A Randomized trial of prophylactic platelet transfusion after cytotoxic chemotherapy in adult acute leukaemia.

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Abstract

Treatment of acute leukaemia with drugs is associated with marked myelosuppression resulting in severe thrombocytopenia which may or may not be accompanied by clinically evident bleeding episodes. This prospective study was conducted to see the effectiveness of chemotherapy by observing evidence of bleeding, clinical evidence of refractoriness and post-transfusion platelet count increment. A total fifty patients with acute leukaemia between 15 to 70 years of age were enrolled during the period of January 2003 to March 2005. History and clinical data were taken accordingly with proper written consent. Diagnostic tests were done both in BSMMU and BIRDEM, Dhaka. Bone marrow aspiration biopsy was done in BSMMU. All patients diagnosed as acute leukaemia under written consent received chemotherapy ; platelet transfusion was given during the period of nadir to observe post transfusion satisfactory count increment ; here 20,000/μL was used as a 'transfusion trigger'. ABO and Rh identical cross-matched platelets for transfusion were prepared either by refrigerated centrifuge method from pool platelet cencentrates or by platelet pheresis method. This study showed 70% patients had AML and 30% had ALL. Adult with age group of 31 to 50 years were mainly sufferer of acute leukaemia. Male and female ratio in this study was 2:1. Transfusion reaction occurred among 9 (18%) patients.10% patients had evidence of bleeding, 6% had major bleeding and 6% had minor bleeding. Post transfusion increment was satisfactory in 45 patients (90%) where as 5 patients (10%) received pooled platelet concentrate showed clinical evidence of refractoriness and also had less satisfactory corrected count increment .From our study we can suggest that platelet transfusion helps in chemotherapy induced thrombocytopenia and platelet pheresis is better option to rise platelet count increment.

Key words: *Acute leukaemia, chemotherapy, prophylactic platelet transfusion , platelet count increment.*

Introduction

The Leukaemias are a group of disorders characterized by the accumulation of malignant white cells in the bone marrow and blood[1]. Acute leaukaemia are usually aggressive disease[1].It is defined pathologically as blast cell leukaemia or malignancy of immature haemopoietic cells[2]. Treatment of acute leukaemia with drugs is associated with marked myelosuppression resulting in severe thrombocytopenia which may or may not be accompanied by clinically evident bleeding episodes[3-5]. As the major causes of death in adults with leukaemia are failure to achieve complete remission or relapse after achieving complete remission, so large numbers of red cell and platelet transfusions are given to the patients during the period of recovery from aplasia, which is caused by cytotoxic chemotherapy given during remission induction[3-5].Platelet transfusions are given to patients undergoing myelotoxic chemotherapy for acute leukaemia over a two to three week period, during the period of thrombocytopenia, when count is < 20 x 10^9 /L or <50 x 10^9 / L with sign of bleeding [6-10]. Platelet concentrate may be obtained from whole blood collected into a multiple plastic bag set. Platelets for transfusion can be prepared either by separation of units of platelet concentrates (PCs) from whole blood, or prepared by apheresis[6-10].The use of platelets to prevent hemorrhage is called the prophylactic approach. The choice to transfuse platelets prophylactically stems from several studies showing a decrease in the incidence of hemorrhagic deaths in leukaemic patients following this policy[3, 6-10]. The platelet count above which platelet transfusion is not necessary is termed the platelet transfusion trigger. 20 X 10^9 /L is commonly used as a transfusion trigger[6-10]. Transfusion at higher levels may be necessary in patients with hemorrhage, fever, infection or a large spleen, called detrimental factors[3, 6-12]. Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in thrombocytopenic patients with bone marrow

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failure. Although considerable advances have been made in platelet transfusion therapy in the last 30 years, some areas continue to provoke debate on the use of prophylactic platelet transfusions for the prevention of thrombocytopenic bleeding. So there are many trials in various countries like United Kingdom, USA, Italy, Spain, Netherlands, Pakistan to determine the optimal use of platelet transfusion for the prevention of haemorrhage (prophylactic platelet transfusion) in patients with haematological malignancies undergoing chemotherapy[3,5, 8,9,13-20]. These study showed that, platelet transfusion is considered effective when it is associated with a CCI ≥7.5 X 10^9 / L at 1 hour or CCI ≥ 4.5 X 10^9/L at around 24 hours[6,10,19, 23].

