

ORIGINAL PAPER

Factors related to allergic transfusion reactions and febrile non-haemolytic transfusion reactions in children

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Vox Sanguinis

Background and Objectives Allergic transfusion reactions (ATRs) and febrile non-haemolytic transfusion reactions (FNHTRs) are the two major types of transfusion-related adverse reactions (TRARs). Although prestorage leucocyte reduction and diversion of the first aliquot of blood (LR/D) could reduce FNHTRs and bacterial contamination in adult transfusion, ATRs are still problematic. In addition, there is little information about TRARs in paediatric population.

Materials and Methods We conducted a single-centre retrospective analysis of all transfusions, except washing products, and TRARs for 153 months to evaluate related factors such as delivery of treatment and the characteristics of recipients.

Results Most TRARs were FNHTRs and/or ATRs in children. In delivering blood products with LR/D, the frequencies of not only FNHTRs but also ATRs were significantly reduced with both platelet concentrates (PCs) and red cell concentrates (RCCs). TRARs of fresh-frozen plasma were infrequent in children. In addition, even after the introduction of LR/D, ATRs were significantly more frequent in patients with primary haematological and malignant diseases who received PCs and RCCs, older patients who received PCs and patients who received frequent RCCs.

Conclusion These results suggest that leucocytes or mediators from leucocytes are underlying cause of ATRs in addition to FNHTRs in children. Furthermore, particular characteristics of patients would be other risk factors for ATRs.

Key words: allergic transfusion reaction, diversion method, febrile non-haemolytic transfusion reaction, platelet concentrate, red cell concentrate, transfusion-related adverse reaction.

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Introduction

Although blood transfusion is an effective and essential treatment for numerous diseases and surgery, transfusion-

related adverse reactions (TRARs) are problematic. Allergic transfusion reactions (ATRs) and febrile non-haemolytic transfusion reactions (FNHTRs) are the two major types of TRARs [1]. Further, serious reactions such as transfusion-related acute lung injury (TRALI), haemolytic transfusion reaction and transfusion-associated circulatory overload may occur [2]. Leucocyte reduction (LR), which removes leucocytes from cellular blood compo-

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nents, reduces the rate of FNHTRs when patients are transfused with red cell concentrates (RCCs) and platelet concentrates (PCs) [3]. In particular, single-donor apheresis and prestorage LR reduce the frequency of FNHTRs [3]. However, LR is not effective for preventing ATRs, according to a previous report in adults [4]. In contrast, diversion of the first aliquot of blood (*diversion method*: D) reduces the risk of bacterial contamination of blood components [5–7].

In Japan, the criteria for blood collection were revised in 1986 to recommend collection volumes of 400 ml for whole-blood donation and apheresis, and the Japanese Red Cross Society started distributing irradiated blood components for transfusion in 1998. LR and the diversion method were first implemented in Japan in October 2004 and October 2006, respectively [1]. These measures gradually improved several years later (Fig. 1). Prestorage LR and the diversion method from a single donor were completely integrated into transfusion procedures after January 2008 in all products, including PC, RCC and fresh-frozen plasma (FFP). Nevertheless, the frequency of the TRARs associated with PCs remains high, with the majority representing ATRs [1, 8–10]. Another modification is necessary, such as the use of washing processes for recurrent ATRs associated with PCs [1, 8].

Although an abundance of data is available for adult patients, the limited information available from published studies on TRARs among paediatric patients. To address this issue, we conducted a single-centre retrospective analysis of all transfusions and TRARs including ATRs/FNHTRs during a 153-month period to evaluate factors related to ATRs that focused on blood components and collection techniques, as well as the backgrounds of recipients.

Materials and methods

Patient selection and transfused products

This retrospective study included paediatric patients (aged ≤ 18 years) who received transfusions at Nagano Children's Hospital from April 2002 to December 2014. The transfusion products included PCs, RCCs and FFPs that were each divided into control (C), LR, and LR and diversion method (LR/D) procedures based on product transition (Fig. 1). Because of the staggered introduction for the products, we categorized each products based on the day the blood drawn for that product. We excluded transfusion using secondary products such as washed PCs and RCCs that are used to prevent TRARs of patients with a history of TRAR. The Institutional Review Board of Nagano Children's Hospital approved

this study (approval number: 26-27). Written informed consent was signed by parents or guardian of the patients.

