconstituted with 250 mL of warm saline solution before transfusion. A total of 250 group O units were transfused to 74 patients without any recorded hemolytic reaction. In another study, 135 trauma patients were initially resuscitated with group O blood that had not been crossmatched. A total of more than 400 units were transfused without any major transfusion reaction.[41]

Military use of group O blood as "universal blood" for transfusion

During World War II, almost all blood used in the US Army for the treatment of battle casualties was group O

blood without any regard to the potential hazards of the simultaneously transfused A/B antibodies.[42] However, in 1944, a severe hemolytic reaction caused by the transfusion of 75 mL of a group O blood unit to a group A patient group was reported. The anti-A agglutinin titer of the unit was 8000, and the evaluation of this and some similar events led to a US Army transfusion policy where all group O units with an anti-A or -B saline titer of 250 or more were labeled "high titer" and used only for group O recipients.[43] This policy was continued in the Korean War, and only "low titer" group O blood was sent to the military hospitals. During 1952, over 60,000 blood units were transfused without any reports of hemolytic transfusion reactions from the use of this "universal blood."[44,45] However, a slow destruction of the recipients' RBCs was observed, and this was attributed to the presence of antibodies not detected by the laboratory methods used. In addition, several cases were identified where the passively transfused A- and B-antibodies had caused a severe IHTR when the patient later received transfusion with blood of his own blood group. This led to the introduction of a general rule that after a massive transfusion with "universal blood," the patient should not receive type-specific RBCs within 2 weeks following the massive transfusion or until a negative crossmatch shows that the transfused antibody is not detectable.[45]

In the beginning of the Vietnam War, the US Army only used low titer group O "universal blood" as described above. However, as the need for blood transfusions increased, all blood groups were used from late 1965. Between September 1967 and February 1969, a total of 230,323 units of blood were transfused in Vietnam. Twenty-four hemolytic transfusion reactions were reported, of which only one was caused by transfusion of group O blood. This blood unit, correctly labeled high titer, was by mistake released to a field medical unit and transfused to a group A recipient. The anti-A saline titer was 256, but the IgG titer was 32,768. The patient had oliguria and hemolysis for 2 days and then recovered.[43,45]

During the wars in Iraq and Afghanistan, fresh whole blood has been used in far-forward surgical teams mainly as a source of platelets. In emergency situations, group O blood was used regardless of the blood group of the patient. In published evaluations of this use of fresh whole blood under austere conditions, there is no mention of hemolytic complications.[3,46-48]

During the 18-day Yom Kippur War in Israel 1973, with 548 military causalities, a total of 894 whole blood and 122 RBC units were issued. Screening for units with a high titer anti-A or anti-B was not performed, and only plasma-reduced group O RBCs suspended in saline were used for transfusion to nongroup O patients. In all, only four group O RBC units were transfused to nongroup O recipients, and no adverse effects were reported.[49]

Camp and Shield[15] found that if applied together, the three criteria recommended by the American Association of Blood Banks excluded 68% of the potential group O donors in a civilian population from being "universal donors." In a review on the use of universal donors and uncrossmatched blood units for transfusions, Barnes[45] stresses the importance of strict transfusion policies and a well-trained technical staff familiar with the policies and protocols.

For the Special Forces of the Swedish Armed Forces, a mobile blood bank has been created at the Department of Transfusion Medicine at Örebro University Hospital. All donors are accepted as a regular Swedish donor but registered in a military section of the hospital-based blood center. All group O donors accepted as "universal donors" are prescreened for both IgM and IgG class anti-A and anti-B, with cutoff values of 100 and 400, respectively.[50,51]

Platelet transfusions

Although the problems related to the transfusion of group O blood to nongroup O patients in the civilian medical care disappeared with the introduction of RBC concentrates, they still remained for the transfusion of platelets. A therapeutic unit of platelets is usually the platelets from 4-6 whole blood donations each containing 60-70 mL of plasma or a single donor apheresis unit with 300-500 mL of plasma. As platelets mostly are transfused to hospitalized patients under medical treatments, adverse effects including a hemolytic reaction are easily noticed and reported. Table 1 shows published case reports of patients with a severe hemolytic reaction following a platelet transfusion with ABO-incompatible plasma (children of age <8 months excluded). Twenty-one of the 30 reported patients had a diagnosis of a systemic malignancy, and three were surgical cases. In recent years, procedures have been introduced whereby the amount of plasma can be reduced and substituted with an additive solution, and as for the RBCs, this may be a solution to the hemolytic problems.

