ACETAMINOPHEN AND DIPHENHYDRAMINE AS PRE TRANSFUSION MEDICATION IN THE INCIDENCE OF FEBRILENON-HAEMOLYTIC TRANSFUSION REACTION PLATELET RECIPIENTS

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ABSTRACT

Background. *Blood transfusion can save lives, patients get the benefit but also the risk of transfusion-related. Febrile non-haemolytic transfusion reaction (FNHTR) most frequently found and have similar symptoms of other transfusion reactions, causing delays in transfusion and decrease the quality of life. Platelet recipients have a higher incidence risk FNHTR than recipients of other blood products. Pre-transfusion medications with acetaminophen and diphenhydramine reduce the incidence FNHTR.*

Aim of Study. *To investigate the effect of Acetaminophen and Diphenhydramine to prevent FNHTR in platelet recipients.*

Methods.*The study was conducted from May to November 2010 Internal Medicine Wards, Dr. Sardjito Hospital, Yogyakarta using the method of double-blind randomized controlled trial. Inclusion criteria were first recipient of random donornon leucodepleted platelets in thrombocytopenia malignant patients and willing to participate. Exclusion criteria were fever is when will transfusions orin 2x24 hours, allergies of acetaminophen and diphenhydramine, acetaminophen and diphenhydramine consumptionin the last 6 hours, the consumption of continuous corticosteroids, history of transfusion reactions and critical conditions/sepsis. Assessment of the incidence FNHTR 15 minutes before transfusion to 4 hours after transfusion. Medication group will receive a capsule containing 650mg acetaminophen and 25mg diphenhydramine dissolved in 5m l0.9% Na Clintravenously. The control group received a placebo. Drugs are given 30 minutes before the first transfusion bag. Data were analyzed using Chi-square test and p <0.05 was considered statistically significant.*

Results. *Thirty-two patients met the criteria, 15 patients (46.87%), medication group and 17 (53.13%) patients of control group. Eleven (31.43%) patients had FNHTR, 8 (47.06%) patients of control group and 3 (20%) patients. There are differences in the proportion of incident FNHTR in both groups although not statistically significant (P =0.04). Every patient has different risk factors on parity, history of transfusion, history of FNHTR and the long of platelet storage.*

Conclusion. *As pre-transfusion medications, Acetaminophen 650 mg and diphenhydramine 25 mg reduced the incidence of FNHTR compared to placebo in the first platelet recipients in malignancy.*

Key words: *Acetaminophen, diphenhydramine, pre transfusion medication, FNHTR.*

INTRODUCTION

Until the last of 1960, platelets can not be widely use dexceptin the form of fresh whole blood transfusion. The difficulties include the risk of bacterial contamination and optimal storage conditions to maintain viability and function platelets are still not clear[1,2]. Febrile non-haemolytic transfusion reaction (FNHTR) and allergies are the most frequent reaction, the rate of incidence of ± 1% in the packed red cells transfusion and could reach 30% in transfusion platelet[3, 4, 5, 6, 7].

Symptoms and signs of FNHTR are difficult to distinguish from other severe transfusion reactions. Allergy and FNHTR effect on satisfaction, cost and management of transfusion that is necessary to reduce the incidence. FNHTR

risk can be lowered with leucodepleted blood process, medicine or the use of new blood products. Leucodepleted needed more process, greater cost and may reduce the potential for blood products. The combination of acetaminophen and diphenhydramine is most commonly used as pre-transfusion medications in the United States and Canada, ±50% -80% through out transfusion[8].

In this study, we aimed to investigate the effect of Acetaminophen and Diphenhydramine to prevent FNHTR in platelet recipients.

METHODS

The study design was randomized double-blind controlled trial (RCT) in Internal Medicine Wards, Dr. Sardjito Hospital, and Yogyakarta from May 2010 to November 2010. Target population is thrombocytopenia patients the recipient of random donor non-leucodepleted platelets. Affordable is the first recipient population (naïve) random donornon-leucodepleted platelets in Internal Medicine Wards, Dr. Sardjito Hospital,Yogyakarta who met the study criteria.

