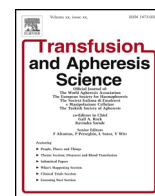




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A national survey of premedication for transfusion reactions in Japan

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ABSTRACT

Background: Premedication before transfusion is commonly administered in clinical practice despite a lack of evidence for its efficacy. The aim of this study was to clarify the status of premedication and evaluate expert opinions regarding its use in Japanese medical institutions.

Method: Between May and July 2016, we conducted a questionnaire survey on premedication before transfusion in 252 medical institutes that were certified by an academic society or employed transfusion experts.

Results: A total of 141 institutes (54.2%) responded, and hematologists (n = 113) comprised the most frequent respondents. The purpose of premedication was to prevent urticaria, pruritus, and fever, and washed blood products were used for anaphylactic shock or refractory transfusion reactions before. Drugs for premedication were intravenously administered either just before or 30 min before transfusion. Both inpatients and outpatients were premedicated in a similar manner, and institutional guidelines were not established. More than half of the experts recognized premedication as efficient and necessary, and premedication for previous transfusion reactions was frequently implemented, particularly for platelet transfusion or in patients with hematological diseases. Some institutions administered one or more drugs for premedication from the first transfusion. Antihistamines and hydrocortisone were the most frequently used as premedication.

Conclusion: Our study reports the current status of premedication for transfusion in Japan. Antihistamines and hydrocortisone were most commonly used for premedication despite a lack of evidence of their use. These findings may help clarify the indications for premedication and the use of washed blood products.

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1. Introduction

Transfusion-related adverse effects are classified into hemolytic or non-hemolytic reactions, and the latter can be further classified into immunological or non-immunological reactions. Among

these reactions, non-hemolytic immunological reactions such as fever and allergic reactions account for the majority of transfusion reactions [1]. It is generally accepted that leukocyte reduction in transfusion products alleviates immunological reactions [2]. In Japan, the Japanese Red Cross Society performs prestorage leukoreduction on red blood cell and platelet product. However, non-hemolytic reactions to leukoreduced transfusion have been still reported [3]. The removal of plasma from platelets via washing or replacing is also reportedly effective for reducing immunological reactions [4]. Considering the cost and effort of producing these

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manipulated blood products, guidelines advocate that washed or replaced platelets be used in only patients who experience serious adverse reactions such as anaphylactic shock or more than two or three adverse reactions to transfusion [5].

In daily practice, premedication with various drugs is widely conducted to prevent transfusion reactions, but the effectiveness of this approach remains uncertain. Systematic review including randomized studies showed that premedication with acetaminophen and diphenhydramine was not superior to placebo in the prevention of transfusion reactions [6–8]. Furthermore, the results of some retrospective studies on premedication have been controversial [9–11]. Although evidence-based medicine has become common, guidelines for premedication have not been established and the use of premedication has not been investigated to date in Japan. The aim of this study was to clarify the current status of premedication and evaluate expert opinions regarding its use in Japanese medical institutions.

2. Material and methods

A nationwide survey was conducted between May and July 2016. Eligible institutions were those that were certified by the Japan Society of Transfusion Medicine and Cell Therapy or those that employed certified transfusion experts (doctors, medical technologists, or nurses). Questionnaires were sent to the director of the blood transfusion department at each institution. The questions used in the survey were designed to obtain information about the institutional policy, clinical practice, and specific protocols for premedication (Fig. 2). In this study, primary premedication was defined as premedication from the first transfusion regardless of patient history of transfusion reactions, and secondary premedication was defined as premedication implemented after any transfusion reaction. The differences in categorized features between two groups were compared using the Fisher's exact test. This study was approved by the Bioethics Committee for Clinical Research, Jichi Medical University and the Japan Society of Transfusion Medicine and Cell Therapy.

3. Results

The response rate was 54.2% (141 of 260 institutions). Responses were obtained from hematologists (n = 113), physicians (n = 31), surgeons (n = 26), oncologists (n = 6), gynecologists (n = 7), pediatricians (n = 12), emergency physicians (n = 5), and other medical doctors (n = 13).

Signs and symptoms that would be prevented by premedication were urticaria (89.2%), pruritus (66.9%), fever (56.8%), chills (36.7%), respiratory distress (30.2%), anaphylactic shock (30.2%), hypotension (22.3%), transfusion-related acute lung injury (TRALI) (5%), and transfusion-associated circulatory overload (TACO) (0.7%). The purpose of premedication was most frequently reported to be the prevention of mild immunological reactions, including urticaria, pruritus, fever, and less frequently the prevention of severe immunological reactions, such as anaphylactic shock and TRALI.

