

Analysis of Acute Transfusion Reactions and Their Occurrence Times

Yuki Hatayama,*† Satoko Matsumoto,* Eiko Hamada,* Nao Kojima,* Ayako Hara,* Norihiko Hino*‡ and Toru Motokura†

*Division of Clinical Laboratory, Tottori University Hospital, Yonago 683-8504, Japan, †Division of Clinical Laboratory Medicine, Department of Pathophysiological and Therapeutic Science, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8503, Japan, and ‡Division of Blood Transfusion, Tottori University Hospital, Yonago 683-8504, Japan

ABSTRACT

Acute transfusion reactions (ATRs) are significantly relevant to the morbidity and mortality of patients. ATRs are mostly not severe and rarely cause severe conditions, including anaphylactic shock. The aim of this study was to clarify the frequency of ATRs and the time of event occurrence. A total of 18,745 transfusions were administered to 11,718 patients during a 3-year period. Adverse reactions including at least one sign or symptom were collected through a report system in 143 of 2,478 (5.7%) platelet concentrate transfusions, 105 of 6,629 (1.6%) red blood cell component transfusions and 51 of 2,307 (2.2%) fresh frozen plasma transfusions. Allergic signs and symptoms accounted for 70% of all adverse events. Severe signs and symptoms were observed in 7.1% of patients. These events appeared significantly earlier than those of non-severe signs and symptoms (median time 20 min vs 100 min, $P < 0.05$). For patients who have had repetitive transfusion-associated adverse events, preventive treatments for adverse events should be proactively promoted.

Key words acute transfusion reaction; blood transfusion; hemovigilance; occurrence time

Transfusion-associated adverse events are mainly immunological acute transfusion reactions (ATRs). It is known that the distribution of signs and symptoms differ according to the types of blood components, numbers of transfusions, and patient's condition.¹⁻³ ATRs are mostly not severe but rarely cause severe diseases including transfusion-related acute lung injury (TRALI) and anaphylactic shock. Thus, it is important for health professionals to monitor patients during and after transfusion.

It is essential to establish a system for monitoring, recording and reporting adverse reactions caused by blood transfusion in each hospital, thereby contributing

to the National Hemovigilance System in Japan. All medical institutions report adverse events following transfusion to the Japanese Red Cross Society if they recognize that the event is due to the transfusion itself. However, there are some problems associated with this self-reporting system; e.g. mild adverse events may not be reported.⁴

We constructed a system to monitor all patients who received transfusion and collected data regarding post-transfusion adverse reactions and event occurrence times.⁵ The aim of this study was to clarify the frequency of ATRs and the time to event occurrence.

MATERIALS AND METHODS

All patients who received transfusion at our facility within a 3-year period from January 2014 to December 2016 were included in this retrospective study. A transfusion was defined as an episode of transfusion of any blood component, regardless of dose or volume transfused. All blood components, i.e., leukocyte-reduced red blood cell (RBC-LR), fresh frozen plasma (FFP-LR), and platelet concentrate (PC-LR), were provided by the Japanese Red Cross Blood Center. The following data were collected for all study subjects: age, gender, clinical department, signs and symptoms of adverse reactions, and event occurrence time.

The transfusion-related signs and symptoms reported were based on the Japanese Society of Transfusion Medicine and Cell Therapy definition of hemovigilance. Respiratory distress, hypotension, disturbance of consciousness and hemoglobinuria were defined as severe signs and symptoms. This study was approved by the Ethics Committee at Tottori University Faculty of Medicine (approval number: 1706A060).

Statistical analysis

Comparisons among qualitative variables (categorical data) were performed using Pearson's chi-square test. A p value of less than 0.05 was considered significant. Time to event occurrence was analyzed with the Kruskal-Wallis test and Mann-Whitney U test. All statistical analyses were performed using SPSS version 16.0 (IBM, Armonk, NY).