Inclusion criteria were thrombocytopenia patients in malignant disease first recipient of random donornon-leucodepleted platelets and willing to participate in the study. Exclusion criteria were being at the time would fever or fever in 2x24-hour, allergy to acetaminophen and diphenhydramine, acetaminophen and diphenhydramine consumption in 6 hours, the consumption of corticosteroids continuously, had an other transfusion reactions and the critical condition/sepsis.

Each patient with thrombocytopenia, first recipient of random donor non-leucodepleted platelets in Internal Medicine Wards, Dr. Sardjito Hospital, Yogyakarta who met the criteria of the study conducted anamnesis, physical examination and laboratory test. Patients were randomized by simple random sampling method and divided into two groups: medication and control groups. Each patient received 2 drugs: the capsules and injection drugs which taken 30 minutes before the first transfusion bags. Medication group received capsules containing acetaminophen 650 mg and 25 mg diphenhydramine in travenously. Diphenhydramine dissolved in 5 ml NaC l0.9% in the syringe. The control group received placebo capsules containing powdered dextrose and 5 ml of NaC l0.9% in the syringe. Vital signs and transfusion reactions may examine before, during and after transfusion. Each examination results are recorded on sheets of follow-up special. Examination carried out 15 minutes before the transfusion started, during the transfusions performed every 15 minutes (in the first 30 minutes), then every 30 minutes until the transfusion is completed and every hour for 4 hours after the transfusion is completed. Ethical clearance was retained from Ethical Committee of Dr. Sardjito General Hospital.

STATISTICAL ANALYSIS

Continuous data are presented in the form of mean ±standard deviation if normally distributed data and in the form of median (with minimum and maximum range) if not normally distributed. Categorical data are presented in the form of proportion. Differences proportion of patients who were not experiencing FNHTR and comparative analysis of categorical test unpaired chi-square test. Differences are considered statistically significant if $p<0.05$.

RESULTS

Thirty-two patients met the criteria, divided 15 patients (46.87%), medication group and 17 patients (53.13%) control group. The basic characteristic is shown in the following table.

Table1. Basic characteristicsof patients

Variables	Medications group N= 15 (46.87%)	Control group N=17 (53.13%)	*P* value
Age	43.94 ± 1.62	44.20 ±1.90	
Sex:			0.08*
Female	6 (40)	12 (70.59)	
Male	9 (60)	5 (29.41)	
Parity:			0.73**
Nullipara	1 (16.67)	2 (16.67)	
history of pregnancy	5 (83.33)	10 (83.33)	
Transfusion history:			0.402**
Yes	13 (86.67)	12 (70.59)	
No	2 (13.33)	5 (29.41)	
Previous transfusion:			0.48**
PRC	13 (100)	11 (91.67)	
WB	0	1 (8.33)	
FNHTR history:			0.645**
Yes	3 (20)	2 (11.76)	
No	12 (80)	15 (88.24)	
Platelet storage:			0.322*
over 3 days	7 (46.67)	5 (29.41)	
less than 3 days	8 (53.33)	12 (70.59)	

Notes:*Chisquaretest, **Fisher'sexacttest,WB=whole blood
FNHTR=febrilenon-haemolytic transfusion reaction; PRC=packed red cell;

The mean age of the patient in this study was 44.06 ±1.73 years, the youngest patient was 19 years old and the oldest was 77 years old. Fourteen patients were male, 9 (60%) medication group and 5 (29.41%) control group. There were 18 female patients, 6 (40%) the medication group and 12 (70.59%) the control group. There were no differences in both gender groups ($p=0.08$).

The parity of female patients divided into nulliparous and had history of pregnancy, 15 patients (83.33%) with a history of pregnancy and 3 patients (16.67%) nulliparous. Five patients (83.33%) in the medication group and 10 patients (83.33%) in the control group had a history of pregnancy, but no difference in parity of both groups of female patients ($p=0.73$).

Twenty-five patients (78.13%) had a history of other blood products before transfusion, 13 patients (86.67%) of the medication group and 12 (70.59%) control group. Thirteen patients (100%) group of medications with a history of PRC transfusion, where as in the control group 11 patients (91.67%) never received PRC and one person had received WB (8.33%). There was no significant difference in the amount of transfusions between the two groups ($p=0.402$).