If premedication was ineffective, the following options were implemented: additional premedication (65.9%), washed blood products (55.1%), a different premedication (47.8%) or no change (8.7%). Washed platelets were considered to be indicated for patients with serious side effects such as anaphylactic shock (76.8%), a median of 2 (range, 1–10) transfusion reactions that could not be prevented with premedication (54.3%), a median of 2 (range, 1–5) transfusion reactions (27.5%) and history of allergy (5.8%).

Drugs for premedication were administered intravenously (79.0%), orally (7%), subcutaneously (0%), intramuscularly (0%), or through other routes (14%). The timing of administration was

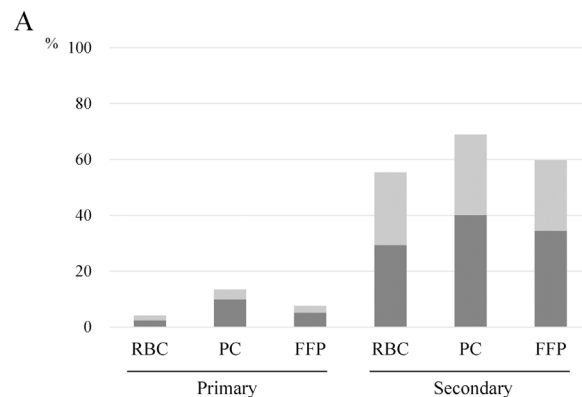


Fig. 1. (A) Primary and secondary premedication rates according to transfusion products and underlying diseases. (B) The rates of drugs used as premedication according to transfusion products and underlying diseases. The light gray and heavy gray bars indicate non-hematological and hematological disease, respectively. RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

just before (52.2%), 30 min before (45.5%), or one hour before transfusion (2%). The same drugs were used as premedication for outpatients and inpatients in 94% of the institutions. Guidelines for premedication had been prepared in 4% of the institutions and not in 89.1%.

The respondents regarded premedication as very effective (2.8%), effective (65.2%), neither (29.1%), ineffective (2.8%), or very ineffective (0%) for efficacy and very necessary (5%) and necessary (51.8%), neither (38.1%), unnecessary (5%), or very unnecessary (0%) for necessity. There was a significant difference in the ratio of responders who regarded premedication as very efficient/efficient according to a specialty (hematologist vs. non-hematologist, 70.8 vs. 47.7%; $P = 0.0013$) but not according to the institute (university hospital vs. medical center/general hospital), sex (men vs. women), or district (east vs. west Japan) (66 vs. 69.1%, $P = 0.7$; 61 vs. 56%, $P = 0.66$; and 69.3 vs. 65%; $P = 0.69$, respectively). Similarly, the ratio of responders who regarded premedication as very necessary/necessary differed according to specialty but not according to the institute, sex, or district (61.6 vs. 39.8%, $P = 0.00272$; 63.8 vs. 53.2%, $P = 0.28$; 50.7 vs. 48%, $P = 0.83$; and 55.6 vs. 60, $P = 0.71$, respectively).

Primary premedication was implemented at 5.1% of institutions for transfusions of red blood cells (RBCs), 21.2% for platelet concentrate (PC), and 10.9% for fresh frozen plasma (FFP) in patients with hematological diseases and at 3.3% for RBCs, 6.5% for PC, and 4.6% for FFP in patients with non-hematological diseases. Primary premedication for PC and FFP transfusion was significantly more frequent in patients with hematological diseases than that in those with non-hematological diseases ($P < 0.001$ and $P = 0.0485$, respectively; Fig. 1A). Although the reason for primary medication was not investigated in this survey, there was no significant difference in the signs and symptoms that may be prevented by premedication between institutes that implemented any primary premedication ($n = 36$) and those that did not ($n = 105$).

Secondary premedication was implemented at 62.6% of institutions for RBCs, 87.3% for PC, and 73% for FFP in patients with hematological diseases and at 48.9% for RBCs, 53.2% for PC, and 47.8% for FFP in patients with non-hematological disease. For all transfusion products, secondary premedication was significantly more frequent in patients with hematological diseases compared with that in those with non-hematological diseases (RBCs, $P = 0.0341$; PC, $P < 0.001$; FFP, $P < 0.001$; Fig. 1A).

Either antihistamine or steroids was used for premedication regardless of underlying diseases or transfusion products (Fig. 1B; Table 1). Antihistamines were used at 71.6% of institutions for the

Table 1

Primary and secondary premedication rates according to transfusion products and administered drugs.

