Incidence of Transfusion-Related Adverse Reactions per Patient Reflects the Potential Risk of Transfusion Therapy in Japan

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Key Words: Hemovigilance; Adverse reactions; Per transfused patient basis; Transfusion practices

ABSTRACT

Objectives: To describe the frequency of adverse reactions (ARs) after transfusion on both per transfused patient and per transfused unit bases.

Methods: We performed a retrospective analysis of data available from records of 6 hospitals on the total number of transfusions and documented ARs between January 2008 and December 2009 for RBCs, fresh-frozen plasma (FFP), and platelet concentrates (PCs).

Results: The incidence of ARs to RBCs, FFP, and PCs per transfused unit was 0.6%, 1.3%, and 3.8%, respectively. The incidence of ARs to RBCs, FFP, and PCs per patient was 2.6%, 4.3%, and 13.2%, respectively—almost 3-fold higher. Most RBC-ARs were febrile nonhemolytic transfusion reactions and allergic reactions, whereas most FFP-ARs and PC-ARs were allergic reactions.

Conclusions: The incidence of ARs per transfused patient may reflect better the potential risk of transfusion with blood components, taking into account the characteristics of the transfused patient.

Although blood transfusion is an essential and effective therapy, it is associated with significant clinical risks due to blood components’ allogeneic origin. As infectious complications from blood transfusion decrease due to improved donor questionnaires and sophisticated infectious disease blood screening,1 noninfectious adverse reactions (ARs) have emerged as the most common transfusion complication. In fact, the risk of transfusion-transmitted infectious diseases has decreased approximately 10,000-fold,2 with death rates due to transfusion-related acute lung injury (TRALI) and hemolytic transfusion reactions responsible for approximately 72% of all transfusion-related fatalities reported to the Center for Biologics Evaluation & Research.3 Although blood components in Japan—as elsewhere—can be considered safe, ARs associated with transfusions have not been eliminated. To understand and manage transfusion risk, reporting systems for ARs—namely, hemovigilance systems—have been established.

Hemovigilance is defined as a system of surveillance, gathering and analyzing untoward transfusion effects from blood collection to recipient follow-up. Its goal is to prevent the recurrence of incidents by identifying their causes. Hence, its system is a tool to improve the quality of the blood transfusion chain, primarily focusing on safety.4

In Europe, the first hemovigilance systems began in France in 19945 and in the United Kingdom in 1996,6 although these 2 systems differ greatly. With the advent of Directive 2002/98/EC,7 the introduction of hemovigilance systems has become a priority throughout the European Community. Reporting to the recently established US Biovigilance Network commenced in 2008.8 Interestingly, however, the Japanese Red Cross Society (JPCS) recognized the importance of a coordinated blood safety system as the very first...
blood transfusion organization and founded an established hemovigilance system in Japan in 1993. In summary, there are many established hemovigilance systems globally.

While most of these systems report the incidence of ARs on a per transfused unit basis, the incidence of such reactions per transfused patient has not been published. It is suspected that the ARs to blood components are affected by specific characteristics of the transfused patients, such as underlying diseases, age, sex, race, type of surgery or medical treatment, and transfusion practices. The true risk of transfusion-related ARs on a patient-by-patient basis is not clearly understood, despite the fact that the occurrence of these reactions is considered important with respect to the patients as well as to the blood components. In the present study, we describe the incidence over a 2-year period of transfusion-related ARs on a per transfused patient and a per transfused unit basis.

Materials and Methods

Study Design

We performed a retrospective observational analysis of data available from records in 6 hospitals with established hemovigilance systems (Aichi Medical University Hospital, Keio University Hospital, Osaka University Hospital, Shinshu University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, and Tokyo Metropolitan Bokutoh Hospital, Japan) between January 2008 and December 2009 regarding the transfusions and documented transfusion-related ARs for RBCs, fresh-frozen plasma (FFP), and platelet concentrates (PCs). The study was approved by the Aichi Medical University Institutional Review Board. For each type of blood component, the data included the total number of transfused units and transfused patients from each hospital, as well as the total number of transfusion-related ARs per blood component with respect to both units and patients.

