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Association of Premedication before Blood Transfusion with Transfusion Reactions in Mohammad Hoesin Hospital Palembang

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Abstract

Background : Premedication before blood transfusion is frequently used in clinical settings, albeit its effectiveness has not been shown. Premedication is used to stop transfusion-related fever and allergy. Unwanted or unanticipated consequences connected to the administration of unstable blood products are known as transfusion reactions.
Aims : The aim of this study is to find out the association of premedication before blood transfusion with transfusion reactions.
Methods : This study is an observational analytic study with cross-sectional design, the data obtained from Mohammad Hoesin Hospital Palembang from January 1st, 2020 to December 31st, 2021.
Results : 43 patients out of 73 samples did not receive premedication before the transfusion procedure, 8 patients (18.6%) experienced transfusion reactions, and 35 patients (81.4%) did not. 35 patients who received premedication, 2 patients (5.7%) experienced transfusion reactions, and 33 patients (94.3%) did not. The incidence of transfusion reactions at Mohammad Hoesin Hospital Palembang in the 2020–2021 period was not significantly associated with pre-transfusion premedication ($p = 0.171$). It is also not associated with blood transfusion history ($p = 0.426$), blood components ($p = 0.793$), or gender ($p = 1.000$).
Conclusion : Based on this finding, there is no significant association between premedication before blood transfusion and the transfusion reactions during period of 2020–2021 at Mohammad Hoesin Hospital Palembang.

Keywords : pre-transfusion premedication; transfusion reaction; blood transfusion.

INTRODUCTION

Blood transfusion is a life-saving procedure in which a patient receives blood or blood products to replace blood lost as a result of surgery, trauma, or other illnesses that result in low blood volume or anemia.[1] Blood transfusions may be essential when a patient has experienced significant blood loss due to trauma or surgery, or when their body isn't making enough blood components. However, blood transfusions carry the risk of acute transfusion reactions.[2] Transfusion reactions are unexpected or unwanted events associated with the administration of unstable blood products. Acute transfusion reactions are categorized into two categories, immune-mediated reactions, which involve the formation of antigen-antibody complexes and non-immune-mediated reactions.[3] The most frequent acute transfusion reactions are allergy responses and fever non-hemolytic transfusion reactions (FNHTR), which are also the least harmful transfusion reactions. Within three hours after receiving a transfusion, blood donor recipients with FNHTR experience fever (defined as a temperature rise of ≥1□ above normal) and/or rigors. Within a few hours following transfusion, urticaria or other rashes, hives, wheezing, or angioedema are the most typical symptoms of allergic responses.[4,5]

According to data gathered by Switzerland's Schweizerische Heilmittelinstitut (Swissmedic), 2,032 (0.74%) complaints of adverse transfusion reactions were made for the 275,343 blood products (frozen plasma, platelet concentrates, and stored blood cells) that were transfused in 2020.[6] Among these, 3 fatalities (or 0.001% every transfusion conducted) resulted from 1,910 (0.69%) responses identified as probable transfusion reactions and 1,486 (0.54%) reactions classified as severe or severe reactions.[6] Further research conducted in 2020 using data gathered by the German Paul Ehrlich Institute (PEI) revealed that 4,400,164 blood products were transfused, with 921 (0.02%) complaints of potentially significant transfusion reactions. In this instance, the reports had no information on potential adverse effects; however, 621 (0.014%) reports showed a causal association between the delivery of blood components and 7 (0.0002%) fatalities per transfusion.[7]

Physicians commonly prescribe premedication before blood transfusion because it is believed to reduce the incidence of transfusion reactions.[8] Premedication before blood transfusion refers to the administration of medications prior to transfusion with the aim of preventing or reducing the severity of transfusion-related adverse reactions.[9] Premedication before transfusion is often used, despite limited evidence supporting its effectiveness.[8,10] Based on previous recommendations, premedication with diphenhydramine and/or acetaminophen is a standard practice to avoid moderate allergic transfusion responses and feverish nonhemolytic transfusion reactions. Randomized-controlled trials, however, have not demonstrated any advantage or effect of premedication.[11] In some developing countries, despite literature supporting the idea that premedication should only be given when transfusion reactions occur, chlorpheniramine maleate and acetaminophen are also used as premedication for preventing transfusion reactions from pre-storage leukoreduced, post-storage leukoreduced, or non-leukoreduced blood products.[12,13]

