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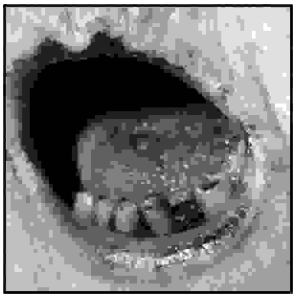


THROMBOCYTOPENIA IN CRITICALLY ILL SURGICAL PATIENTS;

A STUDY EVALUATING ATTRIBUTABLE PATIENT'S MORTALITY AND TRANSFUSION REQUIREMENT

DR MUHAMMAD SIDDIQUE, FCPS
Department of Anesthesiology and Intensive Care
Combined Military Hospital Rawalpindi

Dr Asad Ullah Jaafri, FCPS
Department of Anesthesiology and Intensive Care
Combined Military Hospital Rawalpindi

DR SAYYED NAVEED MASOOD, FCPS
Department of Anesthesiology and Intensive Care
Combined Military Hospital Rawalpindi

Dr Fayyaz Hussain, FCPS
Department of Anesthesiology and Intensive Care
Combined Military Hospital Rawalpindi

DR RUBEENA NAZLI SHAFFI, FCPS
Department of Ophthalmology
Pakistan Institute of Medical Sciences Islamabad

ABSTRACT... drsiddique2002@yahoo.com Thrombocytopenia is a well known complication in the surgical intensive care unit (ICU) patients. The influence of thrombocytopenia on patient's mortality is difficult to assess. Thrombocytopenia results in increased mortality and transfusion requirement of platelets and other blood products, has not been confirmed by previous studies. We performed a case control study in surgical intensive care unit of Combined Military Hospital Rawalpindi in which 119 critically ill surgical patients developed thrombocytopenia of less than $50x10^9$ platelets/L. These patients were carefully matched with control patients for the severity of underlying disease and important variables. Purpose of study was to evaluate attributable mortality and transfusion requirement in thrombocytopenic patients at that unit.. Fifty-two (44%) cases died versus forty (33%) control patients. Eighty one (76%) matched pairs had a concordant outcome and in 25% of those pairs, the cases died (exact binomial probabilities 0.036). The estimated attributable mortality rate was 18.4% (95% confidence interval 3.12-11.8) and the estimated odds ratio was 2.6 (95% confidence interval 1.02-7.10). The estimated attributable transfusion requirement was 23% (95% confidence interval 5.3-43.5) and the estimated odds ratio was 1.51.This study suggests that thrombocytopenia of less than $50x10^9$/L seems to be a marker of severity the illness and increases risk of death. Thrombocytopenia also leads to more blood product consumption.

Key Words: Thrombocytopenia, Transfusion, Sepsis, Intensive Care Unit.

INTRODUCTION

Thrombocytopenia is associated with various risk factors but mainly with sepsis. The incidence of thrombocytopenia of less than 100×10^9 platelets /L has been from 23-41% but lower frequencies (10-17%) have been reported for counts lower than $50x10^9$ platelets /L.

Mortality rates as high as 38-54% have been observed but have been proportional to the nadir of the platelet count[1,2] .Previous studies[3,4] have not clearly demonstrated, that thrombocytopenia results in increased mortality or increased transfusion requirements, however, two independent factors have made this important and seemingly straightforward issue to resolve.

First, mortality rates are high in such patients for many reasons[5]. Severe underlying illness predisposes to the development of thrombocytopenia in ICU patients and the influence of thrombocytopenia on mortality is therefore difficult to assess[2,]. Although thrombocytopenia in the critically ill surgical patients is more often a symptom than a disease process per se, it might increase mortality in everal ways.

Thrombocytopenia can result in mild, moderate or severe hemorrhagic disorders (Figure-I), which could enhance the risk of morbidity and mortality in critically ill surgical paitents[4].Apart from its haemostatic effects; thrombocytopenia also increases the susceptibility and severity of certain infections. Thrombocytopenia has rarely been identified as an independent predictive factor of death using multiple logistic regression.