In our study the efficacy of platelet transfusion, post transfusion increment, refractoriness, assessment of how frequent platelet transfusion needs to be given and complication arise from transfused platelets, in patient having platelet transfusion during the period of nadir (induced pancytopenia due to chemotherapy) after 1st induction chemotherapy in acute leukaemia was observed. Thus aim of this study was to utilize platelet concentrate in proper way and in actual need to decrease bleeding, platelet refractoriness, complication associate with platelet transfusion and to observe corrected platelet count increment in adult acute leukaemia after chemotherapy, as well as, effectiveness of chemotherapy was observed following evidence of bleeding, clinical evidence of refractoriness and post-transfusion platelet count increment. Best method and proper use of platelet transfusion for the prevention of bleeding (prophylactic platelet transfusion) among patients with haematological malignancies receiving intensive chemotherapy was also observed.

Materials and Methods

This prospective study was done on admitted patients in the Department of haematology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2003 to March 2005. This study included adolescents from 15 to 70 years age including both sex, but not younger children and infants. Using a performed data sheet with written consent, data collection was done including case history, previous transfusion history, clinical examination and diagnostic tests. The clinical data for blood component use and morbidity were also collected. Clinical examination was done to find out splenomegly, fever, sepsis, DIC, and active bleeding. The diagnosis of acute leukemia was based upon laboratory results from BSMMU haematology laboratory. To diagnose acute leukaemia peripheral blood film with Leishman's stain was seen under microscope in BSMMU and complete blood count (CBC) was determined by ABBOTT CELLDYNE 3500, USA in BIRDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metaboloc Disorders). In BSMMU (Bangabandhu Seikh Mujib Medical University), bone marrow aspiration biopsy was done by Salah marrow puncture needle, both direct and squashed slides were stained by Leishman's stain and morphological classification including FAB (French-American and British) classification was done. Cytochemical stain (Sigma-Aldrich, UK) for MPO (Myelo peroxidase) and Sudan black -B stains were done to confirm Acute Myeloid Leukaemia(AML) and Periodic acid Schiff (PAS) stain was done as supportive to Acute Lymphoblastic Leukaemia(ALL). Randomly selected fifty adult patients, who were diagnosed having acute leukemia, were recruited during this period to receive full dose induction chemotherapy. Patients were to be excluded from the analysis if they did not have acute leukaemia.

Chemotherapy which is given to the patients

For 35 patients with acute myeloid leukemia, treatment invariably involved initial remission induction with cytosine arabinoside , anthracycline (doxorubicine or mitroxantrone) and thioguanine or etoposide. On the other hand, 15 patients with acute lymphoid leukemia received vincristine, prednisone, L-asparaginase and doxorubicine. Patients with high risk features or those who failed to achieve remission and received additional courses of induction therapy were also included.

Transfusion of Platelet concentrate

This Randomized controlled trials involving transfusions of ABO identical platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given prophylactically to prevent bleeding in patients with haematological malignancies.

Transfusion of platelet concentrate during the period of "nadir" (induced pancytopenia due to chemotherapy), employing 46 patients received whole blood derived from random platelet concentrates by refrigerated centrifuge method (Kubota, Japan) which is ABO identical and 4 patients received ABO cross matched pheresis platelet yield by cell separator (Amicus cell

separator, Baxter, USA). As chemotherapy treatment of acute myeloid leukaemia with drugs is associated with marked myelosuppression, resulting in severe thrombocytopenia, which may or may not be accompanied by clinically evident bleeding episodes. This observation led us to propose platelet therapy in acute leukaemia, when count is <20,000 or has bleeding episode. So, in our study, prophylactic transfusions were consistently given at morning platelet counts of <20 × 10^9/l and usually with bleeding patients where count is <50 × 10^9/l or 50,000 with major bleeding. Before prophylactic platelet transfusion and also when needed, platelet count was done by automated full blood counter (ABBOTT CELLDYNE 3500,USA) and compared with manual platelet count. It is to be mentioned that, although modern automated cell counters are quite accurate at low platelet counts, there can be modest variations in count because of limitations of the counting technology.

