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Acetaminophen and Diphenhydramine as Premedication for Platelet Transfusions: A Prospective Randomized Double-Blind Placebo-Controlled Trial

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Non-hemolytic transfusion reactions (NHTR) occur in up to 30% of patients receiving platelet transfusions. Premedication with acetaminophen and diphenhydramine is a common strategy to prevent NHTR, but its efficacy has not been studied. In this prospective trial, transfusions in patients receiving pre-storage leukocyte-reduced single-donor apheresis platelets (SDP) were randomized to premedication with either acetaminophen 650 mg PO and diphenhydramine 25 mg IV, or placebo. Fifty-one patients received 98 transfusions. Thirteen patients had 15 NHTR: 15.4% (8/52) in the treatment arm and 15.2% (7/46) in the placebo arm. Premedication prior to transfusion of pre-storage leukocyte reduced SDP does not significantly lower the incidence of NHTR as compared to placebo. Am. J. Hematol. 70:191–194, 2002. © 2002 Wiley-Liss, Inc.

Key words: transfusion reaction; platelets; premedication

INTRODUCTION

Non-hemolytic transfusion reactions (NHTR) occur in up to 30% of platelet transfusions using non-leukocyte-depleted products [3,10,18]. Recipient leukoagglutinins directed at passenger donor leukocytes are a common cause of NHTR, and leukocyte-reduced platelets can reduce NHTR [1,5,6,15,16]. Cytokines accumulate in the plasma of older platelet units [10,11,18,20], and plasma-poor platelets result in less NHTR than post-storage leukocyte-reduced platelets [9]. In prior studies of NHTR to platelet transfusion, the use of premedication was not controlled [11]. Despite this lack of controlled data, many physicians routinely premedicate patients prior to platelet transfusions. We conducted a prospective randomized double-blinded placebo-controlled trial to evaluate the efficacy of acetaminophen and diphenhydramine as premedication for leukocyte-reduced platelet transfusions.

METHODS

Patients in the Hematology Oncology Ward and Infusion room at the University of California—Davis Medical Center were enrolled from March 1998 to March 2000. In order to have a more homogeneous population, the majority of patients treated had a hematological malignancy and/or were undergoing stem-cell transplant. Eligible patients were ≥18 years of age and able to provide written informed consent and complete the study questionnaire. Exclusion criteria were fever on two occasions in the prior 24 hr, fever at the onset of transfusion, history of hemolytic transfusion reaction, concurrent corticosteroid therapy, or acetaminophen or diphenhydramine administered within the past 6 hr. Patients with history of NHTR were included; however,

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patients with a history of hemolytic transfusion reaction were excluded because hemolysis occurs primarily with cellular components and patients usually request premedication with future transfusions of any type of blood product. The University Human Subjects Review Committee approved the protocol.

Each transfusion in enrolled patients was randomized to premedication or placebo prior to platelet transfusion; thus, the same patient could receive multiple transfusions. Premedication consisted of one unlabeled capsule containing 650 mg of acetaminophen and an infusion of diphenhydramine 25 mg IV, as described in a previous study of NHTR [9]. Placebo consisted of one unlabeled capsule containing 650 mg dextrose and an infusion of 100 mL of normal saline IV. A NHTR was defined as fever (new temperature >38°C, or an increase in temperature >1°C above baseline), subjective chills with or without rigors, urticaria or rash, in the absence of hemolysis. Patients reported symptoms on questionnaires at the beginning of, during, immediately after, and at 2 hr after the transfusion. Nurses recorded vital signs and any symptoms of NHTR every 15 min during the transfusion and at 2 hr after the transfusion. Any NHTR were recorded and then treated appropriately.

Patient questionnaires, nursing data, and blood bank information were correlated for each transfusion. All patients and healthcare workers were blinded, except the investigational pharmacist. Identity of each premedication was revealed only after study closure.

All platelets were irradiated, pre-storage leukocyte-reduced, single-donor apheresis units (SDP). Leukocyte reduction to a level of $<5 \times 10^6$ leukocytes was performed at the time collection at the Sacramento Medical Foundation Blood Center in Sacramento, California.

