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# Risk factors of acute blood transfusion reactions in pediatric patients in Sanglah General Hospital, Bali-Indonesia


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## ABSTRACT

**Background:** Numerous factors may underlie an acute transfusion reaction. The readily available data showing the prevalence and the risk factors of transfusion reactions in Bali are scarce.

**Objectives:** Our study aimed to reveal the prevalence and the risk factors of acute blood transfusion in Pediatric Patients in Sanglah General Hospital, Bali, Indonesia.

**Methods:** A cross-sectional study using consecutive sampling was conducted from August 2015 to August 2016 (13 months). We collected the data from the medical records of our pediatric patients in the pediatric wards, neonatal intensive care unit (NICU), and pediatric intensive care unit (PICU). We examined the relationship between the occurrence of acute transfusion reactions and the types of blood transfusion, the history of blood transfusion, and the age of the patients.

**Results:** A total of 107 acute transfusion reactions occurred from 3,251 blood transfusions. When acute transfusion reactions occurred, the patients were more likely to be over 12 months old compared to 0 to 12 months old (POR=2.81, 95%CI 1.78-4.58, p<0.05). Alternatively, when the transfusion reactions occurred, the patients were more likely to receive thrombocyte concentrate transfusion compared to other blood components (OR=8.11, 95%CI 5.36-12.31, p<0.05).

**Conclusion:** The prevalence of acute transfusion reactions was 3.3%. The pediatric patients who had acute transfusion reactions were more likely to be over 12 months old or more likely to receive a platelet concentrate.

**Keywords:** Blood transfusion, acute transfusion reactions, pediatric, risk factors.

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## BACKGROUND

Transfusion reactions may happen as an immune response to the blood or other components or as a non-immune response caused by a circulation overload, transfusion siderosis, or transmission of infection.[1-3] Based on the onset, there are an acute or delayed transfusion reactions.[4,5] Fever, urticaria, itching, headache, chills, or anaphylactic occur during or following a blood transfusion are symptoms of acute transfusion reactions.[3,5,6]

The Brazillian National Health Insurance Agency survey in 2012 showed a transfusion reaction happened in every 1,065 transfusions.[7] Some factors underlie transfusion reactions are the type of transfusion (the blood component), age, and the history of a blood transfusion.[8,9]

The readily available data showing the prevalence of transfusion reactions in Bali, Indonesia are still scarce. Furthermore, there has not been a published data of the risk factors of transfusion reactions in Bali. It is important to recognize the risk factors to plan a prevention.

## METHODS

We conducted a cross-sectional study using consecutive sampling from August 2015 to August 2016. We collected the data from the medical records of our pediatric patients in two pediatric wards, a neonatal ward, an intermediate ward, neonatal intensive care unit (NICU), and pediatric intensive care unit (PICU). We included pediatric patients from birth to 12 years old who was admitted and received a blood transfusion at Sanglah General Hospital, Bali, Indonesia. We excluded the patients with missing or incomplete medical records.

We examined the association between the occurrence of acute transfusion reactions and the types of blood transfusion, the history of blood transfusion, and the age of the patients. The participants were observed for acute transfusion reactions during or after transfusion. The transfusion reactions are defined as an increase in body temperature of 1.5°C exceeding normal cut-off point, urticarial lesions, angioedema, dyspnoea with or without retractions, oliguria, and tachycardia. The onset of the reactions within 15 minutes, first, a second and third hour of transfusion is measured. The diagnosis was retrieved from the participant's medical record. Next, the diagnosis which was categorized into either hematological (leukemia, thalassemia, hemoglobinopathy, aplastic anemia, *pure red cell* anemia, autoimmune

