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 donor non-leucodepleted platelets in thrombocytopenia malignant patients and willing to participate. Exclusion criteria were fever is when will transfusions or 2x24 hours, allergies of acetaminophen and diphenhydramine, acetaminophen and diphenhydramine consumption in 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 10.9% NaCl intravenously. 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.
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. 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 donor non-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 allergic 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 study criteria.

inclusion criteria:

- Thrombocytopenia patients in malignant disease who met random donor
- Non-leucodepleted platelets
- Willing to participate in the study
- Being at the time would fever or fever in 2x24-hour
- Allergy to acetaminophen and diphenhydramine
- Acetaminophen and diphenhydramine consumption in 6 hours
- Consumption of corticosteroids continuously
- An allergic 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 NaCl 10.9% in the syringe. The control group received placebo capsules containing powdered dextrose and 5 ml of NaCl 10.9% 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 obtained 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.

Table 1. Basic characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medications group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.94 ± 1.62</td>
<td>44.20 ± 1.90</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (40)</td>
<td>12 (70.59)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (60)</td>
<td>5 (29.41)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>1 (16.67)</td>
<td>2 (16.67)</td>
<td>0.73**</td>
</tr>
<tr>
<td>Multipara</td>
<td>5 (83.33)</td>
<td>10 (83.33)</td>
<td></td>
</tr>
<tr>
<td>History of pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (86.67)</td>
<td>12 (70.59)</td>
<td>0.402**</td>
</tr>
<tr>
<td>No</td>
<td>2 (13.33)</td>
<td>5 (29.41)</td>
<td></td>
</tr>
<tr>
<td>Previous transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRC</td>
<td>13 (100)</td>
<td>11 (91.67)</td>
<td>0.48**</td>
</tr>
<tr>
<td>WB</td>
<td>0</td>
<td>1 (8.33)</td>
<td></td>
</tr>
<tr>
<td>FNHTR history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20)</td>
<td>2 (11.76)</td>
<td>0.645**</td>
</tr>
<tr>
<td>No</td>
<td>12 (80)</td>
<td>15 (88.24)</td>
<td></td>
</tr>
<tr>
<td>Platelet storage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>over 3 days</td>
<td>7 (46.67)</td>
<td>5 (29.41)</td>
<td>0.322*</td>
</tr>
<tr>
<td>less than 3 days</td>
<td>8 (53.33)</td>
<td>12 (70.59)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Chi-square test, **Fisher’s exact test, WB=whole blood FNHTR=febrile-non-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 was no significant difference in platelets between the two groups (p=0.645).

The parity of female patients divided into nullipara and had history of pregnancy, 15 patients (83.33%) with a history of pregnancy and 3 patients (16.67%) nullipara. 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).

Five patients (78.13%) had a history of other blood products, 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, which 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 were stored in blood less than 3 days, 25 (80%) 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 platelet storage between two groups (p=0.322).

Febrile non-haemolytic transfusion reaction is a common complication of transfusion (Bansal and Marwaha, 2001). Febrile non-haemolytic transfusion reaction (FNHTR) occurred in both study groups, the proportion of FNHTR shown following table.
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 storage3. In this study, the factors that increase the risk of FNHTR are malignancy patients, recipient random donor-non-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.

FNHTR reactions are more common in platelet transfusion derived from a random donor platelets compared apheresis is single donor, transfusion of patients with recurrent and multi parous women. Incidence FNHTR higher in platelet transfusion compared to packed red cells (PRC)3. 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 mediation 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). 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 erythematosus (SLE). Patient number 9 had a diagnosis of acute lymphoblastic leukemia (ALL), nephrotisisis 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 nulliparous1. 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.

Patients 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 and chronic 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 undergo progressive structural and functional changes that can reduce the function and viability of platelet. Over all transfusion reaction rates higher as long platelet storage1.

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 were less 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 alloimmunization.

Second, factors suspected to affect FNHTR not measured quantitatively. 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.

REFERENCES