We calculated the frequency of ARs per case by having the numerator of the ARs describe the same type of AR. The denominator for units is the number of units transfused, while the denominator for patients is the number of patients who received the components.

This approach is illustrated in patient 1 [Table 1]. This patient received 2 units of RBCs with no ARs. In the frequency calculation, the denominator of units is 2, and the denominator of patients is 1. Patient 2 received 2 units of RBCs, 2 units of FFP, and 2 units of PCs with no ARs. In the frequency calculation, the denominator of patients was listed as 1, the denominator of units was 2. In patient 3, the same type of ARs occurred with 2 of the 3 units of RBCs administered. The denominator of patients was listed as 1 experiencing 1 AR to RBCs. Furthermore, in patient 4, when the same type of AR occurred after 2 of 3 units of RBCs, 2 equal ARs after 2 units of FFP, and none after 2 units of PCs were administered, on a per transfused patient basis, this patient was listed as experiencing 1 AR to RBC and 1 AR to FFP. In summary, in the example in Table 1, on a per transfused unit basis, 4 of 10 units of RBCs, 2 of 4 units of FFP, and 0 of 4 units of PCs were associated with an AR. On a per patient basis, 2 of 4 patients who received transfusions of RBCs, 1 of 2 patients given FFP, and 0 of 2 patients given PCs experienced ARs. The incidence of ARs on a per patient basis was calculated according to the actual number of patients receiving each type of blood component.

The physicians and nurses monitored the patients after the start of each transfusion for the occurrence of any ARs and reported the results of all transfusions to the department of transfusion medicine in each hospital regardless of whether an AR had occurred. When an AR did occur, a physician who was trained in transfusion medicine performed an analysis, and additional clinical and biological information was collected to enable diagnosis and assessment of severity and causality to be made.

A standard AR form was used comprising the following 15 items: fever, chills/rigor, pruritus, skin rash, urticaria, respiratory distress, nausea/vomiting, headache, chest/flank/back pain, hypotension, hypertension, tachycardia, vein pain, disturbance of consciousness, and hemoglobinuria. Any additional findings or comments, including suspected TRALI, transfusion-associated circulatory overload (TACO), or transfusion-transmitted viral and bacterial infection, could be entered as free text and were later analyzed. The definitions

| Table 1 | Example of the Method of Counting Transfused Units and Transfused Patients |
|---------|-----------------------------|-----------------------------|
|         | Transfusion Units           | Transfusion Patients        |
| Patients| RBC | FFP | PC | RBC | FFP | PC |
| Patient 1| Transfusion | 2 | 0 | 0 | 1 | 0 | 0 |
|          | Adverse reactions | 0 | 0 | 0 | 0 | 0 | 0 |
| Patient 2| Transfusion | 2 | 2 | 2 | 1 | 1 | 1 |
|          | Adverse reactions | 0 | 0 | 0 | 0 | 0 | 0 |
| Patient 3| Transfusion | 3 | 0 | 0 | 1 | 0 | 0 |
|          | Adverse reactions | 2 | 0 | 0 | 1 | 0 | 0 |
| Patient 4| Transfusion | 3 | 0 | 0 | 1 | 1 | 1 |
|          | Adverse reactions | 2 | 0 | 0 | 1 | 0 | 0 |
| Total    | Transfusion | 10 | 4 | 4 | 4 | 2 | 2 |
|          | Adverse reactions | 4 | 2 | 0 | 2 | 1 | 0 |

FFP, fresh-frozen plasma; PC, platelet concentrate.
of all signs, symptoms, and specific clinical syndromes used by the Japan Society of Transfusion Medicine and Cell Therapy are based on documents issued by the International Society of Blood Transfusion (ISBT) Working Party for Haemovigilance, which also defined the criteria for grading the severity of ARs. Serious ARs were defined as grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance.