The benefit of administering premedication before transfusion remains questionable for patients.[8] Research on the use of premedication before blood transfusion to prevent transfusion reactions is limited and has never been conducted in Palembang. Therefore, this research is expected to analyze the association of premedication before blood transfusion with the transfusion reactions in Palembang and can be a reference or consideration in giving premedication before blood transfusion to patients who have a history of transfusion reactions in Palembang, especially at Mohammad Hoesin Hospital Palembang.

METHODS

Study Design

This study used observational analysis and cross-sectional design. It was conducted in the Medical Records Installation and Blood Transfusion Unit of Mohammad Hoesin Hospital Palembang. This research was conducted during September 2022 – December 2022 and have obtained ethical approval from the Faculty of Medicine, Sriwijaya University, with the number 261-2022.

Sampling

Data samples was collected with consecutive sampling in January 2020 – December 2021, involved patients who underwent blood transfusion at Mohammad Hoesin Hospital. The minimum sample size to meet the objectives of this study was calculated using the following formula:

$$n = \frac{Z_{\propto}{}^2 PQ}{d^2}$$

Based on the formula, the sample size required in this study is 67. The inclusion criteria were patients who received blood transfusions in the period January 1st, 2020 – December 31st, 2021 taken from the Medical Records Installation and Blood Transfusion Unit of Mohammad Hoesin Hospital, Palembang. Meanwhile, the exclusion criteria were (1) pediatric patients who received blood transfusions, and (2) incomplete, defective, and/or damaged patient medical record data.

In this study, the variable was catagories into premedication and non-premedication, for the variable

of the reaction of tranfusion is present and absent. The premedication given is diphenhydramine and dexamethasone, meanwhile the tranfusion reactions are all adverse side effects or adverse reactions to transfusions that often occur during or shortly after transfusion. All variables are taken from the information in the medical record.

Statistical Analysis

The collected data were processed using IBM SPSS Statistic 24 (IBM, Armonk, United States). All data is presented on a categorical scale. The data were presented descriptively using univariate analysis and then continued with bivariate analysis to determine the association between variables. The test that will be used in this study is the chi-square test.

RESULTS

The distribution of patients receiving blood transfusions based on sociodemographic factors showed in Table 1. Of the 78 patients, the subjects were predominantly aged 50–59 years (29.5%) and female (64.1%).

In Table 2, there are distribution of patients receiving blood transfusions based on blood type. The results showed that the most commonly found blood type was B (29.5%), although it was not very different from the other blood types.

Table 3 shows patients receiving blood transfusions based on blood components. The results show that the blood component most frequently used by patients is PRC (87.2%).

Table 4 shows patients who received blood transfusions based on a history of blood transfusions. Most of patients (68%) never had a history of previous transfusion.

In Table 5, there are data of patients who received blood transfusions based on a history of blood transfusions. The results showed that 78 people (100%) did not have a history of previous transfusion reactions.

Table 6 shows patients receiving blood transfusions based on the provision of premedication. It

TABLE 1
Distribution of patients receiving blood transfusions based on sociodemographic factors

Variables	Number (n = 78)	Percentage (%)
Age		
<20	5	6.4
20–29	7	9.0
30–39	14	17.9
40–49	11	14.1
50–59	23	29.5
≥60	18	23.1
Gender		
Male	28	35.9
Female	50	64.1

TABLE 2
Distribution of patients receiving blood transfusions based on blood type

Blood Type	Number (n)	Percentage (%)
A	21	26.9
B	23	29.5
O	21	26.9
AB	13	16.7
Total	78	100

TABLE 3
Distribution of patients receiving blood transfusions based on blood components

Blood Components	Number (n)	Percentage (%)
PRC	68	87.2
WE	3	3.8
TC	4	5.1
TP	2	2.6
FFP	1	1.3
Total	78	100