**Table 1** Sample Characteristics

| | Transfusion Reaction | | | | |
|---|---|---|---|---|---|
| | Present | | Absent | | Total |
| Characteristics | f | % | f | % | f |
| Age | | | | | |
| 0-4 months | 26 | 1.34 | 1.306 | 0.07 | 1332 |
| >4-12 months | 1 | 0.05 | 224 | 11.51 | 225 |
| > 12 months | 80 | 4.11 | 1614 | 82.93 | 1694 |
| Gender | | | | | |
| Male | 65 | 2.00 | 1850 | 56.91 | 1915 |
| Female | 42 | 1.29 | 1294 | 39.80 | 1336 |
| Nutritional status | | | | | |
| Malnutrition | 47 | 1.45 | 896 | 27.56 | 943 |
| Normal | 60 | 1.85 | 2248 | 69.15 | 2308 |
| Blood Type | | | | | |
| A | 14 | 0.43 | 438 | 13.47 | 452 |
| B | 26 | 0.80 | 1434 | 44.11 | 1460 |
| AB | 3 | 0.09 | 150 | 4.61 | 153 |
| O | 64 | 1.97 | 1122 | 34.51 | 1186 |
| Blood Component | | | | | |
| PRC | 41 | 1.26 | 2073 | 63.76 | 2114 |
| WRC | 0 | 0.00 | 127 | 3.91 | 127 |
| TC apheresis | 0 | 0.00 | 65 | 2.00 | 65 |
| TC | 61 | 1.88 | 442 | 13.60 | 503 |
| FFP | 5 | 0.15 | 235 | 7.23 | 240 |
| Cryoprecipitate | 0 | 0.00 | 202 | 6.21 | 202 |
| History of blood transfusion | | | | | |
| Positive | 72 | 17.56 | 2769 | 675.37 | 2841 |
| Negative | 35 | 8.54 | 375 | 91.46 | 410 |
| Diagnosis | | | | | |
| Hematology | 38 | 1.17 | 1081 | 33.25 | 1119 |
| Disorders | | | | | |
| Oncology | 27 | 0.83 | 301 | 9.26 | 328 |
| Other surgical | 3 | 0.09 | 78 | 2.40 | 81 |
| Disease | | | | | |
| Others | 39 | 1.20 | 1684 | 51.80 | 1723 |
| Total | 107 | 3.29 | 3144 | 96.71 | 3251 |

hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), oncological (solid tumor), or surgical or other disorders. The demographic data such as age, gender, nutritional status, blood type, history of transfusion and diagnosis were collected. All statistical analyses was conducted with SPSS 16. The prevalence odds ratio was used for analyzing the association using chi-square test ($p<0.05$).

**Table 2** Symptoms and Onset of Transfusion Reactions

| Transfusion Reaction | f | % |
|---|---|---|
| Symptoms | | |
| Fever | 67 | 63.81 |
| Urticaria | 20 | 19.05 |
| Itching | 10 | 9.52 |
| Rash | 5 | 4.76 |
| Chills and face flush | 2 | 1.90 |
| Tachycardia | 1 | 0.95 |
| Onset from the start of the transfusion | | |
| 15th minute | 7 | 6.54 |
| 1st hour | 68 | 63.55 |
| 2nd hour | 31 | 28.97 |
| 3rd hour | 1 | 0.93 |

## RESULTS

A total of 3251 samples received blood transfusions during this study period. Of these transfusions, the reaction was mostly observed in male children and the age group of more than 12 months for 2% and 4.11%, respectively. While, within the blood type and components, the highest prevalence of transfusion reaction was observed in blood type O (1.97%) and thrombocyte concentrate (TC) (1.88%). The prevalence was higher in those who have the previous history of blood transfusion than those having a blood transfusion for the first time. A total of 1.17% transfusion reaction was observed in hematological disorder patients who required transfusions. (Table 1)

The transfusion reactions were fever (63.81%), urticaria (19.05%), and itching (9.52%) (Table 2). The onset of the reaction was mostly observed in the first (63.55%) and the second hour of transfusion (28.97%). The prevalence odd ratio for age is 2.8 ($p<0.05$), thrombocyte transfusion 8.1 ($p<0.05$), and history of blood transfusions 0.3 ($p<0.05$) (Table 3).

