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ORIGINAL PAPER

Allergic transfusion reactions from blood components donated by IgA-deficient donors with and without anti-IgA: a comparative retrospective study

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Background and Objectives IgA deficiency is common (1/500) and up to 40% of affected individuals will develop anti-IgA. A few studies suggested that passive transfusion of anti-IgA was not associated with an increased risk of allergic reactions. This study was designed to assess the safety of transfusing blood components containing anti-IgA.

Materials and Methods IgA-deficient blood donors with and without anti-IgA were identified from Héma-Québec's (HQ) computerized database. IgA deficiency was confirmed by an ELISA method and the presence of anti-IgA by a passive hemagglutination assay. Blood donations from IgA-deficient donors issued to hospitals between March 1999 and December 2004 were retrieved. Medical charts of recipients were reviewed for the occurrence of a suspected transfusion reaction. Presence and nature of transfusion reactions were assessed blindly by an adjudicating committee.

Results A total of 323 IgA-deficient blood products were issued by HQ to 55 hospitals. Of these, 48 agreed to participate [315 blood products (97·5%)]. A total of 272 products were transfused: 174 contained anti-IgA, and 98 did not. Only two minor allergic reactions occurred in each group. Incidence of allergic reactions was 1·15% in the anti-IgA group and 2·04% in the group without anti-IgA (P = 0·91). There was no anaphylactic reaction in either group.

Conclusions This study indicates that the proportion of allergic reactions does not appear to be greater in recipients of blood components containing anti-IgA compared to recipients of non-anti-IgA-containing components. Allowing donations from IgA-deficient donors with anti-IgA may therefore be contemplated.

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Introduction

Allergic transfusion reactions are amongst the most common adverse transfusion events. Incidence of minor allergic reactions has been estimated to be 0·4% after red blood cell (RBC) transfusions and as high as 4·1% after platelet (PLT) transfusions [1]. The same authors estimated the risk of major allergic reactions to be 0·043% after RBC transfusions and 0·626% after PLT transfusions. An estimate of the incidence of minor and major allergic reactions after plasma transfusions from the Québec Hemovigilance System (QHS) was 0·16% and 0·025%, respectively [2].

Transfusion-related allergic reactions can be mediated through pre-existing IgE antibodies in the serum of the blood recipient, giving rise to an immediate hypersensitivity reaction [3]. These reactions can also be caused by an

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interaction between a transfused antibody and an antigen already present in a recipient or the reverse situation [3]. All classes of immune globulins (IgE, IgG, IgM and IgA), albumin, haptoglobin, transferrin, complement (C3 and C4), HLA, food allergens (gluten, lactose, etc.), medications and numerous other molecules were associated with transfusion-related allergic reactions [3,4]. Passive transfer of antibodies through blood transfusion has also been associated with allergic reactions in recipients [5–7].

IgA deficiency (< 0·05 mg/dl) is the most common immune deficiency; in Canada, its prevalence is estimated to be 1 in 500 [8,9]. This deficiency can either be congenital or acquired through immune regulation, isoimmunization or be drug-induced. Such a deficit can lead to recurrent upper respiratory or gastrointestinal tract infections in some of the affected individuals [10]. IgA-deficient recipients who have developed anti-IgA (up to 40% of cases) of IgE or IgG class are at risk of developing allergic reactions that can be severe if transfused with blood components containing IgA [3,8,11,12]. Although the frequency of such reactions has not been clearly established, blood manufacturers usually maintain an inventory of IgA-deficient blood products for these patients to prevent this type of reactions.

Starting in 2001, Héma-Québec, sole blood manufacturer for the province of Québec, tested 38 759 blood donor samples for the level of IgA to increase its registry of IgA-deficient blood donors. During this screening, 70 IgA-deficient blood donors were identified, and 54% of them had detectable levels of anti-IgA [9]. The fact that most of these blood donors had previously donated blood offered us a unique opportunity to evaluate the risk associated with the passive transfer of anti-IgA to recipients during transfusion of anti-IgA-containing blood products. Although a few studies have suggested that transfusing anti-IgA-containing blood components was not associated with an increased risk of allergic reaction, the safety of such a practice has not been clearly established. Vyas *et al.* [12] did not identify any adverse reactions in a group of 13 blood recipients of components with anti-IgA. More recently, Winters *et al.* [13] did not find a significant difference in the rate of adverse reactions between blood recipients of apheresis PLTs with or without anti-IgA. Nevertheless, blood donors having detectable levels of anti-IgA in their plasma are disqualified as IgA-deficient blood donors in Canada. However, these donors remain eligible for whole blood donations but only the RBC units may be used for transfusion after being carefully washed while plasma units derived from these donations are only sent for fractionation.

The objective of this study was to compare the incidence of allergic reactions in recipients of blood components from IgA-deficient donors with and without anti-IgA.