TABLE 4
Distribution of blood recipient patients based on blood transfusion history

Blood Transfusion History	Number (n)	Percentage (%)
0	53	68.0
1–2 times	19	24.4
3–4 times	3	3.8
≥5 times	3	3.8
Total	78	100

TABLE 5
Distribution of patients receiving blood transfusions based on a history of transfusion reactions

History of Transfusion Reaction	Number (n)	Percentage (%)
Positive	0	0.0
None	78	100.0
Total	78	100

was found that the majority of patients receiving blood transfusions were not given premedication (55.1%). All patients who received premedication were from the internal medicine ward, whereas those who did not receive premedication were from the surgical, obstetrics and gynecology (OBGYN), ear nose and throat (ENT), and emergency departments.

Table 7 shows patients who received blood transfusions based on the incidence of transfusion reactions. It was found that the majority of patients receiving blood transfusions never experience transfusion reactions before (87.2%).

Table 8 shows the association between several variables and transfusion reaction. The results of this study were analyzed using the chi-square statistical test. There is no association of gender, blood type, blood components, history of transfusion reactions, and premedication with transfusion reactions. In the other hand, there is association between the age of patients receiving blood transfusions and the transfusion reactions.

DISCUSSION

The distribution of patients receiving transfusions based on the most age was the age group 50–59 years as many as 23 people (29.5%). This is in line with a study conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which showed that the distribution of the largest age group was the age group >50, with a total of 56 people (54.3%).[14] In contrast to the research conducted by Kohorst *et al* in one of the research centers in America

TABLE 6
Distribution of patients receiving blood transfusions based on the provision of premedication

Premedication	Number (n)	Percentage (%)
Positive	35	44.9
None	43	55.1
Total	78	100

TABLE 7
Distribution of patients receiving blood transfusions based on the incidence of transfusion reactions

Transfusion Reaction History	Number (n)	Percentage (%)
Positive	10	12.8
None	68	87.2
Total	78	100

which showed that the distribution of patients receiving blood transfusions based on age was the largest age group 19–25 years with a total of 84 people (41.8%).[15] This could be due to the increased risk of diseases requiring blood transfusions above the age of 50 years. The presence of conditions or diagnoses such as bleeding or cancer in adult patients over 50 is increased so that patients receiving transfusions is also increased.[16]

The patients receiving transfusions was mostly female patients as many as 50 people (64.1%). This is in line with a study conducted by Purwati *et al* at UTD Dr. M. Djamil Hospital Padang which showed that the distribution of the most gender was female, as many as 63 people (61.6%).[14] While this is not in line with a study conducted by Kohorst *et al* in one of the research centers in America which showed that the distribution of patients receiving blood transfusions based on gender was mostly male, with a total of 115 people (57.2%).[15]

Based on the literature, the exact reason for the influence of gender on the need for and consideration of blood transfusion, which is usually given to treat symptoms such as anemia, has not been determined.[17] However, it is possible that gender influences the number of blood transfusion distributions due to clinical influences such as anemia, which usually has level of hemoglobin level <12 g/dL in females and <13 g/dL in males, causing more female than male transfusion patients based on this classification because females have a lower normal lower limit than males.[18]

The most commonly found blood type was B (29.5%), although it was not very different from the other blood types. This is not in line with study by Grandi *et al* conducted in Brazil which shows that the distribution of transfusion recipients based on the most blood groups is blood group O with a total of 762 people (49.2%).[19] This is different from the study conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which shows that the distribution of patients receiving blood transfusions based on the largest blood group is group A, with a total of 39 people (37.8%).[14] There is no definite basis between the number of patients receiving transfusion based on blood type because transfusion itself is given according to the indication of the patient's condition, such as in patients with acute or active bleeding, patients with symptoms associated with anemia (eg, dyspnea on exertion, weakness, tachycardia), and patients with hemoglobin level <8 g/dL. So, there is no direct impact on the distribution of patients by blood type. However, there are blood groups such as blood group O, which is a universal blood group, which indirectly makes the number of patients receiving transfusions with blood group O increase.[20]