Analysis of TRARs

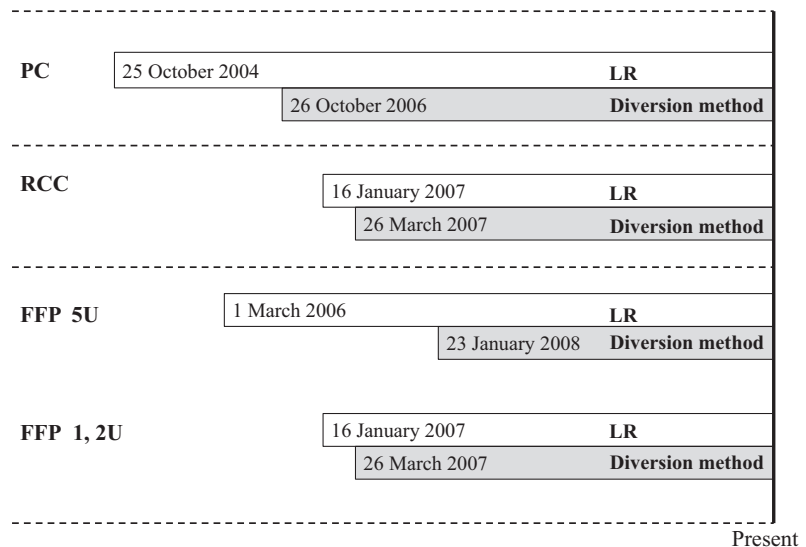
All TRARs and suspected symptoms related to transfusion were defined to physicians and/or nurses, who reported them to the Division of Blood Transfusion in our institution during the study period. All reported and suspected TRARs and symptoms were reviewed and re-evaluated by clinical course and data based on the medical records. We analysed the frequency of TRARs in each patient and product according to the type of product and then evaluated the frequencies of ATRs, FNHTRs and other reactions and total frequencies of TRARs.

To evaluate the association between ATRs/FNHTRs and a patient's background, we analysed the records of all patients who were transfused with PCs, RCCs or both that were manufactured after 26 March 2007. These PC and RCC products (and not FFP) were replaced completely by LR/D products after this date. We compiled data for age (<1 year; ≥ 1 year, <11 year; ≥ 11 years; classification was based on the previous report [11]), sex, history of allergy (food, rhinitis, other allergic disease and drug allergy), primary diseases (e.g. neonatal disorders, haematological and malignant diseases), ABO and Rh blood groups, number of each transfusion product received (more than six units or less, classification was based on the previous report [12]), history of transfusion using other products and history of TRARs caused by other products. If the same patient developed multiple ATRs/FNHTRs, we counted the number of transfusions to the first ATRs/FNHTRs.

Definitions of ATR and FNHTR

ATRs were assessed according to criteria described previously [1]. ATR was defined as the presence of at least two of the following during or within 4 h of transfusion: maculopapular rash with/without pruritus; urticaria; pruritus; generalized flushing; localized angioedema; oedema of lips, tongue and uvula; erythema and oedema of the periorbital area; conjunctival oedema; respiratory distress; bronchospasm; and hypotension. FNHTRs were characterized by fever ($\geq 1^\circ\text{C}$ elevation) that may be accompanied by chills, rigour, hypertension, tachycardia and dyspnoea without other clinical symptoms [3]. When the diagnosis of TRARs was difficult, the patients underwent several tests such as blood examination, urinary examination, culture and radiology examination to rule out differential diagnoses such as TRALI, infection.

Fig. 1 Timelines of the transitions to modified transfusion products in Japan designed to reduce the frequency of TRARs. Diversion method, diversion of the first aliquot of blood; FFP, fresh-frozen plasma; LR, prestorage leucocyte reduction; PC, platelet concentrate; RCC, red cell concentrate; TRAR, transfusion-related adverse reaction; U, unit.



