Original Article

Comparative Study of Prophylactic and Non-prophylactic Use of Apheretic Platelet among Hematological Cancer Patients

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Abstract:

Background: *Apheretic platelet transfusion reduce mortality and morbidity by reducing the risk of bleeding after chemotherapy. The effectiveness of platelet transfusions to prevent bleeding in patients with hematological cancers remains unclear. This trial assessed whether a policy of not giving prophylactic apheretic platelet transfusions was as effective and safe as a policy of providing prophylaxis.* ***Method:*** *We conducted this randomized controlled trial at Bangabandhu Sheikh Mujib Medical University. Patients were randomly assigned to receive, or not to receive, prophylactic platelet transfusions when morning platelet counts were less than 10×109per liter. Eligible patients were persons 16 years of age or older who were receiving chemotherapy and who had or were expected to have thrombocytopenia. The primary end point was bleeding of World Health Organization (WHO) grade 2, 3, or 4 up to 30 days after randomization.* ***Result:*** *A total of 600 patients (301 in the no-prophylaxis group and 299 in the prophylaxis group) underwent randomization between 2013 to 2016. Bleeding of WHO grade2, 3, or 4 occurred in 151 of 300 patients (50%) in the no-prophylaxis group, as compared with 128 of 298 (43%) in the prophylaxis group. Patients in the no-prophylaxis group had more days with bleeding and a shorter time to the first bleeding episode than did patients in the prophylaxis group. Platelet use was markedly reduced in the no-prophylaxis group.* ***Conclusion:*** *The results of our study support the need for the continued use of prophylaxis with platelet transfusion and show the benefit of such prophylaxis for reducing bleeding, as compared with no prophylaxis.*

Key words: Prophylactic, Apheretic platelet, Hematological cancer

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Introduction:

In patients with hematologic cancers, severe thrombocytopenia frequently develops as a consequence of the disease or its treatment. Most platelet transfusions are administered as prophylaxis, to increase low platelet counts and reduce the risk of bleeding [1]. However, the degree to which prophylactic platelet transfusions benefit patients with severe thrombocytopenia has been unclear [2-4]. A recent trial suggested that a policy of giving platelet transfusions only as treatment for bleeding might become a new standard of care in selected patients, although the primary end point was a reduction in the number platelet transfusions, not a clinical outcome such as bleeding [5]. We conducted a randomized, controlled trial to assess whether a policy of no prophylactic platelet transfusions was non-inferior to prophylactic platelet transfusions with regard to the frequency of hemorrhage, on the basis of a platelet-count threshold of less than 10×10^9 per liter, which represents the current standard of practice for patients with hematologic cancers [6-9].

Materials and Methods:

Study Design and Objective: We conducted a randomized, parallel-group, open-label, non-inferiority trial at Bangabandhu Sheikh Mujib Medical University. The primary objective was to determine whether a policy of not giving platelet transfusions as prophylaxis against clinical bleeding was as safe and effective as the provision of prophylaxis. Clinical bleeding was defined as bleeding of World Health Organization (WHO) grade 2 or higher, up to 30 days after randomization. The WHO grading system is the most commonly used assessment of the severity of bleeding events in platelet-transfusion trials [10]. In the WHO system, bleeding episodes are categorized as grade 1 (mild), grade 2 (moderate; red-cell transfusion not needed immediately), grade 3 (severe; requiring red-cell transfusion within 24 hours), or grade 4 (debilitating or life-threatening) [10-13].

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Eligibility Criteria: Eligible patients were persons 16 years of age or older who were undergoing, or about to undergo, chemotherapy or stem-cell transplantation to treat a hematologic cancer and who had or were expected to have thrombocytopenia (platelet count, $<50\times10^9$ per liter) for at least 5 days. Exclusion criteria were a previous bleeding episode of WHO grade 3 or 4, a bleeding episode of WHO grade 2 during the current admission, an inherited hemostatic or thrombotic disorder, a requirement for therapeutic doses of anticoagulant agents, a diagnosis of acute promyelocytic leukemia, known HLA antibodies, or prior randomization in this trial.