## DISCUSSION

Blood transfusion is a series of blood transferring process from a donor to a recipient in an attempt to maintain the donor's health, the biological state of the blood or its components to benefits the recipients.[10] Blood is a multi-antigenic biological material which can potentially lead to immunologic reactions to the recipient.[10] The World Health Organization (WHO) recommends that all activities related to blood collection, examination, blood processing, storage, and distribution be coordinated

**Table 3** **Chi-square Test and Prevalence Odds-Ratios**

| | | Transfusion Reactions | | | | | |
|---|---|---|---|---|---|---|---|
| | | Present | Absent | | | | |
| **Risk Factors** | | **F** | **f** | **p-value** | **$x^2$** | **POR** | **95% CI** |
| Age | >12 months | 80 | 1614 | <0.05 | 22.7637 | 2.808757 | (1.78, 4.58) |
| | 0-12 months | 27 | 1530 | | | | |
| Blood component | Thrombocyte Concentrate | 61 | 442 | <0.05 | 145.9626 | 8.106532 | (5.36, 12.31) |
| | Others | 46 | 2702 | | | | |
| History of blood transfusion | Present | 72 | 2769 | <0.05 | 40.5542 | 0.278595 | (0.18, 0.44) |
| | Absent | 35 | 375 | | | | |

at the national level through an effective organization and integrated blood supply network.[1] Following the recommendation, the Indonesian government regulates that the Blood Transfusion Unit (BTU) is responsible for blood supplies and safety transfusions.[11]

A safe blood for transfusion can be obtained through careful selection from healthy donors. It has to be free from the infections which may harm the recipients, processed through reliable test methods, especially in the process of component production, storage, and transport and is only given to the patients if indicated for the health and their conditions improvement.[12]

During the study, between the August 2015 and 2016, a third of pediatric patients had a transfusion (3,251 out of 8,438 pediatric patients). The most common blood component used was packed red cell (PRC) for 2,114 times (65%). The total volume of the transfusion was 427,249ml which mainly consisted of PRC (275,197ml). Oakley et al. reported the similar proportion of blood transfusion in pediatric and adults patients. [8] The study involving 750,356 pediatric inpatients from January 2011 to February 2013 showed 24 per 1000 patients received transfusions.[8] The most common blood components for transfusion were PRC, plasma, TC, and cryoprecipitates for 79,933, 31,605, 20,179 and 2,154 transfusions, respectively.[8] Similarly, Kato et al. reported a total of 11,155 PRC, 3,151 FFP, and 3,604 TC were transfused from January 2008 to December 2009.[9]

In 2012, The National Health Surveillance Agency in Brazil observed one transfusion reaction for every 1,065 transfusions.[7] Around 85% was mild, 12.7% was moderate, and 2.2% was severe .[7] Our study found 107 (3.3%) transfusion reactions happened. Waiswa et al. reported 53 transfusion reactions were observed from a total of 507 transfusions. As many as 49 of them were acute reactions (9.6%).[13] In the United States, 20,933,000 units of Whole Blood (WB) and blood components were transfused in 2011, in more than 4,200 health facilities. As many as 51,000 transfusion reactions were reported.[14] While in Canada, a total of 11 transfusion reactions from 179 pediatric oncological cases were found, with the most common reaction observed in the acute leukemia cases (46%).[15]

Patients who are receiving transfusions are at risk for transfusion reactions.[6] These reactions can be caused by the binding of the donor's leukocyte antigens and the recipient's antibody which activates the monocyte complex, cytokine release (interleukin (IL ) 1β, IL-6 and tumor necrosis factor (TNF) α) and pyrogens.[16] Other reaction-inducing factors are: the allergens and antibodies interaction resulting in an allergic reaction, the anaphylactic reactions of the antibodies against the plasma donor proteins (immunoglobulin (Ig) A, haptoglobin, and C4). The incompatibility of the blood products that produce antibody-antigen responses with complement activation and intravascular hemolysis, volume overload, and infections.[12]