Calculation of corrected count increment

On-line calculation is done by "platelet corrected count increment calculator" (http://hccapps.musc.-edu/hemonc/cci.htm.)[20-23]. Formula of corrected platelet count increment was CCI= "the rise in platelet count observed (absolute increment) multiplied by the surface area (in m^2) divided by (the number of platelets transfused x 10^{11}). Thus if transfusion of 4x10^{11} platelets produced an increment of 40,000/μL in a 2 m^2 recipient the CCI= 40,000x 2/4 = 20,000[20, 22]. According to Mollison[20] (1994) that, the transfusion to adult weighing 70 kg of one unit of fresh platelets (containing approximately 0.7 x 10^{11} platelets) produces an immediate post transfusion increment of approximately 11 x 10^9/l; i.e. a 70 kg adult having a surface area of 1.7 m^2, the corrected increment would be 11x 10^9 / l x 1.7 / 0.7 = approximately 27 x 10^9 / l. So the expected increment for an average size adult (i.e. a 70 kg adult), is a rise in the count of 5,000 to 10,000 /µl for each unit in the pool platelet transfusion; where as, one unit of aphaeresis platelet should increase the count 30,000 to 60,000/µl[20].

Following procedure done to determine poor response to platelet transfusion:

It has been observed if the patient is really having a poor response. Start by seeing if one hour post-transfusion platelet counts have been obtained. A one hour post-transfusion platelet count measures recovery of platelets transfused and gives different information than a 24 hour post-transfusion platelet count, which measures survival of those platelets. From this 1 hour information, it has been checked that, the platelet count has gone up a lot, a little, or not at all. Some rise in platelet count at 1 hour, but back to baseline at 24 hours, suggests non-immune causes of poor platelet response. No appreciable rise in count at either 1 or 24 hours, suggests alloantibody destruction[20-23]. We consider this in our study. Transfusion reactions were also reported and evaluated. A new fever or new rigors occurring during or shortly after a transfusion was considered a reaction, whereas a fever or rigor that occurred shortly before the transfusion started was considered unrelated.

Results

Among total 50 patients majority 12(24%) patients were in age group of 31-40 years. From January 2003 to March 2005, a total of 50 patients were registered on the study. All patients were given chemotherapy and each patient received prophylactic platelet concentrate during period of nadir. Out of total 50 patients between 15 to 70 years of age, 35 (70%) cases were diagnosed as AML and 15 (30%) as ALL.

The incidence of AML was 40% among 31-50 years of age group and highest incidence of ALL is 30% among the same age group. Out of 50 cases of leukaemia, 34 (68%) patients were male and 16 (32%) patients were female (Table-I). So the male and female ratio is 2: 1.

Among AML patients, most common sub types were M2 (28%), M1 (22%), and M4 (18%). Beside this M3 is 12 % and M5 is also 12 %(Figure-1). Majority patients of ALL were, ALL-L2 variety (20 %) shown in Figure-2.

Among these patients, highest blood group was O (42%) and lowest was AB (10%), B is 28% and A is 20 %. Rh D blood group shows 94% positive and 6% RhD negative result. 20,000/µL was used in this study as a "transfusion trigger" for platelet transfusions. The total initial platelet counts before chemotherapy varied from < 30 X 10^9/ L to >150 X 10^9/ L. Most of the AML patients had platelet counts ≥ 50 X 10^9/ L (60%).Where most of the patients with ALL had platelet count < 50 x 10^9 / L in this study. Among total 50 patients, after chemotherapy in nadir phase, pre-transfusion platelet count was <20,000/ µl in 43 patients (86%) and count was 50,000/ µl or had bleeding in 7 patients (14%) (Table-II). In our study, post-transfusion platelet count measures satisfactory recovery of platelets by platelet-pheresis (cell separator) both after one hour and after 24 hours (Table-III).