The distribution of the most accepted blood components was packed red cell (PRC) as many as 68 recipients (87.2%). This is in line with research conducted by Grandi *et al* conducted in Brazil which shows that the distribution of patients receiving transfusions based on the most blood components is the PRC blood component as many as 1,122 people (72.5%).[19] Research by Rujkijyanont *et al* in one of the hospitals in Thailand showed different result, that the distribution of patients receiving transfusions based on the most blood components was the blood component of leukocyte poor packed red cell (LPRC) as many as 99 people (67.4%).[12] Packed red cells (PRC) can be transfused to individuals who have or are at high risk of developing symptomatic anemia in order to enhance their ability to transport oxygen.[21] According to US guidelines PRCs are

TABLE 8
The association of sociodemographic factors, blood type, blood components, transfusion history, premedication before blood transfusion with the incidence of transfusion reactions

Variables		Transfusion Reaction				Total n (%)	*p* value	95% CI	
		Yes		No					
		n	%	n	%			Lower	Upper
Gender	Male	3	10.7	25	89.3	28 (100)	1.000	0.175	3.110
	Female	7	14.0	43	86.0	50 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Age	<20	3	60.0	2	40.0	5 (100)	0.021		
	21–29	0	0.0	7	100.0	7 (100)			
	30–39	2	14.3	12	85.7	14 (100)			
	40–49	0	0.0	11	100.0	11 (100)			
	50–59	2	8.9	23	91.3	23 (100)			
	≥60	3	16.7	18	83.3	18 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Type	A	4	19.0	17	81.0	21 (100)	0.744		
	B	3	13.0	20	87.0	23 (100)			
	O	2	9.5	19	90.5	21 (100)			
	AB	1	7.7	12	92.3	13 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Components	PRC	10	19.0	58	81.0	68 (100)	0.793		
	WE	0	0.0	3	100.0	3 (100)			
	TC	0	0.0	4	100.0	4 (100)			
	TP	0	0.0	2	100.0	2 (100)			
	FFP	0	0.0	1	100.0	1 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Transfusion History	0 times	8	15.1	45	84.9	53 (100)	0.426		
	1–2 times	1	5.3	18	94.7	19 (100)			
	3–4 times	1	33.3	2	66.7	3 (100)			
	≥5 times	0	0.0	3	100.0	3 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Premedication	Non-premedicated	8	18.6	35	81.4	43 (100)	0.171	0.52	1.341
	Premedication	2	5.7	33	94.3	35 (100)			
	Total	10	12.8	68	87.2	78 (100)			

transfused if hemoglobulin is at 7 g/dL in asymptomatic patients or in patients with suspected anemia. Additionally, guidelines suggest a threshold of 8 g/dL for individuals undergoing orthopedic surgery or those with coronary artery disease.[22] This is why PRC is used more frequently than other blood components.

Most of patients in this study (68%) never had a history of previous transfusion. This is different from a

study conducted by Sanders *et al*. in the United States, which showed that the largest group of patients receiving blood transfusions were those with a prior history of transfusion, totaling 3,429 individuals (43.4%).[16] This is also different from the research conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which shows that patients receiving blood transfusions based on the history of blood transfusions are the largest group of patients who have had previous transfusions before as many as 60 people (58.2%).[14] In theory, the frequency of a patient's blood transfusion history depends on their clinical diagnosis. Conditions such as thalassemia and hemophilia require patients to undergo regular transfusions, which consequently leads to a higher number of transfusions over time.[23,24] In this study, the majority of patients were found to be anemic and/or experiencing bleeding, which explains the high number of patients who had never received a blood transfusion before.