		RBC	PC	FFP
Acetaminophen	Primary premedication	0%	0.3%	0.3%
	Secondary premedication	3.4%	1.6%	1.2%
Antihistamines	Primary premedication	2.7%	9.7%	5.9%
	Secondary premedication	36.3%	45.5%	38%
Steroids	Primary premedication	1.4%	7.2%	1.7%
	Secondary premedication	39.7%	52.5%	44.6%

RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

transfusion of RBCs, 71.8% for PC, and 68.2% for FFP in patients with hematological disease and at 70.9% for RBCs, 64.1% for PC, and 75.3% for FFP in patients with non-hematological diseases. Antihistamines included chlorpheniramine, hydroxyzine, diphenhydramine, olopatadine, epinastine, fexofenadine, and bepotastine. Among antihistamines, chlorpheniramine was most frequently used. Hydrocortisone was used at 63.7% of institutions for transfusions of RBCs, 73.3% for PC, and 70% for FFP in patients with hematological disease, and at 59.5% for RBCs, 62.4% for PC, and 62.3% for FFP in patients with non-hematological diseases. Glucocorticoids other than hydrocortisone were rarely used for the prevention of any transfusions.

4. Discussion

The results of this study demonstrated that, although primary premedication was infrequent in Japanese medical institutes, secondary premedication was frequently implemented, particularly in patients with hematological diseases and for platelet transfusion. Antihistamine or hydrocortisone was mainly used for the prevention of transfusion reactions together with all transfusion products.

It is uncertain whether the clinical practice of premedication was changed after the publication of negative results in randomized studies. A national survey of 87 Canadian institutions showed that up to 25% of RBC or PC transfusions in pediatric patients were accompanied by premedication [12]. Another observational retrospective study in Canada showed that the frequency of premedication with antihistamines was 1.2% (3 of 258 patients) [13]. Compared with the data in these reports, the frequency of secondary premedication in Japanese institutions was high, ranging from approximately 50% to 80%. This difference may be explained by that most Japanese transfusion specialists regarded premedication as very effective or effective and very necessary or necessary. Furthermore, the frequency of transfusion-related adverse reactions has been reported to be higher in Japan than in foreign countries [14,15]. This may be because all adverse reactions, including milder reactions that are less easily identified in other hemovigilance systems, are reported by the strict observation of patients during and after transfusions [14]. The difference in recognizing transfusion reactions may be related to the frequent implementation of premedication in Japan.

The significance of premedication may vary according to transfusion products, underlying diseases, adverse event types, medications used, or alternative precautions. In this study, differences were observed in the frequency of premedication according to transfusion products or underlying diseases. The secondary premedication rate with PC transfusions in patients with hematological disease reached 87.3%, whereas that with RBCs and FFP for patients with non-hematological disease was less than 50%. It is speculated that patients with hematological diseases were likely to have transfusion reactions owing to frequent transfusions and thus were more often premedicated than those with non-hematological disease.

Regarding the drugs used for premedication, the infrequent use of acetaminophen or diphenhydramine in most institutes may

result from the negative results of randomized trials (7). Antihistamine or hydrocortisone was used in more than 60% of institutions for the prevention of transfusion reactions. Among antihistamines, chlorpheniramine was used most frequently, i.e., in approximately half of the surveyed institutes. This result may be explained by that most responders was inclined to use intravenous premedication and, unlike other antihistamines, chlorpheniramine can be administered intravenously. Chlorpheniramine is widely used in daily practice for allergic reactions other than transfusion reactions, for example drug eruption and dermatitis. On the other hand, few published studies have evaluated the efficacy of steroids as premedication for transfusion reactions. Hydrocortisone was likely used most frequently owing to its immediate effect, whereas steroids other than hydrocortisone were used only rarely. Given its relatively strong anti-inflammatory effect compared with that of antihistamines, hydrocortisone may be selected for moderate to severe transfusion reactions that cannot be prevented by antihistamines.

The main purpose of premedication was to prevent urticaria, pruritus, or fever. Despite a lack of evidence for prevention of such symptoms with antihistamines [8], premedication with antihistamines or hydrocortisone may be conducted to relieve these mild allergic reactions. The rate of prophylactic administration for severe reactions such as anaphylactic shock was low. The results of this survey suggest that washed blood products are considered appropriate for these life-threatening transfusion reactions.

In 2008, the Japanese Society of Transfusion Medicine and Cell Transfusion issued guidelines for the use of washed and replaced platelets [5]. In our survey, only half of the respondents answered that they used washed platelets when serious transfusion reactions with ineffective premedication occurred. This choice appears to be affected by the fact that additional labors and costs are required for producing washed platelets in the transfusion division of a hospital. In September 2016, after the completion of our survey, the Japanese Red Cross Society began providing washed platelets as approved blood component. Due to the lack of clinical trials of washed platelets, the price of the new products and the usual products are same. Because both platelet products can now be used in all institutions, occasions of premedication before platelet transfusions will decrease, and the purpose of premedication will change.