**Blood Components**

Blood collection, preparation, and testing were performed according to the prescriptions of the Blood Service Headquarters of the JRCS. Since January 2007, only prestorage leukoreduced blood components have been manufactured. After venipuncture, the first 25 mL of blood was discarded to decrease the risk of bacterial contamination. RBCs were prepared in the additive solution MAP (mannitol adenine phosphate) and stored for up to 21 days at 5°C. All PCs were prepared from single donors by apheresis and the products stored for up to 4 days at 22°C. Fresh-frozen plasma was prepared from whole-blood plasma or by apheresis from single donors.

**Statistical Analysis**

Data were analyzed on a per patient and per transfused unit basis. To calculate the frequency of ARs, we correlated the number of confirmed ARs with the total number of transfused units and transfused patients. The frequency calculation referred to the period of 1 year. All statistical analyses were performed by the χ² test, with Yates correction for continuity and/or a t test. Probability values less than .05 were considered statistically significant.

**Results**

**Number of Transfusions**

During this study, 62,210 units of RBCs were transfused to 11,155 patients, 25,787 units of FFP to 3,151 patients, and 27,992 units of PC to 3,604 patients. The number of units of RBCs administered represented 53.6% of all blood components, with FFP and PCs at 22.2% and 24.2%, respectively.

**ARs Following Transfusion of Blood Components**

On a per transfused unit basis, 377 (0.6%) of 62,210 units of RBCs, 331 (1.3%) of 25,787 units of FFP, and 1,068 (3.8%) of 27,992 units of PCs administered were associated with an AR, showing that the incidence of ARs to FFP was around twice that to RBCs. Furthermore, the incidence of ARs to PCs was almost 6 times higher than to RBCs and nearly 3 times higher than to FFP.

On a per patient basis, 291 (2.6%) of 11,155 patients receiving RBC transfusions experienced ARs, and 136 (4.3%) of 3,151 patients experienced ARs to FFP and 477 (13.2%) of 3,604 patients to PCs. Thus, the AR incidences to RBCs, FFP, and PCs were significantly different.

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Incidence per Transfused Unit</th>
<th>Incidence per Transfused Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Absolute No. of Adverse Reactions</td>
<td>Incidence, %</td>
</tr>
<tr>
<td>RBC 62,210</td>
<td>377</td>
<td>0.6</td>
</tr>
<tr>
<td>FFP 25,787</td>
<td>331</td>
<td>1.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PC 27,992</td>
<td>1,068</td>
<td>3.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

FFP, fresh-frozen plasma; PC, platelet concentrate.

<sup>a</sup>P < .01 compared with RBC.

<sup>b</sup>P < .01 compared with RBC and FFP.
each blood component on a per patient basis were higher than those on a per transfused unit basis. Similar to the results on a per transfused unit basis, the incidence of ARs to PCs was higher than to RBCs or FFP.

Characteristics of Clinical Signs and Symptoms Associated With ARs

During the study, 28 serious ARs, including serious allergic reactions, TRALI, TACO, hemolytic transfusion reactions, and transfusion-transmitted infection, were reported. These 28 serious ARs occurred in 7 (0.1%) patients who received RBC transfusions, in 9 (0.3%) patients receiving FFP, and 12 (0.3%) patients transfused with PCs. The proportions of serious ARs out of the total ARs to RBCs, FFP, and PCs were 2.4%, 6.6%, and 2.5%, respectively (Figure 2), and thus most ARs were not life-threatening.

On a per transfused patient basis, most ARs to RBCs were allergic reactions (44.7%), consisting of pruritus, skin rash, and/or urticaria, and febrile nonhemolytic transfusion reactions (FNHTRs) (33.3%), consisting of fever and/or chills/rigor (Figure 2). Most ARs to FFP and PCs were allergic reactions (75.8% and 78.1%, respectively), whereas FNHTRs to FFP and PCs were observed in only 6.6% and 9.6% of patients, respectively.