Five patients (31.25%) had a history of FNHTR, medication group 3 patients (20%) and control group 2 women (11.76%). There was no significant difference FNHTR history in both groups ($p=0.645$).

Platelets storage was divided into less than 3 days and over 3 days. Twenty men (60.5%) received platelets storage less than 3 days, 8 patients (53.33%), medication group and 12 patients (70.59%) control group. Twelve patients received platelet storage over 3 days, medication group of 7 patients(46.67%) and 5 (29.41%) control group. There was no significant difference in platelets storage between two groups ($p=0.322$).

Febrile non-haemolytic transfusion reaction is a common complication of transfusion (Bansaland Marwaha, 2001). Febrile non-haemolytic transfusion reaction (FNHTR) occurred din both study groups, the proportion of FNHTR shown following table.

Table2.
Differences proportion of incident FNHTR medication group compared with control group

	FNHTR (+) N (%)	FNHTR (-) N (%)	*P* value	RR (95% CI)
Control group	8 (47.06)	9 (52.94)	0.04*	3.5 (0.58-1.37)
Medications group	3 (20)	12 (80)		

There were 11 patients (34.38%) of 32 patients who had FNHTR, 8 patients (47.06%) in the control group and 3 patients (20%) in the medication group. There are significant differences the incidence of FNHTR in both groups (p=0.04). Incidence FNHTR this study was 34.38%, the high incidence of FNHTR in our study was probably because the platelets from random donors, non-leucodepleted and platelet storage over 3 days. Incidence FNHTR this study is still in the range of previous studies. Incidence of FNHTR on platelet transfusion range from 1.7% -31%. Wide Range of possibilities because the characteristics of the different blood products processing. FNHTR incidence was higher in platelets, random donor, non-leucodepleted, non-apheresis, patients with malignancy and repeated transfusions (Baldwin, 2002).

In medication group, there were 3 patients (20%) who experienced FNHTR although they have got acetaminophen and diphenhydramine. Whilepatients 12 (80%) did not experience FNHTR. Each patient had risk factors of FNHTR in different events. Profile of 12 patients who did not experience FNHTR in medication group displayed the following table.

Table 3.
Profile of patient medication group who did not experience FNHTR

Patients	The Age (years)	Sex	Diagnosis	Parity	History of transfusion	History of FNHTR	Age of platelets
3	28	P	ITP, SLE	+	+	-	over 3 days
5	71	L	MDS	-	+	-	less than 3 days
6	34	L	AML	-	+	-	over 3 days
7	21	P	ALL	-	+	-	over 3 days
9	49	P	ALL	+	+	-	over 3 days
10	26	L	Suspected Haematological Malignancy	-	+	-	over 3 days
11	67	L	AML	-	+	-	less than 3days
12	38	L	BMFS	-	+	-	over 3 days
13	44	L	AA	-	-	-	less than 3days
16	22	P	ITP	+	+	-	less than 3days
18	52	L	ITP	-	-	-	over 3 days
20	77	L	AML, AKI	-	+	-	over 3 days

Description: L=male; P=female, Par=parity, +=yes. AA=anaemia aplastika, AKI=acute kidney injury, ALL=acute lymphoblastic leukemia, AML=acute myeloblastic leukemia, BMFS=bone marrow failure syndrome, ITP=idiopathic thrombocyt openiapurpura, MDS=myelodysplasia syndrome, SLE=systemic lupuserythemathosus.

Incidence FNHTR affected by the type of blood components, storage conditions and specific factors recipients. Pyrogenin the plasma collected and the numbers increase with duration of platelet storage[9]. In this study, the factors that increase the risk of FNHTR are malignancy patients, recipient random donornon-leucodepleted platelets, parity, history of transfusion and get a platelet transfusion which have been in storage over 3 days. In addition to pre-transfusion medication acetaminophen and diphenhydramine, the following will discuss the factors suspected to affect the incidence FNHTR. All patients in this group had no history of FNHTR.

FNHTR reactions are more common in platelet transfusion derived from a random donor platelets compared aphaeres is single donor, transfusion of patients with recurrent and multi parous women. Incidence FNHTR higher in platelet transfusion compared to packed red cells (PRC)[10]. In our study, patient number 3, 5, 6, 7, 9, 10, 11, 12, 13, 16, 18 and 20 were the patients of medication group who did not get FNHTR. Four female patients and 8 patients were male. Transfusion reactions do not occur possibly due to medication effects, the absence of risk factors that could cause events FNHTR or both.