Intervention: Patients were randomly assigned to receive either prophylactic platelet transfusions, or no prophylaxis, if the platelet count was less than 10×10^9 per liter. In the prophylaxis group, typically, a single adult dose was given on the same day that the platelet count was recorded to be less than 10×10^9 per liter [6]. The assigned treatment policy applied for 30 days after randomization, regardless of whether the patient was an inpatient or outpatient. In both trial groups, platelet transfusions were given therapeutically for bleeding, given before invasive procedures, or given at the clinician's discretion (the rationale was recorded). Therapeutic platelet transfusions for bleeding episodes of WHO grade 2 were given according to standard practice, followed by prophylactic platelet transfusions per protocol, if indicated. Patients who had bleeding of WHO grade 3 or 4 during the study received platelet transfusions at the clinician's discretion; these patients no longer received treatment according to the trial protocol, but assessment continued for 30 days after randomization.

The type of platelet component was not specified. All platelet components were leuko-reduced, platelets were collected by means of apheresis in approximately 80% of cases, and common hospital practice was to transfuse platelets that were ABO and RhD identical. For applicable national standards for platelet components. The threshold for red-cell transfusion (in the absence of blood loss due to bleeding) was a hemoglobin level of less than 90 g per liter.

Randomization: Patients were randomly assigned to the two study groups in a 1:1 ratio by means of an independent, centralized, computerized randomization service. The first 10 patients were assigned with the use of simple randomization. The remaining patients were assigned with the use of minimization. Minimization factors were study center, diagnosis, and treatment plan. Patients were assigned to the preferred treatment with a probability of 0.75. Owing to the nature of the intervention, patients and clinicians were aware of study-group assignments.

Data Collection: Data collection continued for 30 days after randomization. Daily bleeding assessment forms were completed by trained staff members each day that the patient was in the hospital. Patients who were discharged home during the follow-up period completed bleeding diaries; if patients reported bleeding, clinical bleeding-assessment forms were completed at the next hospital visit. To ensure the accuracy and uniformity of bleeding assessments, repeated training sessions, scenario training, and guide notes (laminated information sheets) were provided for study staff, and on-site monitoring was performed, including duplicate bleeding assessments. All written descriptions of bleeding episodes were examined by two assessors who were unaware of the treatment assignments.

Outcomes: The primary outcome was the percentage of patients who had bleeding events of WHO grade 2, 3, or 4 up to 30 days after randomization. Before study commencement, piloting of the bleeding assessments indicated that certain forms of grade 1 bleeding were considered clinically significant in patients with severe thrombocytopenia and platelet counts of less than 10×10^9 per liter and acted as triggers for therapeutic platelet transfusions [14,15]; these events included spreading or generalized petechiae and nosebleeds lasting more than 30 minutes. The grade of the bleeding event was assigned centrally with the use of a computer algorithm, which was validated by means of comparison with a manual assignment system (98% agreement for bleeding events of WHO grade 0 or 1 vs. ≥2 for 1472 bleeding assessments from 148 patients). Secondary outcomes included the number of days with bleeding events of WHO grade 2, 3, or 4; time from randomization to first bleeding event of WHO grade 2, 3, or 4; bleeding event of WHO grade 3 or 4; numbers of platelet and red-cell transfusions; number of days with a platelet count of less than 20×10^9 per liter; time until recovery from thrombocytopenia (platelet count, $>50\times10^9$ per liter for 3 days without platelet-transfusion support); and time in the hospital. Data on adverse events related to transfusion were collected from hospitals on the basis of the standard.

Results:

Study Population: 600 underwent randomization (301 patients were assigned to non-prophylaxis and 299 to prophylaxis) between August 2013 and August 2016. Baseline characteristics were well matched between the two study groups (Table I).

Bleeding Assessments: Bleeding assessments were completed on 93% of study days (8405 of 9030 days) for patients in the non-prophylaxis group and on 97% of study days (8733 of 8970) in the prophylaxis group. The majority of patients in both

groups had bleeding information completed on each study day (Table II).