Among 43 patients(86%) of total study group , received platelet concentrate prepared from pool

donor by refrigerated centrifuge method, as four small bags for each unit, their initial count was <20,000/µl, post transfusion platelet count rose to 150 x 10^9 and was satisfactory among 34 patients (68%), after one and 24 hours of platelet concentrate transfusion. Whereas, in 9 patients (18%) with initial count <50,000 or 50,000 /µl with bleeding, 5 (10%) patients showed no satisfactory result. Among these 5 (10%) of total 50 patients , persistent sign of bleeding after transfusion of platelet concentrate, regarded as clinical evidence of platelet refractoriness. In these patients, count increment was less than 5000 (not satisfactory) after per unit of platelet transfusion (Table- IV).

Thus in this study post transfusion increment was satisfactory in 45 patients (90%), who received both apheresis and pool donors platelet. Where as, 5 patients (10%) showed clinical evidence of refractoriness and also had less satisfactory corrected count increment. Among all, these 5 patients (10%) cannot achieve satisfactory rise of platelet count (range is 5000-10,000 / µl.), i.e. their CCI 7.5 x 10^9 / L in first one hour and CCI ≥4.5 x 10^9 / L after 24 hours; four patients (8%) still had less satisfactory count (3000/ µl) and one patient (2%) had about near (4000/ µl) the CCI .

In our study clinically evident bleeding[25] was uncommon, occurred in only 5 out of 50 patients (10%) and major bleeding[25] occurred in only 3 of 50 patients (6%). Minor bleeding[25] also occurred in 3 patients (6%). Only 5 patients among 50 in this study group showed signs with clinical evidence of refractoriness(10%). In this study, there were nine transfusion reactions out of fifty i.e. 18% showed transfusion reactions reported due to intercurrent fever including two reported allergic reactions (rash and/or urticaria). There were one transfusion reaction with intercurrent fever and five with rigor. No history of reactions among 41 patients (82%) was recorded.

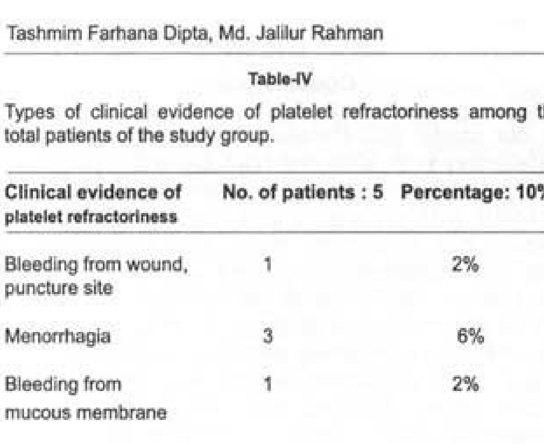

Figure-1: Morphologic (FAB) classification of AML patients

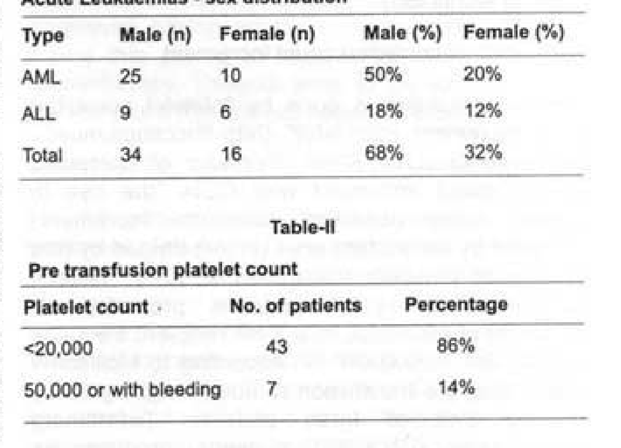

Figure-2: Morphological (FAB) classification of ALL

Table-I

Acute Leukaemias - sex distribution

Type	Male (n)	Female (n)	Male (%)	Female (%)
AML	25	10	50%	20%
ALL	9	6	18%	12%
Total	34	16	68%	32%

Table-II

Pre transfusion platelet count

Platelet count	No. of patients	Percentage
<20,000	43	86%
50,000 or with bleeding	7	14%

Table-III

Post transfusion platelet count: one hour and 24 hours after transfusion: Platelet concentrate prepared by platelet pheresis

No. of patients	4 out of 50 (i.e. 8%)	Platelet Corrected count increment
Initial count	<20,000	
After one hour	No. 1 Pt. = 85,000	satisfactory
of transfusion	No. 2 Pt. = 67, 000	
	No. 3 Pt .= 60, 000	
	No. 4 Pt. = 58,000.	
After 24 hour of transfusion	> 100,000	Satisfactory

Table-IV

Types of clinical evidence of platelet refractoriness among the total patients of the study group.