A study of single-donor platelet transfusions with leucodepleted process 15.4% of patients with medication acetaminophen and diphenhydramine had FNHTR, while 15.2% of patients had FNHTR the control group. The incidence of FNHTR was higher in patients with a history of FNHTR (25.9%) compared with no history FNHTR (11.3%) (p=0.06)[6].

Patients number 3 and 9 were women with a history of pregnancy, had received platelet transfusions and get a platelet transfusion which have been in storage over 3 days. Patient number 3 had a diagnosis idiopathic thrombocytopenia purpura (ITP) and probable systemic lupus erythemathosus (SLE). Patient number 9 had a diagnosis of acute lymphoblastic leukemia (ALL), nefrolithiasis and major depression. Pre-transfusion medication may play a role in these patients so that FNHTR not happen. FNHTR Risk factors include pregnancy, history of transfusion, and history of FNHTR or malignant disease. Women with a history of pregnancy have a higher risk than nulliparous[5].

Patients number 7 was a female, nulliparous, with a history of platelet transfusion and get a platelet transfusion which have been in storage over 3 days..This patient with a diagnosis of acute lymphoblastic leukemia(ALL), has a history of risk factors FNHTR received platelet transfusion and platelet storage over 3 days.

Patient number 5, 6, 10, 12 and 20 were male, with a history of transfusion and received transfusion of platelets storage was over 3 days. Patients number 5 with a diagnosis of myelo dysplasia syndrome (MDS), hypertension andc hronic heart failure. Patients number 6 with a diagnosis of acute myeloblastic leukemia (AML), severe anemia with retinal hemorrhage and gums. Patients number 10 with a diagnosis of suspected hematologic malignancy. Patients number 12 with a diagnosis of suspicious bone marrow failure syndrome. Patients number 20 with a diagnosis of AML and acute kidney injury. Febrile reaction does not occur in these patients the possible effects of medication pre-transfusion, without risk factors of pregnancy and history FNHTR.

Platelet storage over 3 days is a risk factor for incident FNHTR. Risk of complications increased if the transfused blood had been stored in a longer time. Stored blood can under go progressive structural and functional changes that can reduce the function and viability of platelet. Over all transfusion reaction rates higher as long platelet storage[3].

Patient number 16 was a woman with a diagnosis of suspected ITP, hypertension and hypertensive heart disease. These patients have a history of receiving platelet transfusions and wereless than 3 days. Medication pre-transfusion may have an effect so FNHTR not happen although there are risk factors parity and history of transfusion. Patient number 11, a man with a diagnosis of acute myeloblastic leukemia (AML), has a history of platelet transfusion and get platelet which have been in storage for less than 3 days. The patient has a history of transfusion risk factor but this patient did not experience FNHTR. The risk of FNHTR increased in patients with a history of

transfusion due to the formation of HLA antibodies from previous exposure through transfusion or pregnancy, called alloimunization[5].

Patients number 18 was a manget aplatelet transfusion which have been in storage over 3 days. This patient was diagnosed with suspected ITP and bleeding gums. These patients did not experience the event may be due to the effects of medication FNHTR pre-transfusion and because there is only risk factor platelet stored over 3 days.

Patient number 13 was a man with a diagnosis suspect of anemia aplastica and urinary tract infections. Patients never been get platelet transfusion and get sold less than 3 days. The FNHTR did not happen may be due to the effects of medication pre-transfusion.

Another study concluded that the duration of platelet storage less than 3 days associated with the lower incidence of FNHTR[11,12]. Incidence of FNHTR higher after infusion of platelets stored of about 4 to 5 days[13]. This study has several limitations. First, the number of samples of this study is less than the minimum sample size calculation that will affect the statistical analysis. Second, factors suspected to affect FNHTR not measured quantitatively.

CONCLUSION

Pre-transfusion medications with acetaminophen 650 mg and diphenhydramine 25 mg reduced the incidence of FNHTR compared to placebo in the first platelet recipients in malignancy.

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