Table-I: Baseline Characteristics of the Study Patients, According to Study Group

Characteristic	Non-Prophylaxis (N= 301)	Prophylaxis (N = 299)
Age (years) [Mean±SE]	55.7±10.4	55.3±11.2
Diagnosis [no. (%)]		
Acute myeloid leukemia	55 (18)	55 (18)
Acute lymphoid leukemia	5 (2)	1 (<1)
Chronic myeloid leukemia	1 (<1)	2 (1)
Lymphoma	102 (34)	104 (35)
Myeloma	125 (42)	124 (41)
Other	13 (4)	13 (4)
Treatment plan [no. (%)]		
Chemotherapy		
Induction	35 (12)	37 (12)
Consolidation	15 (5)	11 (4)
Relapse [no. (%)]	92 (31)	110 (37)
Documented prior fungal infection [no. (%)]	5 (2)	8 (3)
Any coexisting disorder or organ failure [no. (%)]	25 (8)	19 (6)
Platelet count (×10−9/liter) [Mean±SE]	43.6±25.6	43.5±31.3

Table-II: Bleeding outcomes of study population

Outcome	Non-Prophylaxis	Prophylaxis
Acute myeloid leukemia	27	24
Acute lymphoid leukemia	10	7
Chronic myeloid leukemia	6	4
Lymphoma	20	18
Myeloma	10	8
Other	20	17

Discussion:

A general finding across all trials of prophylactic platelet transfusions, including the two largest studies that compared different thresholds for prophylaxis or doses, has been a lack of significant difference between trial groups in hemostatic outcomes (i.e., no increased bleeding with a restrictive policy of prophylaxis, regardless of whether the comparison was with a lower threshold for platelet count or a lower platelet dose for prophylaxis) [7,15]. This has raised questions about the benefit of prophylaxis. In our study, more bleeding events occurred in the no-prophylaxis group than in the prophylaxis group, with a significant increase in the number of days with bleeding events. The results of our study support the need for the continued use of prophylaxis with platelet transfusion and show the benefit of such prophylaxis for reducing bleeding, as compared with no prophylaxis.

However, even though patients who received prophylactic platelet transfusions had fewer bleeding events overall, Despite this finding, the authors suggested that a strategy of "therapeutic only" transfusion might become the standard of care at selected centers. In our trial, the treatment effect was larger in the subgroup of patients with hematologic cancers who were treated with chemotherapy. Prophylactic platelet transfusions were associated with a marked reduction in the proportion of patients in whom bleeding events developed.

In the study by Wandt et al., higher rates of bleeding events were also reported among patients with acute myeloid leukemia who received no prophylaxis, as compared with those who received prophylaxis, although the study protocol specified cranial imaging only in cases of patient-reported headaches in the no-prophylaxis group [5]. On the basis of these findings, the use of prophylactic platelet transfusions in patients with hematologic cancers treated with chemotherapy.

The strengths of our trial include good protocol adherence and little loss to follow-up. There was a large decrease in platelet transfusions among patients in the no-prophylaxis group, as compared with those in the prophylaxis group, and evidence of a clear difference in mean platelet counts between the two groups. Rates of recorded bleeding can vary considerably among studies, and a potential limitation of our study was heterogeneity in the assessment of bleeding at different participating centers [10]. To address this issue, multiple measures were taken to standardize the documentation and recording of bleeding in our trial, including training and monitoring of the assessors. Several issues are pertinent to trials of platelet transfusions, specifically those designed as non-inferiority studies. Defining acceptable limits for increased rates of bleeding is challenging because little research has been done to understand how patients' and clinicians' perceptions of bleeding may vary. Bleeding events are heterogeneous and may be considered to have varying degrees of clinical significance. However, such events (including skin bleeding) account for a large proportion of the primary-outcome events in this and other trials.

The results of these two analyses differed: the intention to treat analysis showed that the no-prophylaxis policy was statistically inferior, whereas the per-protocol analysis showed that it was non-inferior. The reason may be related to the proportion of patients with bleeding who were excluded from the no-prophylaxis group, as compared with the prophylaxis group, leading to a potentially biased per-protocol analysis in favor of the no-prophylaxis group. One of the challenges of conducting transfusion trials is to select a primary outcome with clinical relevance instead of simply using a change in the number of transfusions as the primary outcome [16]. This trial shows that transfusion studies with primary clinical outcomes can address fundam ental issues of effectiveness [12]. Our results indicate that prophylactic platelet transfusions reduced rates of bleeding events in patients with hematologic cancers. The proportion of patients who had bleeding events was reduced by 15% overall in the group that received prophylactic platelet transfusions.

Conclusion:

The results of our study support the need for the continued use of prophylaxis with platelet transfusion and showed the benefit of such prophylaxis for reducing bleeding, as compared with no prophylaxis.

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