Statistical Analysis

Premedication was randomized by transfusion, not by patient. Comparisons between study arms used nonparametric and resampling techniques to obtain standard errors that accounted for within-person correlation of transfusion outcomes. The difference in rates of NHTR between the two arms was estimated by the observed difference in rates per transfusion, and the standard error of the difference was estimated by a permutation procedure, under the null hypothesis that relabeling the treatment arms for a given patient would have no effect on the outcome. The permutation distribution of the difference in rates of NHTR between the two treatments under the null hypothesis of no effect was estimated by simulation, with 100 replications. In each replication, each patient was randomly assigned to have the pretreatment and no treatment labels switched or left untouched, with probability one-half each. The difference was calculated for each permutation and the standard error from the permutation distribution calculated. The resulting permutation distribution was approximately normal, so the z score for the observed difference was calculated and a P value obtained from the standard normal distribution. A 95% confidence interval for the true difference in NHTR rates was calculated by bootstrap resampling [4]. For each bootstrap replicate, a new sample of patients was generated by sampling with replacement from the original group of patients, and the difference in rates of NHTR was calculated for the new sample of patients. Two hundred bootstrap replicates were generated, and the standard deviation of the rate differences used as an estimate of the standard error to calculate a confidence interval. All calculations were carried out in S-Plus on a Sun workstation.

TABLE I. Patient Characteristics

	Received only premedication	Received only placebo	Received both premed and placebo (separate transfusions)
Total	21	16	14
No. of women	12	7	7
No. of men	9	9	7
History of NHTR	4	5	6
Primary diagnosis			
Stem-cell transplant	7	6	7
AML	8	7	6
ALL	2	1	1
CML	0	1	3
Lymphoma	5	0	2
Solid tumors	4	5	1
Myeloma	1	2	0
Waldenström's macroglobuminemia	0	0	1
Amyloidosis	1	0	0

RESULTS

Approximately 75% of patients asked to participate were enrolled. Patients who declined to participate usually cited a history of prior reaction. Many patients were ineligible due to exposure to steroids or nonsteroidal anti-inflammatory drugs. Others were excluded because they received premedication for transfusions of packed red blood cells prior to a platelet transfusion. Fifty-five patients were enrolled and 122 transfusions given. Of these, 51 patients and 98 transfusions were assessable (range 1–10 transfusion per patient). Reasons that transfusions were not assessable included premedication distributed or given, but no transfusion actually given ($n = 15$); no questionnaire or vital signs recorded ($n = 8$); and PRBC given instead of platelets ($n = 1$). There were no significant differences between each group of patients (Table I). Thirty-five patients received 52 transfusions with premedication, and 30 patients received 46 transfu-

TABLE II. Transfusion Reactions

	Premedication	Placebo
Total no. of transfusions in all patients	52	46
NHTR	8	7
Fever only	2	0
Fever with chills	0	1
Chills only	5	3
Chills with rigors	1	0
Hives	0	3
Transfusions in patients with history of NHTR	14	13
NHTR	4	3
Transfusions in patients with no history of NHTR	38	33
NHR	4	4

sions with placebo. Fourteen patients received transfusions in both arms of the study. Twenty-nine patients had leukemia, and 20 patients were undergoing stem-cell transplant. Fifteen patients reported a history of NHTR. The average age of the platelets was 3.3 days in the placebo arm and 3.2 days in the treatment arm.

Among the 98 transfusions, 15 NHTR were recorded in 13 patients (one patient reacted three times) (see Table II). In the treatment arm, 8 of 52 transfusions resulted in NHTR (15.4%), and in the placebo arm, 7 of 46 transfusions resulted in NHTR (15.2%). The difference in NHTR rates was 0.2% (95% CI (–)8.5%–9.4%, P value = 0.94). Of the transfusions given to patients with a history of NHTR and who were given premedication, four of 14 were complicated by NHTR. Thirteen transfusions were given to patients with a history of NHTR after placebo; three of these 13 transfusions were complicated by reactions. NHTR occurred more often in patients with a history of NHTR than in patients with no history of NHTR: 7 of 27 (25.9%) and 8 of 71 (11.3%) transfusions, respectively (permutation two-sided P = 0.06). Patients who experienced NHTR had an average platelet increment of 23,000/μL while patients with no reactions had an increase of 22,000/μL. No patient was clinically refractory, but serological alloimmunization was not directly determined.