Zoes and colleagues[53] in 1976 reported an IHTR from transfusion of group O platelets containing 500 mL plasma to a leukemic patient of group $A_{int}B$. The platelets were transfused without any adverse reactions and were followed next day by a transfusion of an A_1B RBC unit. After about 20 mL had been infused, the patient got very ill with chills, rise of body temperature, and developed a severe hemoglobinemia. The plasma from the platelet pack showed a high titer of anti-AB and also anti-A_1 of IgG class (see Table 1) reacting with both the transfused A_1B RBCs and the patient's $A_{int}B$-cells but not with the patient's pretransfusion sampled $A_{int}B$ cells. The authors proposed that the reaction with the transfused A_1B cells somehow triggered a reaction with the patient's own cells.

In a survey of the literature, Larsson and colleagues[62] found that the incidence of dangerous universal donors

TABLE 1. Case reports of hemolytic transfusion reactions in platelet transfusions containing ABO-incompatible plasma

Reference (nr)	Year	Patient blood group	Patient age (years)/sex	Infused volume, mL	Renal complication	Severe coagulopathy	Titer anti-A and anti-B		Diagnosis (recovered = R; died = D)
							Saline	AHG	
Lundberg[52]	1975	A_2B	40/M	80	None	None	NR	NR	Leukemia (R)
Zoes[53]	1976	AB	44/F	500	None	None	A: 256	256	Leukemia (R)
							B: 64	NR	
McLeod[54]	1982	A	45/M	200	None	None	A: 1,280	10,240	Erythroleukemia (R)
Siber[14]	1982	A	20/M	199	None	None	A: NR	8,192	Leukemia (R)
Conway[55]	1984	A	15/F	200	Dialysis	DIC	A: 8,192	4,096	Leukemia, BMT (R)
Pierce[56]	1985	A	21/2/F	200	Uremic	DIC	A: 51	32,000	Leukemia, ABMT (D)
		B	58/F	50	None	None	B: 512	16,384	Cardiac surgery (R)
Ferguson[57]	1988	A	66/M	50	None	None	A: 256	>4,000	Leukemia (R)
Reis[58]	1989	B	56/M		None	None	B: NR	4,096	Aplastic anemia (R)
Murphy[59]	1990	A	30/F		Uremic	None	A: 512	2,048	Leukemia, ABMT (R)
Chow[60]	1991	AB	18/F	NR	None	None	A: 1,024	NR	Leukemia (R)
Mair[18]	1998	A	28/M	225	None	None	A: 128	NR	Neuroblastoma (R)
McManigal[61]	1999	AB	78/F	300	None	None	A: NT	NR	Cardiac surgery (R)
Larsson[62]	1999	A	44/F	371	None	None	A: 16,384	NR	Leukemia (R)
Valbonesi[63]	2000	A	55/F	35	None*	None*	A: 128	8,000	Breast cancer (R)
		A	16/F	35	Dialysis**	None**	A: 128	8,000	Aplastic anemia (R)
Sauer-Heilborn[64]	2002	B	35/M	526	Uremic	None	B: 4,096	2,048	BMT (R)
Gresens[65]	2003	A	29/M	250	None	None	A: 1,024	NR	Gunshot, abdomen (R)
Ozturk[66]	2003	A	21/M	600	Dialysis	None	NR	NR	Myelodysplasia (R)
Josephson[19]	2004	A	Adult/NR	50	None	None	A: 256	8,192	Leukemia (R)
		A	Adult/NR	50	None	None	A: NR	1,024	Leukemia (R)
Fauzie[67]	2004	A	NR/NR	598	None	None	A: 256	512	Leukemia
		A	NR/NR	390	None	None	A: 32	32	Leukemia
Angiolillo[68]	2004	A	8 months/M	15/kg	Anuria	Multi.-organ failure	A: 128	NR	Langerhans cell histiocytosis (D)
Reinardt[69]	2005	A	NR/NR	NR	None	None	A: 512	NR	NR
Sapatnekar[70]	2005	A	2/F	145	None	DIC	A: 2,048	16,384	Medulloblastoma (R)
Sadani[71]	2006	A	65/F	200	None	None	A: 128	1,220	Leukemia (R)
Harris[72]	2007	A	8/F	300	None	None	A: 256	4,096	Leukemia (R)
Daniel-Johnson[16]	2009	B	40/M	100	None	None	B: 16,384	16,384	Leukemia (R)
		B	5/M	37	None	None	B: 16,384	16,384	Aplastic anemia (R)

*Acute erythroexchange (1×) and ** erythro-plasmaexchange (2×) were performed.
ABMT = autologous bone marrow transplantation; AHG = antihuman globulin; BMT = bone marrow transplantation; DIC = disseminated intravascular coagulation; NR = not reported; nr = number of reference.

varied widely depending on the methods used in defining the group. Nevertheless, in most studies, they found that approximately 10%-20% of group O donors showed a high titer anti-A or anti-B, labeling them as dangerous universal donors although the actual incidence of transfusion reactions was low. In 2002, Oza[73] reported 1%-2% of ITHR from about 1600 ABO mismatched platelet transfusions. All reactions with the exception of one were mild to moderate and nonfatal.