In this survey, premedication protocols did not differ between inpatients and outpatients at more than 90% of institutions. First-generation antihistamines such as chlorpheniramine can easily cross the blood–brain barrier and cause central nervous system symptoms such as dizziness and cognitive impairment. Therefore, antihistamines are considered inappropriate for outpatients who need to drive home. Compared with the care of inpatients, in the clinical setting for outpatients, in which time is limited, the discontinuation of transfusion owing to adverse events is a crucial issue. It is desirable to tailor premedication protocols based on the clinical settings. However, the results of our survey showed that premedication guidelines have not been prepared in approximately 90% of institutions. Some foreign single-institutions proposed the algorithm for premedication according to degree of adverse events and treatment responses [16,17]. In the context of evidence-based

Questionnaire regarding premedication for transfusion reactions

1. Do you think that the prophylaxis is effective?
- ☐ Very effective ☐ Neither ☐ Very ineffective
- ☐ Effective ☐ Ineffective
2. Do you think that the prophylaxis is necessary?
- ☐ Very necessary ☐ Neither ☐ Very unnecessary
- ☐ Necessary ☐ Unnecessary
3. What adverse effects are prevented by premedication? (Multiple answers allowed)
- ☐ Fever ☐ Respiratory distress ☐ Anaphylactic shock
- ☐ Chills ☐ Hypotension ☐ Others
- ☐ Urticaria ☐ TRALI
- ☐ Pruritus ☐ TACO
4. If transfusion reactions are not prevented by premedication, what will you do? (multiple answers allowed)
- ☐ Addition of premedication ☐ No change
- ☐ Change of premedication ☐ Other
- ☐ Use of washed red blood cells or washed platelets
5. In what case do you use washed or replaced platelets? (multiple answers allowed)
- ☐ Some adverse effects (Number of adverse effects: ____)
- ☐ Some unpreventable adverse effects of premedication (Number of adverse effects: ____)
- ☐ Serious adverse effects such as anaphylactic shocks
- ☐ History of allergy ☐ Other
6. How do you administer premedication?
- ☐ Intravenous ☐ Subcutaneous ☐ Other
- ☐ Oral ☐ Intramuscular
7. When do you administer premedication?
- ☐ Immediately before ☐ 1 h before
- ☐ 30 min before ☐ Other
8. Are there differences in premedication protocols between outpatients and inpatients?
- ☐ Same ☐ Different
9. Do you prepare institutional guidelines for premedication?
- ☐ Yes ☐ No ☐ Other
- 10-1. When transfusing red blood cells (RBCs) to patients with hematological diseases, do you implement premedication from the first transfusion?
- ☐ Yes ☐ No ☐ Other
- 10-2. When transfusing RBCs to patients with hematological diseases, do you implement premedication after any transfusion reaction?
- ☐ Yes (Number of transfusion reactions: ____)
- ☐ No ☐ Other
- 10-3. When transfusing RBCs to patients with hematological diseases, which drugs do you administer as premedication?
- ☐ Acetaminophen, tablet () mg ☐ Methylprednisolone () mg
- ☐ Acetaminophen, solution () mg ☐ Dexamethasone () mg
- ☐ Chlorpheniramine () A ☐ Glycyrrhizin () ml
- ☐ Antihistamines () ☐ Combination
- ☐ Hydrocortisone () mg ☐ Other
- ☐ Prednisolone () mg
- 11-1. When transfusing platelet concentrate (PC) to patients with hematological diseases, do you implement premedication from the first transfusion?
- ☐ Yes ☐ No ☐ Other
- 11-2. When transfusing PC to patients with hematological diseases, do you implement premedication after any transfusion reaction?
- ☐ Yes (Number of transfusion reactions: ____)
- ☐ No ☐ Other
- 11-3. When transfusing PC to patients with hematological diseases, which drugs do you administer as premedication?
- ☐ Acetaminophen, tablet () mg ☐ Acetaminophen, solution () mg
- ☐ Chlorpheniramine () A ☐ Dexamethasone () mg
- ☐ Antihistamines () ☐ Glycyrrhizin () ml
- ☐ Hydrocortisone () mg ☐ Combination
- ☐ Prednisolone () mg ☐ Other
- ☐ Methylprednisolone () mg

12-1. When transfusing fresh frozen plasma (FFP) to patients with hematological diseases, do you implement premedication from the first transfusion?