Corresponding author: Yuki Hatayama

y-hata@umin.ac.jp

Received 2017 November 22

Accepted 2017 December 25

Abbreviations: ATR, acute transfusion reaction; FFP, fresh frozen plasma; LR, leukocyte-reduced; PC, platelet concentrate; RBC, red blood cell; TRALI, transfusion-related acute lung injury

Table 1. Frequency of acute transfusion reactions

	RBC-LR		FFP-LR		PC-LR		Total	
Transfusions	6,629	(100)	2,307	(100)	2,487	(100)	11,423	(100)
Adverse Reactions	105	(1.6)	51	(2.2)	143	(5.7*)	299	(2.6)
Signs and Symptoms	121	(100)	77	(100)	207	(100)	405	(100)
Urticaria	28	(23.1)	40	(51.9)	91	(44.0)	159	(39.3)
Pruritus	12	(9.9)	18	(23.4)	54	(26.1)	84	(20.7)
Skin rash	5	(4.1)	6	(7.8)	22	(10.6)	33	(8.1)
Fever	30	(24.8)	1	(1.3)	11	(5.3)	42	(10.4)
Feverishness	5	(4.1)	0	(0.0)	6	(2.9)	11	(2.7)
Hypotension	5	(4.1)	5	(6.5)	5	(2.4)	15	(3.7)
Nausea/vomiting	7	(5.8)	1	(1.3)	5	(2.4)	13	(3.2)
Respiratory distress	5	(4.1)	2	(2.6)	3	(1.4)	10	(2.5)
Tachycardia	8	(6.6)	2	(2.6)	0	(0.0)	10	(2.5)
Hypertension	5	(4.1)	1	(1.3)	0	(0.0)	6	(1.5)
Chill/rigor	4	(3.3)	1	(1.3)	5	(2.4)	10	(2.5)
Vein pain	5	(4.1)	0	(0.0)	0	(0.0)	5	(1.2)
Others	1	(0.8)	0	(0.0)	2	(1.0)	3	(0.7)
Disturbance of consciousness	0	(0.0)	0	(0.0)	3	(1.4)	3	(0.7)
Hemoglobinuria	1	(0.8)	0	(0.0)	0	(0.0)	1	(0.2)

Values are expressed as numbers with percent in parentheses. The underlined items are defined as severe signs and symptoms. * $P < 0.05$, Chi-squared test. FFP, fresh frozen plasma; LR, leukocyte-reduced; PC, platelet concentrate; RBC, red blood cell.

RESULTS

Frequency of ATRs

Between January 2014 and December 2016, a total of 18,745 transfusions were administered to 11,718 patients. Blood components administered were 3,728 PC-LRs, 10,246 RBC-LRs and 4,478 FFP-LRs. No differences in age and gender were found between patients for whom ATRs were reported and those for whom ATRs were not reported. ATRs having at least one sign or symptom were 143 of 2,478 (5.7%) PC-LR transfusions, 105 of 6,629 (1.6%) RBC-LR transfusions, and 51 of 2,307 (2.2%) FFP-LR transfusions. The frequency of ATRs in PC-LR transfusions were significantly higher than those in RBC-LR and FFP-LR transfusions (chi-squared test, $P < 0.05$).

Frequency of signs and symptoms reported

The frequency of signs and symptoms are shown in Table 1. Allergic signs and symptoms including urticaria, pruritus and skin rash accounted for 70% of all signs and symptoms. PC-LR and FFP-LR showed high frequencies of 80.7% and 83.1%, respectively, while RBC-LR showed only 37.1%. On the contrary, fever, tachycardia and hypertension were more frequent with RBC-LR than PC-LR and FFP-LR. Severe signs and symptoms (respiratory distress, hypotension, disturbance of consciousness and hemoglobinuria) comprised 7.1% of all signs and symptoms.

Time to event occurrence

We evaluated the time from initiation of transfusion to the occurrence of signs and symptoms (Fig. 1). There was no significant difference among blood components (100 min vs 100 min vs 102.5 min, $P = 0.19$, Kruskal-Wallis test). Severe signs and symptoms appeared significantly earlier than non-severe ones (20 min vs 100 min, $P < 0.01$, Mann-Whitney U test).