Second, the threshold value for severe thrombocytopenia that is suppose to jeopardize the prognosis is difficult to determine. A platelet count less than 50 $x10^9$/L is associated with a poor prognosis[3]. Moreover guidelines for platelet transfusion have proposed that the threshold value of $50x10^9$platelets/L is an indication of platelet transfusion to surgical patients[5].

We therefore designed a case controls study to determine to what extent severe thrombocytopenia (defined as $<50x10^9$ platelets /L) increases mortality and blood product requirements in surgical ICU patients.

MATERIAL AND METHODS

We performed a matched cohort with a match-controlled patient without thrombocytopenia for each thrombocytopenic patient (1:1) study in the Intensive Care Unit of Combined Military Hospital, Rawalpindi. This 9-bedded ICU admits patients from all surgical departments and operating rooms of the hospital. The laboratory back up for this intensive care unit was provided by the Armed Forces Institute of Pathology (AFIP) Rawalpindi and the blood product requirement was met by Armed Forces Institute of Transfusion (AFIT) Rawalpindi. Although, it is a multi disciplinary intensive care unit, yet critically ill surgical patients occupy most of the beds. The study period was from 1st May 2000 to 30th April 2001, during which 1078 critically ill surgical patients were admitted to the ICU and thrombocytopenic patients were prospectively identified.

CASE IDENTIFICATION

Platelet count was performed daily for all patients who experienced even a single episode of thrombocytopenia of less than $50x10^9$/L during the ICU stay were classified as “Cases”. Platelet transfusions were administered to actively bleeding patients and patients scheduled for emergency surgery if their platelet count fell below $50x10^9$/L. Likewise, platelet transfusions were administered to patients at risk for bleeding complications i.e. post-operative patients or after gastrointestinal bleeding, when their platelet count fell below $20x10^9$/L.

MATCHING AND SELECTION OF CONTROL PATIENTS

Control patients had no evidence of severe thrombocytopenia (less than $50x10^9$ platelets/L) at any time during hospitalization in ICU. Control patients were selected according to the following matching criteria. Age (± 5 years), primary diagnosis, duration of stay in ICU (±5 days) and APACHE II score[6] calculated on the first day of ICU admission (±5 points).

In the case of multiple acceptable control patients, the one with the date of ICU admission closest to that of patient was chosen. The control patients were selected out of the total number of patients (1078) admitted to surgical ICU, CMH Rawalpindi from May 1, 2000 to June 30, 2001.

DATA COLLECTION

The information recorded were:-Name, age, sex, date of admission, date of first episode of thrombocytopenia either ultimately fatal or non-fatal, previous health status, primary diagnosis, duration of stay in ICU (in days), APACHE II score[6], ODIN model on admission based on the presence or absence of cardiac, respiratory, hematological, neurological, hepatic failure or any infection, total number of organ dysfunction[7], transfusion requirement of platelets and red cell concentrates[5].

Fig-I Optic fundal hemorrhage in a thrombocytopenic patient

STATISTICAL ANALYSIS

The attributable mortality due to severe thrombocytopenia was defined as the crude mortality rate of the control patients subtracted from that of cases. The point estimate of attributable mortality and 95% of confidence interval (CIs) were calculated. The data was presented in tabular and graphic forms.

Null hypothesis was tested. Values were expressed as Means±SD. Proportion was represented as numbers and percentage. Student t test was analyzed with continuous variables. Discrete variables were analyzed by chi square test.