When the incidence on a per patient basis of the various AR types was investigated, the frequency of FNHTRs to RBCs (0.9%) and PCs (1.3%) was significantly higher than that to FFP (0.3%) (Table 3, P < .01). On the other hand, the frequency of allergic reactions to FFP (3.3%) and PCs (10.3%) was significantly higher than to RBCs (1.2%) (P < .01). Furthermore, the incidence of allergic reactions to PCs was significantly higher than to FFP (P < .01). Thus, PCs give rise to statistically more allergic reactions than RBCs and FFP. Allergic reactions were observed in almost 10% of patients transfused with PCs. Other, nonspecific signs and symptoms, such as respiratory distress, nausea/vomiting, headache, hypotension, hypertension, and tachycardia, were each observed in approximately 0.1% to 0.5% of patients transfused with each type of blood component.

**Table 3**

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>RBC</th>
<th>FFP</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNHTR</td>
<td>97 (0.9%)</td>
<td>9 (0.3%)</td>
<td>46 (1.3%)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>130 (1.2%)</td>
<td>103 (3.3%)</td>
<td>372 (10.3%)</td>
</tr>
<tr>
<td>Others</td>
<td>57 (0.5%)</td>
<td>15 (0.5%)</td>
<td>47 (1.3%)</td>
</tr>
<tr>
<td>Serious adverse reactions</td>
<td>7 (0.1%)</td>
<td>9 (0.3%)</td>
<td>12 (0.3%)</td>
</tr>
</tbody>
</table>

FFP, fresh-frozen plasma; FNHTR, febrile nonhemolytic transfusion reaction; PC, platelet concentrate.

* The values are the number of patients with signs/symptoms (incidence per patient, %).
* P < .01 compared with FFP.
* P < .01 compared with RBC and FFP.
* P < .01 compared with RBC.

**Discussion**

We retrospectively analyzed ARs with stringent criteria and uniform standard monitoring case record forms across the study sites over 2 years. Per transfused unit, AR incidences to RBCs, FFP, and PCs were 0.6%, 1.3%, and 3.8%, respectively. In contrast, the AR incidences to RBCs, FFP, and PCs per transfused patient per year were 2.6%, 4.3%, and 13.2%, respectively—almost 3 times higher than on a per transfused unit basis. Platelet concentrates gave rise to significantly more ARs than RBCs and FFP on both per transfused unit and per transfused patient bases (P < .01). While the majority of ARs to RBCs were both FNHTRs and allergic reactions, most ARs to FFP and PC were allergic reactions.

The overall incidence of ARs per transfused unit was 1.5% (data not shown). On the other hand, the incidence of ARs during or after transfusion has been reported as between 0.08% and 0.42%. A possible reason for this discrepancy is that all transfusions must be reported, whether or not ARs occurred, and this system hence detects the milder reactions that are less readily captured in other systems. In fact, since the standard monitoring form used in this study covers most signs and symptoms of transfusion-related ARs, physicians and nurses are able to...
identify all ARs—including nonserious ones—more easily during the strict observation of a patient during and after transfusion. Indeed, the proportions of serious reactions among all reported ARs to RBCs, FFP, and PCs were only 2.4%, 6.6%, and 2.5%, respectively, in this study (Figure 2). Furthermore, some studies have reported ARs as those associated with approximately 0.5% to 3% of transfusions during or within a few hours of the infusion of blood components.\(^{11,12}\) It is, therefore, highly likely that our results reveal the true incidence of ARs (serious and nonserious) for blood components distributed in Japan.