DISCUSSION

Blood transfusion therapy is an effective and indispensable treatment, but adverse events such as infectious diseases and immune reactions cannot be completely avoided. The risk factors of severe transfusion-related diseases including TRALI and anaphylactic shock depend on patient's disease, number of transfusions, and history of adverse events.⁶⁻⁹ Thus, it is necessary to list the patients who have ever had signs and symptoms after transfusion. We constructed a system of transfusion-associated signs and symptoms to be reported for all transfused patients, which made it possible to accurately assess the frequency of adverse reactions.⁵

The frequency of adverse events with all blood products in the current study was higher than those in other facilities.^{1-3, 10-12} This is because even minor symptoms are fully reported in our facility and there are many patients who had adverse events repetitively, especially in the departments of hematology and pediatrics, in which blood transfusions were repeated in patients, exposing

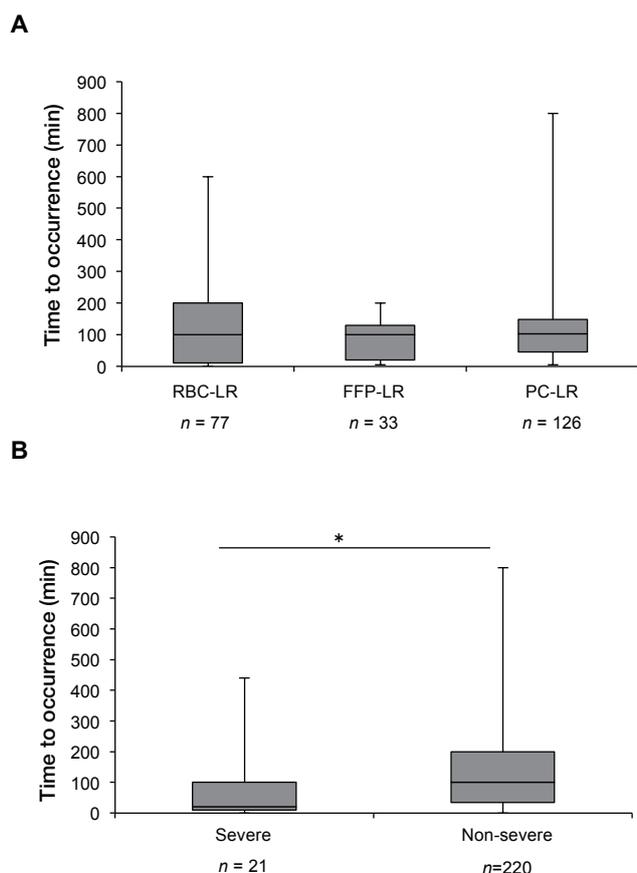


Fig. 1. Comparison of times from transfusion start to event occurrence (**A**) among blood components and (**B**) between severe and non-severe signs and symptoms. Respiratory distress, hypotension, disturbance of consciousness and hemoglobinuria are defined as severe signs and symptoms * $P < 0.05$, Mann-Whitney U test. FFP, fresh frozen plasma; LR, leukocyte-reduced; PC, platelet concentrate; RBC, red blood cell.

them to the plasma components of multiple donors.^{6,7} In addition, prophylactic administration was infrequent and the use of washed blood components was rare. There are some reports that prophylactic administration and use of washed blood components are effective for prevention of allergic transfusion reactions.^{13, 14} Because history of adverse events is one of the risk factors for severe transfusion-related disease for patients who had recurrent adverse events, even with mild symptoms, these treatments should be enforced to prevent severe transfusion-related diseases.

There was no significant difference in event occurrence times among blood components, but severe signs and symptoms appeared significantly earlier than non-severe ones. However, fatal transfusion-related events were not reported. There were cases in which adverse reactions occurred after 10 hours or more; it is therefore necessary to be vigilant during and after

transfusion. These data may be useful to determine the observation time after blood transfusion at the outpatient clinic or at home. The 95th percentile of severe signs and symptoms occurrence time was 130 min, suggesting that we should observe patients for at least 2 hours after starting blood transfusion.

In conclusion, a high frequency of transfusion-related signs and symptoms was found through the report system. For patients who have transfusion-associated adverse events repetitively, the use of prophylactic medications or washed blood components and preventive treatments for adverse events should be proactively promoted.

Acknowledgements: We would like to thank Editage (www.editage.jp) for English language editing.

The authors declare no conflict of interest.