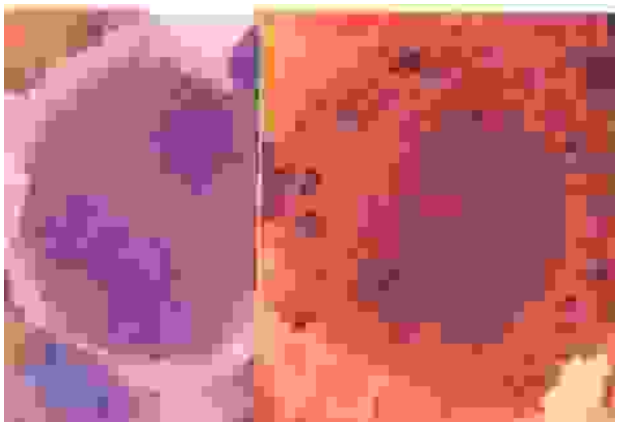


Fig-II Immune Thrombocytopenia

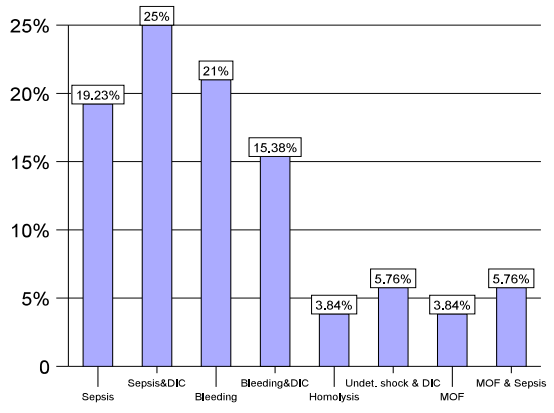
RESULTS

During the study period 119(11%) of the 1078 studied surgical ICU patients, developed severe thrombocytopenia of less than $50x10^9$ platelets/L that occurred 3.2±4.8 days (median 2 days, inter-quartile range 2.5 days, range 0-26 days) after ICU admission, for a mean duration of 3.4±2.9 days (median 2 days, inter-quartile range 4 days, range 1-13 days).

Thrombocytopenia was related to sepsis in 23(19.23%), sepsis and DIC in 29(25%), bleeding 25(21%), bleeding and DIC in 18(15.38%), undetermined shock and DIC in 5(3.84%), HELLP syndrome in 7(5.76%), multi-organ failure in 5(3.84%), multi-organ failure and sepsis in 7(5.76%) patients. Matching was performed for the 119 patients.

On admission to ICU, the mean platelet count was 125±75x10^9/L, median 114 versus 190±125x10^9/L, median 153 in cases and control patients respectively (not significant).

During ICU stay mean nadir platelet count was 30±15 x 10^9/L, median 28.3 versus 175±150 x10^9/L, median 116, mean nadir hemoglobin value was 6.6±1.9 g/dl, median 7.4 verses 8.5±2.4 g/dl, median 8.0 and mean nadir leucocyte count was 6±4.2x10^9/L versus 9.1±4.7 in cases and control patients respectively.



Graph- Diseases associated with thrombocytopenia

Table I		
Criteria	**Proportion of cases matched to control pts**	
	n/n1	**%age**
Same primary/diagnosis	117/119	98.31%
Same duration of stay in ICU(±5 days)	114/119	95.79%
Same APACHE II score (±5)	115/119	96.63%
Same age (±5 years)	113/119	94.95
Key:n = Number of cases *n1 = Number of control patients*		

CLOSENESS OF MATCHING

The median age of the cases was 51 years (range 22-91 years, mean 56.5 years) versus 51 years (range 22-88 years, mean 55 years) for control patients. Seventy-one (60%) case controls pairs differed by no more than 3 years, 83(69.5%) by no more than 5 years. The median APACHE II score of cases was 21 (range 5-41, mean 20.8) versus 21 for control patients (range 4-37, mean 22.7). The median duration of ICU stay of cases was 5 days (range 1-35 days, mean 8.3 days) versus 4 days for control patients (range 1-26 days, mean 6.4 days). Of the pairs, 117 were matched for primary diagnosis. Success rate is given in the table-I. Matching was successful in 85.5% variables.

MORTALITY

The study end point_**mortality**_is strongly related to severity of illness. Fifty-two (44%) cases died, versus forty (33%) control patients. Eighty-one (76%) matched pair had a concordant outcome (54 lived and 27 died). Thirty-eight (24%) had dis-concordant outcome and in 25% of those pairs, the cases died (exact binomial probabilities 0.036). The estimated attributable mortality rate was 18.4% (95% CI 3.12-36.6), and the estimated Odds ratio was 2.6 (95% CI 1.02-7.01) as shown in table -II.

Primary diagnosis in the 38 discordant case control pairs was: - septic shock in 24(61%), acute pancreatitis in 5(14%), undetermined shock in 4(11%) and hemorrhagic shock in 5(14%) pairs. Causes of mortality included refractory septic shock in 24(46%), multi-organ failure with sepsis 14(27%), uncontrolled bleeding 9(18%) and undetermined shock 5(9%), verses 12(40%), 9(30%), 6(20%) and 3(10%) in cases and control patients respectively.