The majority of patients in this study were not given premedication (55.1%). This contrasts with a study conducted by Sanders *et al*. involving 7,900 transfusion recipients at a pediatric cancer center in the United States. The study showed that the highest proportion of transfusion reactions occurred among patients who had received premedication, totaling 5,379 individuals (67%).[16] However, this is consistent with a study conducted by Rujkiyanont *et al*. involving 147 transfusion recipients at a hospital in Thailand, which found that the largest proportion of patients, 74 individuals (50.34%), had not received premedication prior to transfusion.[12] In theory, the use of premedication prior to blood transfusion remains controversial. In the United States, premedication, particularly with antipyretics and antihistamines, is commonly administered to prevent transfusion reactions such as fever and urticaria. One large American hospital, for example, reported a premedication rate of 80%. In contrast, a healthcare facility in Canada reported a reduction in premedication use from 73% to 50% following the implementation of institutional guidelines.[11,25]

Among the 78 transfusion recipients, 68 patients (87.2%) never experienced any transfusion reactions. This is consistent with research conducted by Sanders *et al*. on transfusion recipients in the United States, which showed that the majority of patients, as many as 7,841 individuals (98.9%), did not experience transfusion reactions.[16] This is also consistent with research conducted by Rujkijyanont *et al*. at a hospital in Thailand, which showed that the majority of transfusion recipients, as many as 120 individuals (81.6%), did not experience transfusion reactions.[12] Epidemiologically, acute transfusion reactions occur in approximately 1 in 70,000 blood product transfusions. Because most patients do not exhibit symptoms, delayed transfusion reactions can be difficult to detect and are therefore underreported, making their true incidence unclear. Studies on delayed transfusion reactions vary widely in scope, with estimates ranging from approximately 1 in 800 to 1 in 11,000 transfusions. The frequency of non-immune hemolytic reactions is also uncertain, although they are believed to be relatively rare.[26]

There is significant association between age and transfusion reactions in this study. This is consistent with a study conducted by Kohorst *et al*. at, which demonstrated a significant association between age and the incidence of transfusion reactions.[15] It was reported that transfusion reactions occurred in only 2% of the general adult patient population. However, the profile of transfusion reactions may differ in immunocompromised populations.[24] In another theory, there are parameters associated with the risk of transfusion-associated circulatory overload (TACO) which are reduced cardiac and renal function, compensatory anemia, pre-existing positive fluid balance, plasma ordered to reverse anticoagulation, cancer diagnosis, and extreme age (people aged <25 or aged >74). So it can be said that younger patients and elderly patients are more susceptible to transfusion reactions such as TACO.[21]

The finding in this study showed no significant association between gender and transfusion reactions. Study conducted by Rujkijyanont *et al*. found that delayed transfusion reactions, particularly in the form of urticarial rash, occurred significantly more often in women than in men. This difference is likely attributed to the influence of estrogen on enzymes lining the blood vessels, which leads to increased nitric oxide production and may result in more prolonged and severe allergic reactions.[12]

There is no significant association between blood component and transfusion reaction. The findings of this study differ from those of a study by Sanders *et al*. conducted at a hospital in the United States, which found a significant association between premedication and the occurrence of transfusion reactions.[16] An adverse reaction or effect is an undesirable response or effect in a patient that is temporarily associated with the administration of blood or blood components.[3] Blood components should be processed from aseptically collected blood from donors who have been evaluated and meet eligibility criteria. The quality of blood components should be ensured through monitoring at all stages from donor selection to delivery at the hospital. The various blood components that can be transfused alone consist of whole blood, PRC, platelets, FFP, cryoprecipitate, apheresis platelets, and apheresis plasma.[27]

No significant association also found between blood transfusion history and transfusion reaction. The results of this study differ from those of Sanders *et al*., conducted at a hospital in the United States, which reported a significant association between a history of blood transfusion and transfusion reactions. Fever and

allergic reactions were more common among individuals with a limited history of blood transfusions and those who received transfusions in general inpatient units. Additionally, the study noted that many of the observed findings could not be fully explained by the current understanding of the pathophysiology of transfusion reactions.[16] History of blood transfusions may increase the risk of delayed hemolytic transfusion reactions (DHTRs), which are typically triggered by immune response to foreign red blood cell antigens from prior exposures, such as pregnancy or previous transfusions. [2]