REFERENCES

- Heddle NM, Blajchman MA, Meyer RM, Lipton JH, Walker IR, Sher GD, et al. A randomized controlled trial comparing the frequency of acute reactions to plasma-removed platelets and prestorage WBC-reduced platelets. *Transfusion*. 2002;42:556-66. PMID: 12084163.
- Savage WJ, Tobian AA, Fuller AK, Wood RA, King KE, Ness PM. Allergic transfusion reactions to platelets are associated more with recipient and donor factors than with product attributes. *Transfusion*. 2011;51:1716-22. PMID: 21214586.
- Kato H, Uruma M, Okuyama Y, Fujita H, Handa M, Tomiyama Y, et al. Incidence of transfusion-related adverse reactions per patient reflects the potential risk of transfusion therapy in Japan. *American journal of clinical pathology*. 2013;140:219-24. PMID: 23897258. Japanese with English Abstract.
- Iwao N, Kato H, Odaka C, Takamoto S, Sagawa K, Fujii Y, et al. UNDERREPORTING IN REPORTING SYSTEM FOR ADVERSE TRANSFUSION REACTIONS. *Japanese Journal of Transfusion and Cell Therapy*. 2015;61:561-6. DOI: 10.3925/jjtc.61.561. Japanese with English Abstract.
- Hatayama Y, Matsumoto S, Hamada E, Kojima N, Hara A, Motokura T. EVALUATION OF THE RENEWAL OF A BLOOD TRANSFUSION MANAGEMENT SYSTEM. *Japanese Journal of Transfusion and Cell Therapy*. 2016;62:684-8. DOI: 10.3925/jjtc.62.684. Japanese with English Abstract.
- Li N, Williams L, Zhou Z, Wu Y. Incidence of acute transfusion reactions to platelets in hospitalized pediatric patients based on the US hemovigilance reporting system. *Transfusion*. 2014;54:1666-72. PMID: 24410992.
- Fujii Y, Tanaka A, Odaka C, Kato H, Yonemura Y, Fujishima N, et al. INVESTIGATIONS OF ADVERSE TRANSFUSION REACTIONS ACCORDING TO CLINICAL DEPARTMENTS OF UNIVERSITY HOSPITALS IN JAPAN. *Japanese Journal of Transfusion and Cell Therapy*. 2016;62:451-8. DOI: 10.3925/jjtc.62.451. Japanese with English Abstract.
- Smith NK, Kim S, Hill B, Goldberg A, DeMaria S, Zerillo J. Transfusion-Related Acute Lung Injury (TRALI)

- and Transfusion-Associated Circulatory Overload (TACO) in Liver Transplantation: A Case Report and Focused Review. *Seminars in cardiothoracic and vascular anesthesia*. 2017;1089253217736298. PMID: 29025378.
- 9 Andreu G, Boudjedir K, Muller JY, Pouchol E, Ozier Y, Fevre G, et al. Analysis of Transfusion-Related Acute Lung Injury and Possible Transfusion-Related Acute Lung Injury Reported to the French Hemovigilance Network From 2007 to 2013. *Transfus Med Rev*. 2018;32:16-27. PMID: 28864336.
 - 10 Negi G, Gaur DS, Kaur R. Blood transfusion safety: A study of adverse reactions at the blood bank of a tertiary care center. *Adv Biomed Res*. 2015;4:237. PMID: 26682203.
 - 11 Kato H, Takamoto S, Odaka C, Sagawa K, Hoshi Y, Fujii Y, et al. ANALYSIS OF TRANSFUSION-RELATED ADVERSE EVENTS BASED ON A PILOT STUDY -TOWARD A COMPREHENSIVE HEMOVIGILANCE SYSTEM FOR JAPAN. *Japanese Journal of Transfusion and Cell Therapy*. 2011;57:178-83. DOI: 10.3925/jjtc.57.178. Japanese with English Abstract.
 - 12 Odaka C, Kato H, Otsubo H, Takamoto S, Okada Y, Taneichi M, et al. Online reporting system for transfusion-related adverse events to enhance recipient haemovigilance in Japan: a pilot study. *Transfus Apher Sci*. 2013;48:95-102. PMID: 22954634.
 - 13 Watanabe J, Sato K, Horiuchi T, Ito K, Iwanaga S, Sakaguchi T, et al. EFFECTIVENESS OF PRE-TRANSFUSION MEDICATION IN PREVENTING PLATELET TRANSFUSION REACTION. *Japanese Journal of Transfusion and Cell Therapy*. 2015;61:8-13. DOI: 10.3925/jjtc.61.8. Japanese with English Abstract.
 - 14 Tobian AA, Savage WJ, Tisch DJ, Thoman S, King KE, Ness PM. Prevention of allergic transfusion reactions to platelets and red blood cells through plasma reduction. *Transfusion*. 2011;51:1676-83. PMID: 21214585.