Materials and Methods

IgA deficiency in donors was defined as < 0·05 mg/dl detectable IgA. IgA deficiency screening was performed using a previously described enzyme-linked immunosorbent assay at Héma-Québec [9]. IgA deficiency was confirmed by the National American Red Cross Immunohematology Reference Laboratory by a sensitive ELISA test, and the detection of anti-IgA in these samples was performed by hemagglutination at the same laboratory [14]. All donations from IgA-deficient blood donors with and without anti-IgA who donated at least once between December 1999 and December 2004 (before their IgA-deficient status was known) were identified from Héma-Québec computerized database.

The donation records of each IgA-deficient donor were reviewed, and a list of all blood components manufactured from each whole blood donation as well as apheresis donations was established. Distribution of products from donors with anti-IgA occurred prior to the knowledge of their anti-IgA status. Autologous donations were excluded. Each hospital that had received blood products from IgA-deficient donors with or without anti-IgA was asked to participate in a lookback study. Approval to review medical charts of recipients was obtained from each participating institution according to local policies, either through local IRB or directly from the local medical director.

From May to December 2006, medical charts of blood recipients were reviewed by a specifically trained research nurse using a standardized collection form to assess whether a transfusion reaction had occurred or whether signs and symptoms suggestive of a transfusion reaction were present. In some instances (< 5% of cases), for smaller remote hospitals with few cases, the local transfusion safety officers (TSO) conducted the chart reviews using the same standard data collection form as the research nurse. These TSOs were already well trained by the QHS in recognition and reporting of adverse transfusion reactions [15]. Information was collected without any patient identifier to ensure anonymity. Data collected included age, gender and diagnosis of the recipient, blood product transfused, premedication, signs and symptoms suggestive of a transfusion reaction and patient outcome. Signs and symptoms suggestive of a transfusion reaction were collected up to 4 h after the end of transfusion through scrutiny of vital signs chart, nursing and medical notes. All data were collected without knowledge of donor anti-IgA status. Data collection forms were reviewed independently by three of the authors (NR, GD, PR) to assess whether a transfusion reaction had occurred and if so, determine its nature and its imputability to transfusion. A minor allergic reaction was defined as the presence of mucocutaneous signs and symptoms like morbilliform rash with pruritus, urticaria (hives),

localized angioedema, oedema of lips, tongue and uvula, periorbital pruritus, erythema and oedema or conjunctival oedema. A major allergic reaction was defined as, in addition to mucocutaneous signs/symptoms, the presence of hypotension or respiratory tract involvement (either laryngeal or pulmonary). This process was performed without knowledge of the donors' anti-IgA status. Final consensus was obtained through an adjudication process. The data from QHS were also assessed to ensure that all possible cases were included.

Categorical variables including rates of adverse transfusion reactions in recipients of components with (Group A) and without (Group B) anti-IgA were compared with chi-square and Fischer's Exact tests. Mean age of recipients in the two groups was compared using the Student's *t*-test. Analyses were performed with SPSS statistical package (SPSS for Windows, Rel. 15·0·1. 2001; SPSS Inc., Chicago, IL) and Open Epi Calculator (http://www.openepi.com/Menu/OpenEpiMenu.htm).

Results

From December 1999 to December 2004, a total of 323 components from IgA-deficient blood donors with or without anti-IgA were issued to 55 hospitals. Of these, 48 hospitals (87·3%) agreed to participate in the study and 315 (97·5%) of the 323 blood components were issued to these hospitals. Medical charts were reviewed for 272 blood recipients (Fig. 1). Table 1 shows the type of blood products issued to participating hospitals according to anti-IgA status of the donor. Approximately, two-thirds (64·0%) of components were from donors with anti-IgA.

The 323 IgA-deficient blood products included in this study were collected from 71 blood donors of whom 40 (56·3%) had anti-IgA antibodies. The 272 blood products that were traced up to the recipients were collected from these 71 donors. The mean number of blood products donated was 4·45 for the 40 IgA-deficient blood donors with anti-IgA (range: 1–14) and 3·16 for the blood donors without anti-IgA (range: 1–9). Two donors without anti-IgA seroconverted during the study period (seroconversion rate of 0·014/donor-year) and are included in the 40 donors with anti-IgA. However, blood components were studied according to the presence or absence of anti-IgA at the time of donation.

IgA-deficient blood components were transfused to 139 women (51·1%) and 133 men (48·9%), none of whom were known IgA-deficient patients. There was no difference in gender distribution between the two groups (Table 2). Mean age of all recipients was 58·5 ± 21·0 (median age 61·0). Seventeen patients were under the age of 18, and six of them were 5 years of age or under. There was no difference between the two groups with respect to mean age. Pre-medication was given to 6·3% of patients; no significant difference between the groups was observed concerning total or specific medication use. There was also no significant difference in the distribution of underlying illnesses in the recipients (Table 2).