In this study, there is no significant association between premedication before transfusion and the transfusion reactions (p = 0.171; p > 0.05). The results of this study are consistent with Sanders *et al*., who reported no significant association between premedication with acetaminophen and the incidence of transfusion reactions (p = 0.896; p > 0.05). The same study also found no significant association between premedication with diphenhydramine and the incidence of transfusion reactions (p = 0.054; p > 0.05).[16] Premedication before blood transfusion refers to the administration of medications prior to transfusion with the aim of preventing or reducing the severity of transfusion-related adverse reactions.[9] Premedication before blood transfusion is commonly administered clinically despite lack of evidence of its efficiency.[8] Premedication with acetaminophen and diphenhydramine was no more effective than administering a placebo in preventing transfusion responses, according to a comprehensive analysis that included randomized trials. Some retrospective investigations on premedication have produced contentious findings.[11,28]

Theoretically, the purpose of pre-transfusion premedication is to prevent fever, pruritus, and urticaria. The medication for premedication itself is administered intravenously either before or 30 minutes before transfusion. In Japan, institutional norms have not been created, and both inpatients and outpatients are premedicated in the same manner. Most experts in Japan recognize that premedication is necessary and efficient in preventing transfusion reactions.[28] The commonly used premedication is antihistamine and hydrocortisone as pre-transfusion premedication despite the lack of concrete evidence for its use.[28] This is not much different in Mohammad Hoesin Hospital where internal medicine ward patients who receive blood transfusion are given diphenhydramine and dexamethasone as pre-transfusion premedication according to the provisions of the standard operating procedure of blood transfusion in the internal medicine department.

Antihistamines, such as diphenhydramine, are commonly used as premedication before blood transfusions due to their ability to inhibit the effects of histamine, a key effector molecule involved in allergic reactions. Histamine, also known as β-aminoethyl imidazole, plays a central role in allergic transfusion reactions (ATRs) by contributing to symptoms such as flushing and tissue edema, which result from the dilation of small blood vessels and increased vascular permeability. However, it is important to recognize that histamine is only one of several bioactive mediators released by activated mast cells during an allergic response. Other substances, including leukotrienes and kinins, also contribute significantly to the overall reaction. Therefore, while antihistamines can partially alleviate allergic symptoms by targeting histamine pathways, they may not fully prevent all manifestations of ATRs due to the involvement of additional mediators.[25] It also should be noted that premedication, such as diphenhydramine, can cause side effects and may lead to significant impairment. Diphenhydramine crosses the bloodbrain barrier and exerts both anticholinergic and antihistaminic effects. These actions commonly result in drowsiness, decreased alertness, impaired cognitive function, and, in rare cases, restlessness and anxiety.[10,16,25]

Patients with a history of transfusion reactions are often prescribed premedication in an attempt to reduce the likelihood of future reactions. However, previous studies have shown no significant reduction in reaction rates with the use of premedication, even among individuals with a history of two or more transfusion reactions. Therefore, routine premedication in such cases is not recommended.[25] This is in line with this study that the incidence of transfusion reactions is not affected by the use of pre-transfusion medication.

A retrospective study by Sanders *et al*. reported a non-significant increase in the risk of transfusion reactions––such as fever and allergic responses––associated with the use of pre-transfusion medication, particularly acetaminophen and diphenhydramine. The study found no evidence that premedication effectively prevents transfusion reactions and noted that the overall incidence of febrile and allergic reactions is very low. However, the same study suggested that premedication may still be appropriate for high-risk individuals, such as those with a history of severe or unpredictable reactions.[16]

CONCLUSION

This study found no significant association between premedication before blood transfusion and transfusion reactions. These findings challenge the routine use of premedication in all transfusion recipients, particularly given the low overall rate of allergic and febrile transfusion reactions observed. Although premedication is often administered with the intention of preventing adverse reactions, the lack of clear clinical benefit, combined with the potential for medication-related side effects, calls into question its indiscriminate use in

standard transfusion protocols. Transfusion practices should be guided by evidence and individualized risk assessment rather than tradition or routine. Limiting premedication to high-risk patients, such as those with a documented history of severe or unpredictable transfusion reactions, may improve patient care and reduce unnecessary medication exposure.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to this work.

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