Table II Grade mortality, attributable mortality and odds ratio of death due to severe thrombocytopenia in surgical ICU Pts			
Variable	**Point estimate**		**95% CI**
	n/n1	**%age**	
Crude mortality (cases)	52/119	44%	-
Crude mortality (control)	30/119	26.8%	-
Attributable mortality	22/119	18.4%	3.12-36.6
Odds ratio	2.6	-	1.02-7.01
Key:n = Mortality rate in cases *n1 = Mortality rate in control patients* *CI = Confidence interval*			

Sensitivity analysis was done to explore whether mortality risk varies according to exposure. 60 cases experienced thrombocytopenia below $50x10^9$ platelets/L for more than 3 days. Mortality rate was 48% versus 52% in patients without prolonged thrombocytopenia. Among the 82 cases that were transfused with platelets, 37(45%) died compared with 19 cases (51%) that were not transfused. In 55 cases, thrombocytopenia occurred more than 2 days after ICU admission. Mortality rate was 63% in these patients compared with 37% in cases in whom thrombocytopenia occurred 2 days or less after ICU admission.

BLOOD PRODUCT CONSUMPTION

Hundred one (85%) cases were transfused with blood products verses 73(64%) control patients. Forty three (36%) pairs) had discordant transfusion requirement and 36 of these pairs, the cases were transfused (paired x^2 =4.91 p<0.04). The estimated transfusion requirement was 23% (95% CI 5.3-43.5) and the estimated odds ratio was 1.32 table-III.

Table III Crude, attributable transfusion and odds ratio of transfusion requirement due to severe thrombocytopenia in surgical ICU patients

Variable	Point estimate		95% CI
	n/n1	%age	
Crude transfusion requirements			
Cases	101/119	85	-
Control	73/119	64	-
Attributable transfusion increment	28/119	23.5	5.3-43.5
Odds ratio	1.32	-	1.03-2.10

Key: n = Transfusion requirement in cases
n1 = Transfusion requirement in control patients
CI = Confidence interval

Seven ±6 (median 6.5) units of RBCs were transfused verses 2 ± 4 (median 2.5) p<0.0001) and units of fresh frozen plasma transfused were 8±7 (median 3) versus 1 ± 2 (median 0.00-p = 0.05) in cases and control patients respectively. Eighty two patients received platelet transfusion (6±7 units) verses no control patient. In 41 patients (5 died), platelet transfusions resulted in rise of platelet count to greater than $58x10^9$/L, with a correction of thrombocytopenia a few days later. In the remaining 41 patients (36 died), only a transient rise in platelet count was noted and thrombocytopenia persisted during the entire ICU stay despite platelet transfusion.

After the onset of thrombocytopenia, 3 ± 6 units of RBC and 4 ± 5 units of fresh frozen plasma were transfused. Thus about 50 % of the entire transfusion requirement was given in the form of RBCs and fresh frozen plasma.

DISCUSSION

Our study is suggestive of thrombocytopenia less than $50x10^9$ platelets/L is related to increased mortality with a relative risk 2.6 (95% CI 1.02-7.01) and with increased transfusion requirement with relative risk of 1.32(95% CI 1.03-2.10).

The frequency of thrombocytopenia in our study was 11%. Many explanations are suggestive of thrombocytopenia in the context of sepsis[2]. DIC, immune mechanisms (Fig-II) and hemophagocytic histiocytes are the commonest mechanisms for platelets destruction during bacterial infection[3]. In critically ill surgical patients, blood loss is the most common problem faced, which is replaced with crystalloid and colloids, when significantly severe. Reduction in platelet count has also been observed in patients who received blood transfusions. The incidence of thrombocytopenia is directly related to transfusion of red cell concentrates[5].