Clinical manifestations suggestive of a transfusion reaction were identified in nine cases. Fever, pruritus and rash were the most commonly reported signs/symptoms. Six cases were ascertained as transfusion reactions after completing the adjudication process. There were two minor allergic reactions in each group. In addition, one volume overload and one indeterminate reaction (chest pain and dyspnea in a patient known to have angina) were reported, both in recipients from donors without anti-IgA (Table 3). The vast majority of patients (97·8%) did not experience a

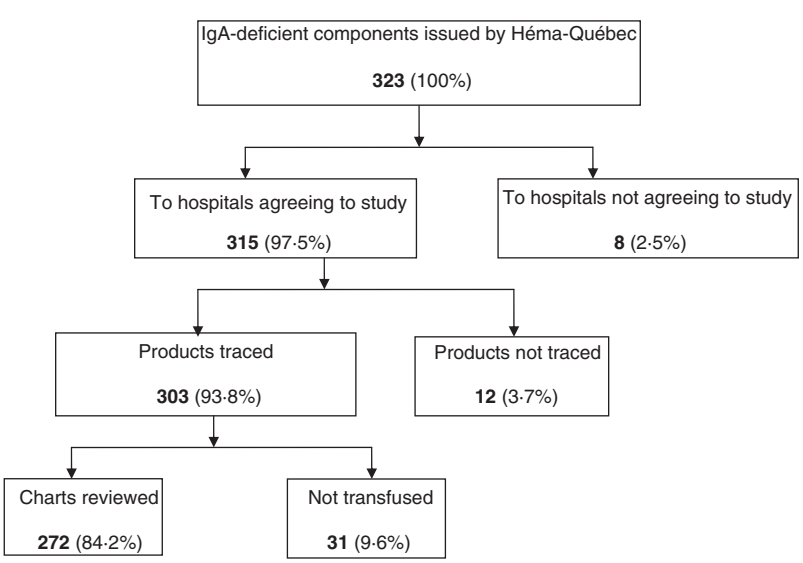

Fig. 1 Participation to study and charts reviewed in % of IgA-deficient blood components issued by the blood product manufacturer.

Table 1 Charts reviewed by type of blood component transfused

	Containing anti-IgA		Containing no anti-IgA	
Type of blood component	**N**	**%**	**N**	**%**
RBC	96	55·1	58	59·2
Whole blood derived PLT	55	31·6	27	27·6
Apheresis PLT	1	0·6	2	2·0
Plasma	17	9·8	8	8·2
Apheresis plasma	2	1·1	-	-
Cryoprecipitate	3	1·7	3	3·1
Total	174	100	98	100

PLT, platelet.

transfusion reaction. No reaction occurred in paediatric patients. Furthermore, no major allergic reactions were reported. Assessment of the data from the QHS did not reveal any additional transfusion reaction related to the transfusion of the products included in the study. There was no significant difference in the proportion of adverse reactions between the two groups (1·15% vs. 4·08%; $P = 0·25$) or in the proportion of allergic reactions (1·15% vs. 2·04%; $P = 0·91$).

Discussion

Our results indicate that the proportion of adverse transfusion reactions, including allergic reactions, does not appear to be greater in recipients of blood components containing anti-IgA compared to recipients of components containing no anti-IgA.

To our knowledge, only a few studies have been published regarding this issue [12,13,16,17]. Winters *et al.* examined whether passive transfer of anti-IgA through transfusion of apheresis PLTs was associated with an increase risk of allergic reactions. A total of 25 apheresis PLTs containing anti-IgA from only four donors were transfused to 22 recipients. No adverse reactions were attributed to transfusion of these products. This was compared to 78 apheresis PLT transfusions from 60 donors without anti-IgA where one allergic transfusion reaction was observed [13]. As in our study, the authors concluded that transfusion of anti-IgA-containing components did not pose an increased risk of reaction in recipients. Vyas *et al.* [12] in a small study of 13 recipients having received a component (type not specified) with anti-IgA did not identify any adverse transfusion reaction.

The overall 1·5% rate of allergic transfusion reactions in our study is comparable with results from published studies, suggesting that our chart review and adjudicating processes were appropriately conducted [3].