In addition, the incidences of ARs per patient per year to RBCs, FFP, and PCs were 2.6%, 4.3%, and 13.2%, respectively—values higher than those on a per transfused unit basis. The main explanation for this is the fact that many patients in this study received more than 1 unit of blood component, with some in multiple-transfusion episodes. The literature has reported that the risk for ARs for patients previously transfused before the index transfusion is higher compared with patients without a transfusion history.\(^{13}\) Although the data in this study were not analyzed for individual patients, the incidence of ARs per patient reflects the potential risk to a patient of transfusion therapy, taking into account the typical spectrum of transfusion patients in the hospitals studied. In particular, more than 10% of patients transfused with PCs had 1 or more ARs.

The present and previous studies\(^{9,14}\) have reported that PCs give rise to statistically more ARs than RBCs and FFP on both a per transfusion and a per patient basis (\(P < .01\)). It is speculated that these differences in AR incidences are due to variations in transfusion practices regarding each blood component. Febrile nonhemolytic transfusion reactions and allergic reactions were particularly frequent. Heddle et al\(^{15,16}\) have reported that FNHTRs to blood components are caused by WBC antigen-antibody interaction and cytokines, such as interleukin (IL) 1\(\beta\), IL-6, and tumor necrosis factor \(\alpha\), released from WBCs and accumulated in blood components during storage. There is general agreement that prestorage leukoreduction will decrease the frequency of FNHTRs.\(^{17}\) Heddle et al\(^{16}\) reported plasma depletion to be more effective than poststorage leukocyte reduction in preventing ARs such as FNHTRs and allergic reactions to PCs. The possible reason for this prevention of ARs is that biological response modifiers in addition to the WBC-derived cytokines implicated in FNHTRs and other reactions are removed by plasma depletion. Also, allergic reactions are decreased by plasma depletion because the idiosyncratic donor proteins are removed by plasma depletion and not by leukoreduction. Furthermore, Paglino et al\(^{17}\) reported a significant decrease in the frequency of FNHTRs—although not allergic reactions—for RBCs and PCs following the introduction of 100% universal prestorage leukoreduction. It is likely that some allergic reactions are caused by mediators in the plasma component of blood components. Although plasma comprised less than 10% in RBCs, it is the main component in FFP and PCs. Indeed, although there were no significant differences in the frequencies of FNHTRs to RBCs (0.9%) and PCs (1.3%) in the present study on the prestorage leukoreduced blood components, the frequency of allergic reactions to FFP (3.3%) and PCs (10.3%) was significantly higher than to RBCs (1.2%) (Table 3). Thus, the different quality of blood components may be one reason for varying incidences of ARs to RBCs, FFP, and PCs.

A second reason might be differences in the characteristics of patients receiving different types of blood components and in the numbers of transfusion they receive. Recipients of PCs, most of whom have hematologic diseases, tend to receive transfusions frequently. Indeed, in this study, the average numbers of transfused units of FFP (25,787 units/3,151 patients) and PCs (27,992 units/3,604 patients) per patient were more than those for RBCs (62,210 units/11,155 patients). Therefore, we speculate that repeated allo-exposure with PCs might induce a high incidence of ARs. A previous study\(^{18}\) reported that a reduction in platelet transfusions is associated with a reduced alloimmunization incidence. In addition, the incidence of ARs per patient was influenced by the number of transfusions per patient,\(^{13}\) hence the suspicion that 1 factor predicting the occurrence of ARs could be transfusion exposure.

In summary, the incidence of ARs per patient reflects the potential risk of transfusion therapy, taking patient characteristics into account. Differences in AR incidences across blood components may be due to varying components and transfusion practices. Despite the limitations, this study provides insight into risks of ARs regarding transfused patients. In the future, more elaborate analyses of the data collected from individual patients may allow recommendations to be made for improvements in transfusion practice. Furthermore, basic and translational research of the pathophysiology behind transfusion-related ARs is necessary to devise novel strategies to minimize these complications, for example, by washed/replaced PCs.

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References