Clinical evidence of platelet refractoriness	No. of patients : 5	Percentage: 10%
Bleeding from wound, puncture site	1	2%
Menorrhagia	3	6%
Bleeding from mucous membrane	1	2%
Purpura or Ecchymosis	1	2%
No significant increase	5	10%

Discussion

From January 2003 to March 2005, a total number of fifty patients were registered on this random prospective study. All patients were given chemotherapy and received platelet concentrate during period of nadir. In this study 20,000/µL was used as a "transfusion trigger" for platelet transfusions, which correlates with other studies[3,8,9,13-20, 24-31] and similar trigger was also used in studies done in USA[13-16], Italy[17] Spain[18], Pakistan[3], UK[27,28] and Netherlands[30]. Calculation in our study was done by "platelet corrected count increment calculator" (http://hccapps.musc.edu/hemonc/cci.htm.)[23]. Formula of corrected platelet count increment was "the rise in platelet count observed, multiplied by the surface area (in m^2) ,divided by (the number of platelets transfused x 10^{11}) which correlates with Mollison[20] and other studies[3,13-20, 24, 27, 28, 31]. As treatment of acute myeloid leukaemia with chemotherapeutics is associated with marked myelosuppression, resulting in severe thrombocytopenia which may or may not be accompanied by clinically evident bleeding episodes, this observation led us to propose platelet therapy in acute leukaemia , when count is <20,000 or has bleeding episode. In our study evidence of bleeding[25] was 10%, major bleeding[25] was 6% and minor bleeding[25] was 6%, which also corresponds with the studies done in USA (6% and 17-18%)[13, 26], Pakistan (28.57%)[3] and an Italian study (20-21.5%)[17]. Our study also correlates with Blumberg[30] (2004), which showed that clinically evidence of bleeding was uncommon, 8 of 43 patients (19%) and major bleeding occurred in only 2 of 43 patients (5%)[30]. In our study platelet count was obtained within 24 hours of transfusion.

For detection of refractoriness for platelet transfusion[3, 6-12, 20, 31] it was recommended that, a platelet count should be performed within one hour after transfusion and a single unit of random platelets (i.e. derived from one unit of whole blood by refrigerated centrifuge method) should increase the platelet count 5,000 to 10,000/µL in a 70 kg recipient or by one unit of apheresis platelets should increase the platelet count 30,000 to 60,000/ µL[20] which was observed in our study and showed similar result with other studies done in USA[13, 14], Italy[17] and Spain[18]. In this study post transfusion increment was satisfactory in 45 patients (90%), who were recipient of either pheresis platelet or pooled platelet concentrate; where as, 5 patients (10%) showed clinical evidence of refractoriness and also had less satisfactory corrected count increment. Among all these 5 patients (10%) satisfactory rise of platelet count cannot achieved and they received pooled platelet concentrate by refrigerated centrifuge method; which showed correlation with other studies [5,6, 13, 14,17, 18, 20,31] (normal range is 5000-10,000 / µl., i.e. ≥ 7.5 x 10^9 / L in first one hour[5/7] and after 24 hours CCI ≥ 4.5 x 10^9 / L, accepted as satisfactory rise [6, 20, 31]).

Our study thus supports Mollison[20] and other studies[3, 6, 13-20, 24, 27, 28, 31] that, a corrected count increment (CCI) of > 7,500 / µl indicates an acceptable response.