DISCUSSION

The overall incidence of NHTR in our group of patients was approximately 15%. This percentage is within the previously reported range of 5–30% [10]. This variation may be due, in part, to the characteristics of the platelet product. In our study, all platelets transfused were pre-storage leukocyte-reduced and SDP, both of which have been shown to decrease the rate of NHTR [3,5]. The average age of platelets in our study was approximately 3 days, which is comparable with the age of platelets in previous studies [9,13,18]. Recent data show that platelets ≤3 days old may be associated with a lower incidence of NHTR [13,18]. We included subjective chills without rigors as a distinct type of NHTR in order to best reflect situations encountered in clinical practice. Previous studies have also included chills as a distinct reaction [5,9,11,17], while others have required chills to occur with fever [13–15].

Prior studies of NHTR to platelet transfusion suggested that premedication was not effective. In a prospective trial that did not control for use of premedication, 61% of the patients received premedication, but 82% of the NHTR occurred in patients given premedication [11]. Morrow et al. studied the incidence of platelets contaminated with bacteria, a rare cause of NHTR. After receiving acetaminophen, five patients had NHTR to contaminated platelets and eight patients had NHTR to sterile platelets [17].

We found that patients with a history of NHTR had a trend toward a higher incidence of subsequent NHTR than did patients without a history of reactions. Although this subgroup was small, the patients had similar rates of NHTR in each arm of the study, suggesting a lack of any treatment effect in this higher risk group. Notably, two patients who were transfused both with and without premedication each had a NHTR after premedication but did not have a reaction after placebo.

The pathogenesis of NHTR may limit the efficacy of premedication. While our study was not designed to measure cytokine levels in stored platelet units nor in recipients, previous studies have described higher levels of IL-6, IL-1β, and TNF-α in platelet units >3 days old, and a higher resulting rate of NHTR [1,5,8,14,19]. These cytokines induce the production of prostaglandin E_2 (PGE_2), which acts on the hypothalamus to increase body temperature [12]. Prophylactic acetaminophen should inhibit the synthesis of PGE_2 and block fever. However, in the setting of NHTR, the amount of cytokines generated may overcome the inhibitory effect of acetaminophen.

The urticaria often seen in NHTR is mediated by a variety of vasoactive substances, including histamine. Histamine acts on several tissues, but the most prominent effects seen in NHTR are small vessel vasodilation, increased capillary permeability, and stimulation of nerve endings resulting in pruritus [7]. Theoretically, diphenhydramine should block all H-1 receptors and prevent most of the clinical effects of histamine. However, some of the vasodilation is mediated by H-2 receptors, which are not bound by diphenhydramine [2]. Kluter et al. recently reported that the chemokine RANTES accumulated in platelet concentrates and that this might also mediate allergic reactions to platelet transfusions [14]. Finally, there is the possibility of β error on the effect of diphenhydramine on hives (7% in the premedication arm versus 0% in the treatment arm). However, nearly 500

subjects in each arm would be required to exclude a 50% decrease in incidence.

There are some limitations to the applicability of our results. We chose to enroll predominantly patients with hematological malignancies and patients undergoing stem-cell transplants in order to have a more uniform population; premedication may be more effective in other populations. At our medical center, we exclusively use pre-storage leukocyte-reduced single-donor apheresis platelets in these patients. It is possible that there might be a benefit to premedication when giving platelets that have not been leukocyte reduced, or when giving pooled random-donor platelets. The dose of diphenhydramine chosen in this study, although used by others [9], might have been inadequate. Despite these limitations, we believe that our results are applicable to a large population of patients receiving platelet transfusions.

In this study, acetaminophen and diphenhydramine given prior to platelet transfusion did not significantly lower the incidence of NHTR as compared to placebo. Premedication does not appear to be necessary prior to transfusion of single-donor pre-storage leukocyte-reduced platelets.

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