Nevertheless, there are several limitations to the present study. Not all hospitals agreed to participate but the proportion of components issued to the non-participating hospitals was probably too small (2·5%) to affect the results. This study was conducted through a retrospective chart review, and the quality of the monitoring of patients during the

Table 2 Characteristics of recipients

	Group A (transfused with components containing anti-IgA)	Group B (transfused with components without anti-IgA)	P-value
No. of recipients	174	98	
Age (mean)	56·8	61·4	0·13
Gender			
Male	84 (48·3%)	49 (50·0%)	0·78
Female	90 (51·7%)	49 (50·0%)	
Pre-medication			
Any	11 (6·3%)	6 (6·1%)	0·95
Antihistamines	9 (5·2%)	5 (5·1%)	0·98
Steroids	7 (4·0%)	3 (3·1%)	0·68
Antipyretics	2 (1·1%)	3 (3·1%)	0·36
Diagnosis			
Haematological malignancies	34 (19·5%)	21 (21·4%)	0·30
Other malignancies	19 (10·9%)	10 (10·2%)	
Surgery	35 (20·1%)	14 (14·3%)	
Gastrointestinal bleeding	24 (13·8%)	16 (16·3%)	
Haematological disorders	15 (8·6%)	7 (7·1%)	
Hematopoietic stem cell transplant	10 (5·7%)	1 (1·0%)	
Others	33 (19·0%)	28 (28·6%)	
Unspecified	4 (2·3%)	1 (1·0%)	

Table 3 Adverse transfusion reactions identified for the 272 blood components with and without anti-IgA

	Anti-IgA		No anti-IgA		Total	
	N	(%)	N	(%)	N	(%)
Minor allergic	2	1·15	2	2·04	4	1·47
Volume overload	–	–	1	1·02	1	0·37
Indeterminate reaction	–	–	1	1·02	1	0·37
No reaction	172	98·85	94	95·92	266	97·79
Total	174	100·0	98	100·0	272	100·0

transfusion was not known. Although some minor reactions could have been missed, major allergic reactions would have probably been noted in the charts, especially since a hemovigilance system is in place since 2000 in Quebec with a high level of sensitization in reporting adverse transfusion events [15]. The review of the charts and the adjudicating processes were conducted blindly to the donor anti-IgA status, thus minimizing the information bias inherent to retrospective studies.

We assumed that if a donor had anti-IgA, all prior donations contained anti-IgA. From Héma-Quebec's experience, once a blood donor has developed anti-IgA, it remains stable over time. However, we know from our work that seroconversion is not a frequent event; the seroconversion rate has been estimated to be 0·014/year/donor. Therefore, assuming stability in anti-IgA status seems a reasonable assumption.

The retrospective nature of our study presents some limitations. We had no control over the quality of monitoring of the recipients during the transfusion; some reactions may have been missed or not recorded in the patient charts. We made sure, however, that the research nurse was well trained to review the charts and was blinded to the anti-IgA status of the products. We also reviewed the QHS data to look for reactions associated with the products included in the study, and none were found. A prospective study would have been the ideal design to clearly answer whether transfusing anti-IgA-containing blood components is a safe practice. However, such a study would require 5196 subjects (2598 in each group) to detect a two-fold difference between the two groups with an estimated incidence of 1% for allergic reactions in general. The study would have to be 10 times larger to study for major allergic reactions.

Another limitation of our study is that there were very few apheresis products transfused in our study. However, there were 75 plasma-containing components (including 19 plasma) transfused, which represents a higher number than in previously published studies. Furthermore, the number of donors involved in our study (31 without anti-IgA and 40 with anti-IgA) as well as the number of recipients represents the largest numbers studied to date. Nevertheless, this study was not adequately powered to detect a difference in rates of allergic reactions between groups, which might explain why no difference was observed.

This study, as others have previously shown, did not find evidence of increased risk of adverse reactions associated with transfusion of anti-IgA-containing blood components. This is possibly because of the rapid dilution of anti-IgA antibodies after transfusion, or to the absence of anti-IgA of the IgE class. It appears from this and previous studies that testing IgA-deficient blood donors for the presence of anti-IgA and implementing a restrictive policy for those known to have developed anti-IgA antibodies may not be justified. Moreover, as only 5·1% of Héma-Québec donors were tested for IgA deficiency and anti-IgA, it is reasonable to assume that a significant number of donors with anti-IgA regularly donate. Allowing donors with anti-IgA would therefore increase the availability of blood components for IgA-deficient recipients because about half of IgA-deficient donors have a positive test for anti-IgA. Furthermore, testing for the presence of anti-IgA antibodies is only available in specialized reference laboratories, thus increasing the cost and complexity of supplying IgA-deficient components to patients in need.

As with other donor selection criteria, it is very difficult to remove criteria once in place. It is important to state that there are no recommendations concerning anti-IgA testing of donors put on IgA-deficient donor registries. In addition to our study and to the other case series cited in our article, there is evidence that anti-IgA in blood products is not a significant factor in transfusion reactions. Since November 2007, Héma-Québec flags in its computer system, all donors involved in a severe allergic reaction reported to them through the QHS. Only one donor was involved in two separate reactions and in that case, the relevant donor history was penicillin allergy. If anti-IgA had been a significant factor, based on our experience in donor screening for IgA deficiency [9], we would expect many more donors to be involved in clusters of severe allergic reactions than what we observed.

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