The outcome of severely thrombocytopenic patients admitted in surgical ICU is adversely affected by the severity of underlying illness[3]. Nadir platelet count and mortality appeared to be proportional to each other, as suggested previously[4]. Recent studies have reported conflicting results, however, Sprung et al in a large prospective study, identified thrombocytopenia ($100x10^9$ platelet/L) as an independent predictor of poor prognosis in septic patients corresponding to relative risk of death of 1.66 (95% CI 1.06-2.60)[2].

Lopez Aguila SC et al in a multi variate study identified the independent risk factors leading to thrombocytopenia and increase mortality in ICU patients[3]. The factors were age >60 years, ASA physical status V, hemorrhagic shock, APACHE II

Score upon admission to ICU (95% CI 3.62-21.38), multi-organ dysfunction (95% CI 3.73-13.92). On the contrary, Pettet et al did not identify thrombocytopenia as an independent predictor of mortality at the onset of sepsis in ICU patients as mentioned in above studies. On the whole, it may not be wrong to conclude that in the entire cohort study of ICU patients, thrombocytopenia was not identified as a variable that was independently associated with death.

Different variables, analytic methods used and complex interactions noted in multivariate analysis were probably the contributors, in one way or the other, to these discrepancies.

From our study concluded that acute severe thrombocytopenia is associated with an increased mortality. It is quite difficult to distinguish clearly the causes from sequel of severe thrombocytopenia in acutely ill patients. Moreover in case control studies, like ours the finding of a higher mortality in cases compared with control patients brings into account an association between mortality and thrombocytopenia.

This study identified clearly a categorical difference in the severity of illness scores, based on various variables, between cases and control patients, between the day of admission and day of onset of thrombocytopenia. In the control patients, the severity of illness decreased over time but remained constant or even worsened in cases; supporting the idea that thrombocytopenia may be an indicator of the unfavorable course of the underlying disease, and probably an aggravating factor during the whole course of disease.

Thrombocytopenia lasting for less than 2 days is associated with a similar risk to that of thrombocytopenia for many days. As the study results showed platelet transfusion in almost 50% of the transfused cases failed to restore a normal platelet count but in the remaining 50%, an improvement in the platelet count was seen a few days after the transfusion and the patients showed a smooth recovery.

Cases who received platelet transfusions, had complex medical problems including sepsis, sepsis with DIC, bleeding, bleeding with DIC, haemolysis, elevated liver enzyme, low platelet count, HELLP(Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome with DIC, undetermined shock with DIC, Multi-organ Failure (MOF) and MOF with sepsis. These are the patients, who therefore, received multiple drugs and frequent blood product transfusions; these were all probably inciting factors for thrombocytopenia[3].

Patients, secondary to sepsis, often required multiple platelet transfusions, although their response was often sub-optimal because of continued platelet destruction, reflecting the unfavorable course of underlying illness[2].

Similarly, in patients who received massive transfusions, persistent thrombocytopenia was due to consumption of platelets, dilution by transfused blood and colloid fluid resuscitation[9].

These patients were also prone to have platelet function defects, due to DIC, hypothermia and “stunned” recently transfused platelets. Some of the patients remained mildly thrombocytopenic for several days, developed a rebound thrombocytosis[10].

From this study, one can gather that the mortality impact of thrombocytopenia occurring during the first two days of ICU admission was quite different from late-onset ICU-acquired thrombocytopenia. This result is in agreement with previous studies indicating that late mortality is associated with the complexity of the underlying disease[1, 3].

CONCLUSION

Our study suggests that thrombocytopenia of less than $50x10^9$ platelets/L is associated with high mortality rate (attributable mortality 18.4% odds ratio 2.6). Patient's age and initial severity of the illness are not that much of contributory factors to this mortality. Thrombocytopenia in critically ill surgical patients leads to more blood product consumption (Attributable transfusion requirement 23.5%, odds ratio 1.32) imposing a significant economic burden.

Thrombocytopenia that leads to increase risk of death seems to be a marker of the severity of underlying disease processes. It requires more work and research to be done to know the exact relationship between thrombocytopenia and mortality, particularly in septic shock patients.. Different modalities of treatment should be chalked out for better management of thrombocytopenia, in various clinical settings, in critically ill surgical patients.

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THERE IS NOTHING EITHER GOOD OR BAD BUT THINKING MAKES IT SO.

Shuja Tahir