Josephson and colleagues[19] investigated the titers of anti-A/AB in 100 unselected group O donors. With an arbitrarily chosen "high titer" of 64 for IgM and titer 256 for IgG, they found 28% and 39% respectively categorized as dangerous donors. Mair and Benson[18] calculated the risk for a clinically significant acute hemolytic reaction to be about 1 in 9000 (0.01%). Looking at over 50,000 platelet transfusions over a 4-year period, Fauzie and colleagues[67] found two cases of IHTR of 3816 platelet transfusions in nongroup O patients receiving group O platelet units (0.05%).

After a severe IHTR from a group O platelet transfusion to a group A recipient, the New York Blood Center 1994 implemented a protocol to screen all group O platelet units before transfusion to nongroup O patients.[74] The screening was discontinued from 1999, and the practice was reevaluated in 2003. During 1994-1998, 1564 platelet units were tested for saline anti-A and anti-B. The 3.6% of the units had a titer >100 and were used only to group O recipients. In 2003, 120 group O units were tested with the same method and four units (3.3%) had titers >100. During the 5-year period without screening, there were no reported hemolytic transfusion reactions from more than 25,000 platelet units transfused, and the conclusion was that IHTR secondary to anti-A or anti-B in platelet transfusion is a rare event and did not warrant a screening protocol.

From an international survey in 2003 covering 16 major centers in Europe, Japan, United States, and Australia, Pietrsz and colleagues[75] found that even if most centers did not exclude "high titer" platelet donors, there were no reported hemolytic reactions from the transfusion of group O platelet units to recipients of groups A, B, or AB. They concluded that other steps taken to minimize the antibody exposure to the recipient like reduction of the amount of plasma, or replacement of plasma with additive solution or AB-plasma had most probably lowered the risk for these hemolytic reactions.

An extensive US survey on the transfusion of platelet units containing ABO-incompatible plasma covering 3156 North American laboratories was published in 2007 by Fung and colleagues[76] They found a great variation in transfusion policies from the use of only units with ABO-compatible plasma to having no specific routines (529 laboratories). Only 53 laboratories routinely screened units for high titer anti-A and anti-B, and there was no general agreement on the critical antibody level.

Cooling[77] found that although most patients showing a severe IHTR in connection with a platelet transfusion recover, there were some deaths. The author concludes that ABO-compatible plasma platelet units should be used for transfusion to neonates, small children, and patients requiring long-term platelet support, but in surgical and other patients with short-term transfusion needs, ABO-compatibility is of less concern. However, based on a titration study of 185 platelet donors, Cooling and colleagues[23] recommended a saline titer of 128-200 for anti-A and anti-B as cutoff titer for group O platelet units transfused to nongroup O recipients.

In an international study by the Biomedical Excellence for Safer Transfusion Collaborative in 2010[78] covering 126 blood centers in 14 countries, the conclusion was that there "exists a considerable variation in the practice of transfusing ABO-incompatible PCs, suggesting an opportunity for research to inform evidence-based practices."

In 2011, Quillen and colleagues[79] introduced a mandatory screening procedure for saline "high titer" ABO-antibodies on all their apheresis platelet units. During 2 years, about 10,000 units had been screened with the use of a saline dilution of 1:250, and with this cutoff, 25% of group O and 5% of group A donors were classified as high titer. No platelet-associated hemolytic transfusion reaction was reported during this period, and the incidence of hemolytic reactions was 1:2460 (0.04%) before the implementation of the screening program.

DISCUSSION

Through evolution, the human organism has developed very sophisticated systems for the defense of the individual integrity starting with the skin and or mucosa, which someway has to be penetrated from the outside. Blood transfusion bypasses most of these safety systems as the biologically disperse blood components are directly introduced to circulation of the recipient.

With the exception of direct physiological effects like volume expansion, the immediate adverse transfusion reactions depend on the immunological recognition and subsequent action by already existing preformed antibodies and cytotoxic cells. Foreign material is bound in immune complexes, and cells are lysed by the antibody-mediated activation of complement and/or the cell-mediated cytotoxicity. Even in cases without a complement-activating antibody and a severe extravascular hemolysis, there may be a release of hemoglobin in excess of the binding and scavenging capacities of the haptoglobin and hemopexin in the plasma.

The transfused noncompatible A-/B-antibodies will immediately form circulating immune complexes with the available A- or B-substance in the plasma of the recipient.[80] When group O plasma with a hemolytic anti-A is mixed with group A blood in vitro, there is

agglutination of the RBCs before the subsequent lysis. If these agglutinated RBCs are transfused, they will show a normal survival, but a large proportion of the cells will temporally disappear from the circulation for some hours.[32] Such immediate agglutination of the RBCs in the recipient may very well happen even in vivo during a blood transfusion with ABO-incompatible plasma and, if so, the noncirculating cells will have a negative effect on the microcirculation. Another possible negative factor may be the reported increase in the osmotic fragility of the RBCs in the recipient[27] that could contribute to the posttransfusion hemolysis.