In Uganda, Waiswa, et al. reported that fever (49%) and allergic reactions (14%) were the most common transfusion reactions.[13] Similar results were observed in a study by Gwaram, et al. The study showed 3.6% of 302 blood transfusions resulted in an acute transfusion reaction.[17] As much as 3.3% and 0.3% were febrile non-hemolytic transfusion reactions (FNHTR) and allergic reactions, respectively.[17] Our study supported the previous findings that fever (62.6%) and allergic reactions (19.05%) were the most common reactions. The fever or the FNHTR is caused by the leucocyte antigens stimulation, resulting in the pyrogenic cytokines or inflammatory mediator responses accumulated in the cellular storage of blood products.[6] In contrast, a study conducted by Sharma et al. found allergic reaction as the most common reactions of blood transfusions (65.6%).[18] Moreover, Harvey et al. reported that allergic reactions were the highest transfusion reaction (111.2 per 100,000), followed by a non-hemolytic febrile (86.4 per 100,000). The difference between these findings can be explained by the absence of leukoreduction in the blood

components separation process in our study. Thus, it contributes to the increase in the incidence of transfusion reaction.

Several risk factors can lead to the transfusion reactions such as the patient's age, transfusion component (the type and age of the blood product), and the previous transfusion history.[9,19] In some countries, there is a substantial difference regarding the distribution of the age of patients receiving a transfusion. In high-income countries, the patients receiving transfusion are predominated by the age group of more than 65 years old, while in low-income countries are predominated by children less than five years old.[1] Our study indicated the age of more than 12 months as a possible risk factor (POR=2.81, 95%CI 1.78-4.58).

A TC is a blood component made from whole blood (WB), consisted of $5.5x10^{10}$ platelets in 45-65ml/unit, erythrocytes (<0.5 ml/unit) and leukocytes ($\geq 5x10^{6}$).[19] The higher leukocytes concentration in PRC than TC components increases the risk of transfusion reaction. Our study obtained 61 out of 107 transfusion reactions (57%) happened in patients receiving TC transfusion (POR=8.11, 95%CI 5.36-12.31). Harvey et al. also reported that the highest incidence of transfusion reactions occurred in the patients receiving TC (427.1/100,000) followed by PRC (205.5/100,000), plasma (127.7/100,000), and cryoprecipitate (5.6/100,000).[14]

However, Sharma et al. reported the highest incidence of transfusion reactions found in patients receiving PRC transfusion (risk 0.76%, p=0.42) and WB (risk 0.68%, p=0.63), with no reaction observed in TC transfusion.[15] The risk of TC and PRC transfusion reactions may be due to the difference in the production method of blood components, immunological mechanisms or the effects of fluid addition.[14] A study by Tobian, et al. on how to prevent transfusion reactions in TC transfusion reported that the incidence of transfusion reactions decreased from 5% to 0.7% (p <0.001) when TC apheresis was used.[20]

The history of previous transfusions increased the risk for transfusion reactions, particularly slow-type transfusion reactions, are often missed.[21] Gwaram et al. suggested that there was a significant association between the acute transfusion reactions and the history of previous transfusion (RP=4.12, p=0.04).[17] In contrast, we found that the history of previous transfusions reduce the risk or provide protection against transfusion reactions (OR=0.28, p-value<0.05, 95%CI 0.18, 0.44). However, the use of diphenhydramine and intravenous dexamethasone can confound the findings as most of the pediatric patients who received recurring transfusions had been given premedication to minimize the reaction. Indeed, Kennedy et al. reported a lower incidence of transfusion reaction in patients receiving premedication before transfusion compared to placebo.[22]

One of the strategies to minimize the transfusion reaction that could prevent FNHTR is leukoreduction, a platelet refraction caused by alloimmunization of human leukocyte antigen (HLA) and cytomegalovirus transmission.[23] The method has not been readily available at Sanglah Hospital. However, it is necessary to provide a standardized blood screening and production process to reduce the incidence of transfusion reactions.

## CONCLUSION

Irrational and improper transfusion can lead to a transfusion reaction. This study identified that age more than 12 months, and platelet transfusion are risk factors for transfusion reactions. The transportation time between the blood bank and transfusion might become a risk factor for the transfusion reaction. However, this study had not take into account the time when the blood was taken from the Indonesian Red Cross (PMI) unit until it was administered to the patients. Therefore, further research is needed to recognize specific risk factors and other possible outcomes of the transfusion reactions

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