Statistical analysis

We compared the frequency of TRARs associated with each product using Fisher's exact test. Candidate risk factors in a patient's background were evaluated using Fisher's exact test and logistic regression analysis. Potential factors with at least borderline significance ($P < 0.15$) identified using univariate analysis were included in multivariate analyses. All statistical analyses were performed using EZR [13]. Statistical significance was defined as $P < 0.05$.

Results

Frequency of TRARs associated with transfused products

We analysed all transfusions administered between April 2002 and December 2014 and compared the frequencies of TRARs associated with PCs, RCCs and FFPs. We defined the three different periods of time to clarify, correlated with the Japanese Red Cross Society approach and the transition of blood products (Fig. 1), that C-period (2002–2007), LR-period (2004–2008) and LR/D-period (2006–2014). The data are expressed as the ratios (%) of patients or products in the number of each of TRARs (Table 1).

TRARs after PC transfusion

In this analysis, total TRARs, including FNHTR and ATR, were significantly reduced through the C-period to LR/D-period, although there were variable of significance in ratio per patients and/or blood product. Furthermore,

transition of C-period to LR-period had also significance in total TRARs including FNHTR and ATR, in the analysis of ratio per products.

TRARs after RCC transfusion

In this analysis, total TRARs, including FNHTR and ATR, were significantly reduced between the C-period and LR/D-period. However, there were no significant differences in analysis findings of each product between C-period to LR-period and LR-period to LR/D-period.

TRARs after FFP transfusion

There were no significant differences in the analysis findings of the effects of FFPs.

Characteristics of patients experiencing ATRs/FNHTRs associated with LR/D-PCs and RCCs

We next analysed the association of ATRs/FNHTRs with the backgrounds of patients who were transfused with PCs and RCCs which manufactured in each LR/D-period. Of the 552 patients who received LR/D-PCs, 42 (7.6%) had TRARs, including 38 (90.5%), 3 (7.1%) and 1 (2.4%) with ATRs, FNHTRs and other reaction, respectively. We next focused on the association of ATRs and FNHTRs with patients' backgrounds. Univariate analysis indicated that the ATRs of patients transfused using LR/D-PC were significantly associated with the variables follows: older age ($P < 0.001$), male ($P = 0.028$), haematological and malignant disease ($P < 0.001$), higher numbers of transfusions ($P < 0.001$) and history of transfusion with other products ($P < 0.001$). Multivariate analysis including these variables revealed significant independent risk

Table 1 Number of transfusions, analysis of TRARs and types of products administered

Transfused product	PC			RCC			FFP		
Treatment for product	C	LR	LR/D	C	LR	LR/D	C	LR	LR/D
Total number of transfused patients	163	149	577	795	50	1454	531	46	746
Total number of transfused products	1218	1296	4337	3789	140	7770	4291	158	2744
Total TRAR									
Number of patients	23	11	46	22	0	11	2	0	1
Ratio per patients (%)	14.11	7.38	7.97	2.77	0.00	0.76	0.38	0.00	0.13
<i>P</i> value	0.069			0.635			1.000		
	0.022			<0.001			0.574		
Number of products	47	14	68	35	0	12	2	0	1
Ratio per blood products (%)	3.86	1.08	1.57	0.92	0.00	0.15	0.05	0.00	0.04
<i>P</i> value	<0.001			0.636			1.000		
	<0.001			<0.001			1.000		
FNHTR									
Number of patients	6	2	3	9	0	1	0	0	0
Ratio per patients (%)	3.68	1.34	0.52	1.13	0.00	0.07	0.00	0.00	0.00
<i>P</i> value	0.287			1.000			1.000		
	0.005			<0.001			1.000		
Number of products	12	2	4	12	0	1	0	0	0
Ratio per blood products (%)	0.99	0.15	0.09	0.32	0.00	0.01	0.00	0.00	0.00
<i>P</i> value	0.006			1.000			1.000		
	<0.001			<0.001			1.000		
ATR									
Number of patients	17	7	41	12	0	9	1	0	1
Ratio per patients (%)	10.43	4.70	7.11	1.51	0.00	0.62	0.19	0.00	0.13
<i>P</i> value	0.087			1.000			1.000		
	0.186			0.041			1.000		
Number of products	31	9	62	21	0	10	1	0	1
Ratio per blood products (%)	2.55	0.69	1.43	0.55	0.00	0.13	0.02	0.00	0.04
<i>P</i> value	<0.001			1.000			1.000		
	0.011			<0.001			1.000		
Other									
Number of patients	4	2	2	2	0	1	1	0	0
Ratio per patients (%)	2.45	1.34	0.35	0.25	0.00	0.07	0.19	0.00	0.00
<i>P</i> value	0.686			1.000			1.000		
	0.024			0.286			1.000		
Number of products	4	2	2	2	0	1	1	0	0
Ratio per blood products (%)	0.33	0.15	0.05	0.05	0.00	0.01	0.02	0.00	0.00
<i>P</i> value	0.439			1.000			1.000		
	0.024			0.252			1.000		