In addition to the direct immune complex-mediated release of proinflammatory factors, there is increasing evidence of the strong proinflammatory effects from free heme molecules resulting from degradation of the excess of hemoglobin.[81] However, a study by Yazer and colleagues[82] showed that ABO-mismatched platelet transfusions did not result in an increase of febrile nonhemolytic transfusion reactions. Several studies have shown that the renal failure often seen in hemolytic transfusion reactions[83,84] is not caused directly by hemoglobin[85] but by a local activation of complement, probably enhanced by the liberation of free stroma from the lysed cells.[86] Free hemoglobin has been shown to inhibit the nitrogen oxide–mediated vasodilation. This results in vasoconstriction with an increase in arterial blood pressure and the glomerular filtration rate of the hemoglobin molecules.[87]

In most trauma and surgical cases, the recipient of a blood transfusion has not been immunized by foreign blood, and the only preformed blood reacting antibodies are the naturally occurring A- and B-antibodies of IgM class. If the recipient has received a transfusion of blood or blood product or, in case of a female, been pregnant, this may have led to an immunization with production of immune antibodies against other blood group antigens. The presence of these immune antibodies is normally detected by the pretransfusion testing, and they are always tested for in regular blood donors. Thus, when group O blood from a regular donor is transfused to a nongroup O recipient, the risk of an immediate IHTR is related to anti-A and or anti-B in the plasma of the transfused blood unit.

As is shown in the studies referred to previously, there is an overwhelming experience, particularly from the transfusion of "low titer" universal donor group O whole blood in the military service, showing that the frequency of severe hemolytic reactions is nearly negligible. This is true for the short-term transfusions to previously healthy and mostly male individuals but more doubtful when it comes to patients with a long-term transfusion need. Most of the patients with a hemolytic transfusion reaction listed in Table 1 are diagnosed with a malignancy, and there are very few surgical cases reported. This is in spite of the large amount of platelet units transfused in cardiac surgery. However, the formation of immune complexes and the introduction of foreign antigenic material will always have some biological effects that mostly are negative but in some cases may be of benefit.

In the group of patients with a severe systemic disease, the risk for an IHTR has been estimated from 1: 2000 to 1:9000.[18,79] Almost all of the patients developing a severe IHTR after the transfusion of whole blood or platelets recovered, and there are very few published reports of a fatal outcome.[35,65,77]

With the introduction of modern blood component therapy, the risk for an IHTR from ABO-incompatible plasma has been minimized as the RBC units only contain 7-10 mL of plasma. In addition, the transfused A/B-antibodies are to a great extent neutralized by the free blood group substance in the plasma of the recipient. One unit of whole blood or platelets (excluding use of additive solutions) still contains 200-300 mL of plasma which, with a high titer of anti-A/-B, may be responsible for a more or less severe hemolytic reaction. Therefore, today, there is a general recommendation to select group O donors with a "low titer" of anti-A and anti-B for the preparation of whole blood and platelet units for transfusion to nongroup O recipients.[77] Even if there is no consensus of methods or cutoff thresholds, anti-A and anti-B titers below 100-200 (saline titer medium) and 250-400 (IgG titer technique) seem to be reasonably safe when group O blood and platelet units are transfused to nongroup O recipients.[19,45,62,77,79] Among the Swedish blood centers, there is a general consensus of a cutoff value of 100 (saline) and 400 (immune) for group O blood or blood products transfused to nongroup O recipients. This has given an incidence of anti-A or anti-B titer above these thresholds in about 5% in regular group O donors compared with more than 25% for active military donors (unpublished data). The difference probably mirrors the military vaccination program and compares well with the figures referred to earlier.[79] For repeat donors with an updated donation register, it is important to recognize that a new titration of anti-A and anti-B is only necessary when the donor interview indicates a new immunization episode, such as transfusion of blood or a blood product, vaccination, and pregnancy.

CONCLUSION

We consider the use of blood group O whole blood as "universal blood" for lifesaving transfusions in trauma emergency situations without the availability of blood component therapy. "Low titers" of anti-A and anti-B are preferable. Even if the current version of the US Emergency War Manual discourages the use of type O fresh whole blood, the use of this therapy is being advocated for in emergency situations under far-forward conditions in the Special Forces of the US Army.[88]

For nonemergency situations, ABO-compatible blood products should be used and, if such are not available, "low titer" group O whole blood or blood components containing a minimum of ABO-incompatible plasma should be mandatory. This conclusion is in line with the concluding remark by Kaufman in a recent editorial.[89]

CONFLICT OF INTEREST

No author has any conflict of interest.

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