If the CCI is <7,500 / µl in the absence of infection, splenomegaly or other circumstances causing platelet destruction, suggested alloimunization; thus our study showed similar results with studies done in different countries like USA[13-16], Italy[17] Spain[18], Pakistan[3], UK[27,28] and Netherlands[30]. Among fifty patients, our study showed that, four patients (8%) still had less satisfactory count (3000/ µl) and one patient (2%) was near the CCI (4000/ µl), which also supports the other studies[3,6,13-20,23,25,31]. In this study poor response with platelet transfusion had been observed and the demonstration in such patients of a poor post-transfusion platelet increment on two occasions suggests that, evidence of platelet-refractory state , which also correlates with other studies[3, 6, 12-20 ,23-25, 27-29,31]. This study also supports Stephan et al[26] (1999) who suggested that, thrombocytopenia of less than 50x 10^9 platelets/L is associated with excessive illness and increase risk of death independent of age and initial severity of illness, and leads to excess blood products consumption imposing a significant economic burden. From 1 hour after platelet transfusion count information, it has been checked

that the platelet count had gone up a lot, a little, or not at all[26]. In this study, it was also considered that, some rise in platelet count at 1 hour, but back to baseline at 24 hours suggested non-immune causes of poor platelet response. No appreciable rise in count at either 1 or 24 hours suggested alloantibody destruction and supports other studies in UK, USA, Spain, Italy, Netherlands and Pakistan[3, 12-18, 24, 27-29]. This study also correlates with Mollison[20] (1994) in calculation, where the corrected increment at 1 hour after transfusion showed important evidence when platelet transfusions are being given to patients who may have formed alloantibodies. In this study, transfusion reactions were reported and evaluated as a new fever or new rigors occurring during or shortly after a transfusion, was considered a reaction; whereas a fever or rigor that occurred shortly before the transfusion started, was considered unrelated and this observation also showed similarities with studies done in different countries[3,12-18,24,27-29]. In this current study reported numbers of transfusion reactions occurred; there were nine transfusion reactions (18%) reported due to intercurrent fever, two allergic reactions (rash and/or urticaria), one transfusion with intercurrent fever and five with rigor, thus showed similarities with other studies in UK, USA, Spain, Italy, Netherlands and Pakistan[3,12-18,24,27-29]. No history of reactions among 41 patients (82%) which is also similar with reactions reported in Blumberg[30]. In this study AML was 70% and ALL was 30% which supports a South East Asian[32], Indian[33] and a Nepali study[34]. In our study most common morphological types of AML were M1 (22%) and M2 (28%) which differs with studies done in Spain[18] and Nepal[34] and supports a South East Asian[32] study. Among ALL patients majority were ALL-L2 variety (20%), which showed similar result with an Indian[33] and a Nepali[34] study. Among total patients, highest prevalence was O blood group (42%) and lowest was AB (10%); B was 28% and A was 20 %. Rh D positive blood groups were 94% and 6% were Rh D negative which supports a Bangladeshi population study[32] with exception in O (33.97 %) and B blood group (35.20%) and also correlates with a study done in Bangladesh on haematological patients [(28%) group A, (30%) group B, (38%) group O and only (4%) AB][35]. We used in our study ABO identical cross-matched platelet which helps to reduce refractoriness[30] , increases survival[30] with reducing morbidity and mortality in bleeding patients and showed satisfactory result with apheresis platelet than pooled platelet , thus also supports studies in different countries [3,13-20, 24, 27- 31].

Conclusions

In our study, post-transfusion platelet count was satisfactory both after one hour and after 24 hours, where platelet concentrate was prepared by platelet pheresis (cell separator) suggested that, pheresis platelet has satisfactory result. Our study showed that, post transfusion increment was satisfactory in 45 patients (90%) out of 50; whereas, 5 patients (10%) showed clinical evidence of refractoriness and also had less satisfactory corrected count increment. Evidence of transfusion reaction was reported in 9 patients (18%). From our study we can suggest that platelet transfusion helps in chemotherapy induced thrombocytopenia and platelet pheresis is better option to raise platelet count increment.

Recommendation

In our country there is least advantage to reduce platelet transfusion refractoriness or reduce bacterial infections. In our study we face the need of leukoreduction to remove white cells from the transfused blood components or use of washed platelets or special filter for prevention of transfusion reactions and HLA alloimmunization. So further comparative studies should also be carried out in a large scale, with a setting of lower transfusion threshold for platelet count , including both pooled platelet by refrigerated centrifuge method and pheresis platelet by cell separator method.

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