ATR, allergic transfusion reaction; C, control; FFP, fresh-frozen plasma; FNHTR, febrile non-haemolytic transfusion reaction; LR, prestorage leucocyte reduction; LR/D, prestorage leucocyte reduction and diversion of the first aliquot of blood; TRAR, transfusion-related adverse reaction; PC, platelet concentrate; RCC, red cell concentrate.

Table 2 Analysis of risk factors for the development of ATRs

(A) Univariate analysis		LR/D-PC			LR/D-RCC		
Transfusion products		Number of patients (total <i>n</i> = 552)		<i>P</i> value	Number of patients (total <i>n</i> = 1448)		<i>P</i> value
Variable			Number of patients with ATR (<i>n</i> = 38)			Number of patients with ATR (<i>n</i> = 9)	
Age							
<1 years	328	2 (0.6%)	<0.001		960	3 (0.3%)	0.053
≥1, <11 years	152	26 (17.1%)			372	4 (1.1%)	
≥11 years	72	10 (13.9%)			116	2 (1.7%)	
Sex							
Male	296	27 (9.1%)	0.028		742	6 (0.8%)	0.508
Female	256	11 (4.3%)			706	3 (0.4%)	
Allergic history							
None	460	28 (6.1%)	0.102		1247	7 (0.6%)	0.251
Food, Rhinitis, Others	51	4 (7.8%)			132	2 (1.5%)	
Drug	41	6 (14.6%)			69	0 (0.0%)	
Primary disease of patients							
Neonatal disorders	136	0 (0.0%)	<0.001		415	1 (0.2%)	<0.001
Haematological and malignant diseases	98	34 (34.7%)			121	6 (5.0%)	
Others	318	4 (1.3%)			912	2 (0.2%)	
ABO blood group							
A	190	14 (7.4%)	0.663		515	4 (0.8%)	0.930
B	127	11 (8.7%)			343	2 (0.6%)	
O	174	9 (5.2%)			440	3 (0.7%)	
AB	61	4 (6.6%)			150	0 (0.0%)	
Rh blood group							
(+)	550	38 (6.9%)	1.000		1440	9 (0.6%)	1.000
(-)	2	0 (0%)			8	0 (0.0%)	
Number of receiving transfusion products							
<6 times	433	20 (4.6%)	<0.001		1054	2 (0.2%)	0.002
≥6 times	119	18 (15.1%)			394	7 (1.8%)	
Other transfusion history							
Yes	415	37 (8.9%)	<0.001		862	3 (0.3%)	0.170
None	137	1 (0.7%)			586	6 (1.0%)	

Table 2 (Continued)