☐ Yes ☐ No ☐ Other

12-2. When transfusing FFP to patients with hematological diseases, do you implement premedication after any transfusion reaction?

☐ Yes (Number of transfusion reactions: ____)

☐ No ☐ Other

12-3. When transfusing FFP to patients with hematological diseases, which drugs do you administer as premedication?

☐ Acetaminophen, tablet () mg ☐ Methylprednisolone () mg

☐ Acetaminophen, solution () mg ☐ Dexamethasone () mg

☐ Chlorpheniramine () A ☐ Glycyrrhizin () ml

☐ Antihistamines () ☐ Combination

☐ Hydrocortisone () mg ☐ Other

☐ Prednisolone () mg

Medical department other than hematology (multiple answers allowed): ()

13-1. When transfusing RBCs to patients with non-hematological diseases, do you implement premedication from the first transfusion?

☐ Yes ☐ No ☐ Other

13-2. When transfusing RBCs to patients with non-hematological diseases, do you implement premedication after any transfusion reaction?

☐ Yes (Number of transfusion reactions: ____)

☐ No ☐ Other

13-3. When transfusing RBCs to patients with non-hematological diseases, which drugs do you administer as premedication?

☐ Acetaminophen, tablet () mg ☐ Methylprednisolone () mg

☐ Acetaminophen, solution () mg ☐ Dexamethasone () mg

☐ Chlorpheniramine () A ☐ Glycyrrhizin () ml

☐ Antihistamines () ☐ Combination

☐ Hydrocortisone () mg ☐ Other

☐ Prednisolone () mg

14-1. When transfusing PC to patients with non-hematological diseases, do you implement premedication from the first transfusion?

☐ Yes ☐ No ☐ Other

14-2. When transfusing PC to patients with non-hematological diseases, do you implement premedication after any transfusion reaction?

☐ Yes (Number of transfusion reactions: ____)

☐ No ☐ Other

14-3. When transfusing PC to patients with non-hematological diseases, which drugs do you administer as premedication?

☐ Acetaminophen, tablet () mg ☐ Methylprednisolone () mg

☐ Acetaminophen, solution () mg ☐ Dexamethasone () mg

☐ Chlorpheniramine () A ☐ Glycyrrhizin () ml

☐ Antihistamines () ☐ Combination

☐ Hydrocortisone () mg ☐ Other

☐ Prednisolone () mg

15-1. When transfusing FFP to patients with non-hematological diseases, do you implement premedication from the first transfusion?

☐ Yes ☐ No ☐ Other

15-2. When transfusing FFP to patients with non-hematological diseases, do you implement premedication after any transfusion reaction?

☐ Yes (Number of transfusion reactions: ____)

☐ No ☐ Other

15-3. When transfusing FFP to patients with non-hematological diseases, which drugs do you administer as premedication?

☐ Acetaminophen, tablet () mg ☐ Methylprednisolone () mg

☐ Acetaminophen, solution () mg ☐ Dexamethasone () mg

☐ Chlorpheniramine () A ☐ Glycyrrhizin () ml

☐ Antihistamines () ☐ Combination

☐ Hydrocortisone () mg ☐ Other

☐ Prednisolone () mg

16. What is your specialty? (Multiple answers allowed)

☐ Physician

☐ Hematologist

☐ Surgeon

☐ Oncologist

☐ Gynecologist

☐ Pediatrician

☐ Emergency physician

☐ Other

Fig. 2. Questionnaire regarding premedication for transfusion reactions.

Fig. 2. (continued)

medicine and patient-specific approaches, premedication guidelines need to be developed in Japan.

This study had several limitations. First, this survey obtained information on institution policy primarily from directors. Because premedication guidelines had not been prepared, the opinions and practices of doctors within the same institution may have varied. Second, the design of the multiple-choice survey did not probe rationales for the use of hydrocortisone or antihistamines as premedication. Third, respondent recognition of evidence for premedication was not evaluated, although the survey was conducted with the assumption that responders understood it. This recognition rate would be useful information for interpreting survey responses to questions on the efficacy and necessity of premedication.

In conclusion, this study is the first to determine the current status of premedication in Japan using a national survey. Transfusion experts considered premedication as efficacy and necessary and the frequency of premedication for patients with previous transfusion reactions was high. Premedication practices varied according to transfusion products and underlying diseases. There is not enough evidence of the prophylactic administration of antihistamines and hydrocortisone as premedication in this survey. As a routine institutional protocol, universal premedication of all transfusion products should be avoided. According to the severity of reactions and response to treatment, antihistamines, steroids, and reduced/washed PC need to be appropriately used. Further studies are required to validate an optimal transfusion premedication practice.

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