(A) Univariate analysis		LR/D-PC		LR/D-RCC	
Transfusion products		Number of patients (total <i>n</i> = 552)		Number of patients (total <i>n</i> = 1448)	
Variable			<i>P</i> value		<i>P</i> value
History of ATR in other transfusion products					
Yes	5	1 (20.0%)	0.301	34	2 (5.9%)
None	547	37 (6.8%)		1414	7 (0.5%)
(B) Multivariate analysis		LR/D-PC		LR/D-RCC	
Transfusion product		Odds ratio (95% CI)		Odds ratio (95% CI)	
Variables			<i>P</i> value		<i>P</i> value
Age	<1 years	0.403 (0.230–0.707)	0.002	ns	
Primary disease of patients	Haematological and malignant diseases	5.840 (3.090–11.000)	<0.001	4.140 (1.670–10.300)	0.002
Number of receiving transfusion products		ns		5.730 (1.100–29.900)	0.038

ATR, allergic transfusion reaction; CI, confidence interval; LR/D, prestorage leucocyte reduction and diversion of the first aliquot of blood; ns, non-significant; PC, platelet concentrate; RCC, red cell concentrate.

factors for ATRs as follows: age <1 year (hazard ratio [HR]: 0.403, 95% confidence interval [CI]: 0.230–0.707; $P = 0.002$) and primary haematological and malignant diseases (HR: 5.840, 95% CI: 3.090–11.000; $P < 0.001$) (Table 2).

Univariate analysis of FNHTRs caused by transfusion using LR/D-PC revealed a significant association with the variables as follows: age (<1 year 0.0% vs. ≥ 1 year, <11 year 0.7% vs. ≥ 11 years 2.8%; $P = 0.016$) and primary disease (neonatal 0% vs. haematological and malignant diseases 3.1% vs. others 0%; $P = 0.005$). However, multivariate analysis did not identify these as significant factors.

In contrast, 11 (0.8%) of 1448 patients who received transfusions using LR/D-RCC experienced TRARs that included 9 (81.8%) with ATRs and one of each of FNHTR and other (9.1%). Univariate analysis of the backgrounds of patients with ATRs caused by LR/D-RCCs revealed significant associations with the variables as follows: haematological and malignant diseases ($P < 0.001$), higher number of transfusions ($P = 0.002$) and history of TRARs caused by other products ($P = 0.017$). Multivariate analysis including these variables revealed the significant independent risk factors as follows: primary haematological and malignant diseases (HR: 4.140, 95% CI: 1.670–10.300; $P = 0.002$) and number of transfusions with LR/D-RCC ≥ 6 (HR: 5.730, 95% CI: 1.100–29.900; $P = 0.038$) (Table 2). Univariate, but not multivariate, analysis revealed that FNHTRs caused by LR/D-RCC in patients with a history of TRARs who received other products was a significant factor (yes 3.0% vs. none 0.0%; $P = 0.024$).

Discussion

In transfusions using PCs and RCCs, introduction of delivery method with LR and LR/D products was effective for reducing the frequencies of not only FNHTRs but also ATRs, when the types of products were analysed. In the analysis of PC products, this achievement was possible mainly after the introduction of LR products. On the other hand, we were unable to detect a significant difference in RCC products between the outcomes of transfusions during LR-period; this may be attributed to the insufficient number of transfusions performed using RCC products during the period analysed as well as the associated insufficient statistical power. Although the role of leucocytes and mediators is well accepted in FNHTRs, transfused leucocytes may cause several transfusion-related immunological responses by immunomodulatory mechanisms (e.g. cancer recurrence, postoperative infection or virus activation), pro-inflammatory mechanisms (e.g. multiple organ failure or mortality) or others [14]. Although the mechanisms of ATRs are not fully

understood, leucocytes and mediators from leucocytes may be the causes of ATRs in children. In contrast, ATRs/FNHTRs associated with FFPs are extremely rare regardless of the transition to the new products. This different frequency from adult transfusions [9, 10] may also support characteristic causes of ATRs in children because FFP does not allow contamination of living leucocytes.

Furthermore, together with FNHTRs, the frequencies of other reactions were reduced during LR/D-period compared with LR-period in PC products, although the differences were not significant. Thus, several responses diagnosed as FNHTR and others might be related to bacterial contamination, even though we did not find any evidence on blood cultures or other diagnostic techniques. Although time-consuming, labour-intensive and not very economical, the introduction LR and LR/D products may considerably enhance protection from TRARs.

Multivariate analysis of patients with haematological and malignant diseases revealed a higher risk for ATRs of patients who received transfusions using LR/D-PC and LR/D-RCC. Further, lower age was associated with a low risk of ATRs in patients who received transfusions using LR/D-PC, and multiple transfusions were associated with a high risk of ATRs in patients who were transfused using LR/D-RCC. One possibility that may explain the high frequency of ATRs in patients with haematological and malignant diseases is an imbalance of Th1/Th2 cytokine profiles [15–18]. An increased Th2 and decreased Th1 profile is exhibited by patients with haematological malignancies and other cancers, suggesting the contribution of other immunological disorders [16]. Moreover, patients with predisposition to allergies might suffer from more severe allergic diseases such as asthma that is accompanied by the initiation or progression of cancer [19]. Although we did not detect an association between allergies and ATRs in the present study, a recipient's atopic predisposition may be an important factor associated with ATRs [20]. Clinical analysis of transfusion recipients who experience ATRs indicates that they are more atopic than those who do not experience ATRs [21]. Therefore, the immunological dysfunction of patients with haematological or malignant diseases might be related to their high frequency of ATRs.

In this analysis, there were significant differences in frequencies of ATRs with PC transfusion as a function of age. Another report supported this bias in higher incidence of paediatric TRARs in older age [22]. The frequency of certain allergic diseases varies with increased age in children based on allergens.[23, 24] Therefore, allergens present in blood products [25] may sensitize paediatric recipients related to older age and cause the higher frequency of ATRs. On the other hand, there was

no statistical difference in the age distribution in other reports [11, 26], although paediatric population had significantly higher number of TRARs than did adults [26]. Therefore, further careful analysis would be necessary because there was only limited report in different method of analysis in this strategy.

The number of transfusions with RCCs, but not PCs, was also significantly associated with ATRs. Although evidence indicates that the pathogenesis of ATRs requires sensitization of patients by plasma [25], the risk of ATRs such as a severe urticarial reaction is highest among the first five transfusions using PCs [12], and repeated exposure to PCs does not appear to increase the likelihood of an ATR [27–29]. A more likely possibility is that the first transfusion of PC induces an ATR [10]. This might be related to the plasma content of PC preparations. Multiple transfusions using PCs does not always affect the frequency of ATRs, because a single PC transfusion may expose the patient to a sufficient amount of plasma to induce a reaction. However, the level of plasma in RCCs may require multiple transfusions to induce sensitization.

In conclusion, the transition to modified transfusion products including LR reduced the frequencies of not only FNHTRs but also ATRs associated with PCs and RCCs in children. This result may indicate the leucocytes and mediators from leucocytes were one of the causes in both ATRs and FNHTRs. In addition, the incidence of ATR was higher in patients with primary haematological and malignant diseases who received transfusions of PCs and RCCs transfusion as well as for older patients who received PCs and those who received multiple transfusions of RCCs. The individual patient factors also influence the rate of ATR in children. However, further evaluation is warranted in the form of prospective studies, particularly for evaluation of factors related to patient characteristics.

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Conflict of interest

The authors have no potential conflict of interests to declare.

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Author contributions

Dr. Yanagisawa conceptualized and designed the study, drafted the initial manuscript and approved the final manuscript as submitted. Dr. Shimodaira designed the data collection instruments, co-ordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. Dr. Saka-

shita and Dr. Hidaka were involved in acquiring study data, played a major role in the conception, design and interpretation of the study, carried out the statistical analysis, critically reviewed the manuscript and approved the final manuscript as submitted. Mr Kojima, Ms Nishijima and Ms Hidaka carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted. Dr. Shiohara and Dr. Nakamura played the principal role in acquiring the study data; played a major role in the conception, design, analysis and interpretation of the study; and critically reviewed the manuscript and approved the final manuscript as submitted.

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