THROMBOCYTOPENIA IN THE INTENSIVE CARE UNIT

Introduction

The occurrence of thrombocytopenia is high in critically ill subjects in intensive care unit (ICU) along with many other comorbidities in these individuals. The platelet count of $< 150 \times 10^9$/L is defined as the thrombocytopenia and $< 50 \times 10^9$/L is considered as severe thrombocytopenia. There are six major mechanisms by which thrombocytopenia can be induced. These are increased consumption of platelets due to disseminated intravascular coagulopathy, bleeding, and trauma, hemodilution, decrease platelet production, increased platelet destruction or laboratory artefact of pseudothrombocytopenia.

Occurrence of thrombocytopenia

The frequency of thrombocytopenia cases in ICU individuals have been observed to be 35% to 45% in various studies and the 5% to 20% of ICU individuals have been found to have severe thrombocytopenia. The incidence of severe thrombocytopenia was high in surgical ICU cases in comparison to medical ICU cases. However, there is difficulty in drawing definitive conclusions due to the inclusion of mixed ICU cases with both surgical and medical issues in most of the studies. It has been observed that 20-30% of the individuals develop have thrombocytopenia at the time of ICU admission whereas during treatment in ICU a similar fraction of individuals also develops thrombocytopenia despite showing normal counts at the time of admission.

Prognostic ability of thrombocytopenia

The nature of thrombocytopenia is multifactorial in critically ill individuals and has the ability to serve as marker for severity of illness (1,2). The evidence in support of this statement comes from the observation of the high Acute Physiology and Chronic Health Evaluation (APACHE) scores, Simplified Acute Physiology Scores (SAPS), and Multiple Organ Dysfunction Scores (MODS) in individuals with thrombocytopenia in comparison to individuals without thrombocytopenia at the admission time (3).

In the studies conducted on evaluation of ability of thrombocytopenia as marker for prognosis in ICU cases, it was found that the platelet counts were inversely correlated with the risk of mortality and prolonged stay in ICU. The rate of mortality was observed to be 31-46% in individuals with

thrombocytopenia in comparison to 16-20% rate of mortality observed in non-thrombocytopenia individuals (3,4). In addition, it was observed that the magnitude of decrease in platelet count was related to the adversity of the outcomes more than the absolute nadir of platelet count. Over the time, the pattern of the platelet count highlights the underlying causes for thrombocytopenia. The appropriate and efficient treatment of individuals requires the differentiation of thrombocytopenia causes.

Review of literature

Dynamics of thrombocytopenia in ICU cases

The identification of individuals who require specific treatment for thrombocytopenia in addition to underlying cause is important due to the multifactorial nature and observed high frequency for thrombocytopenia (table 1). It can be considered that the gradual and slow decrease over 5-7 days in the counts of the platelets may be the result of a bone marrow failure or consumptive coagulopathy. On the other hand, any abrupt change in 1-2 days in the counts of platelets beginning post-surgery after second week, may be the resultant of adverse transfusion reactions or immunological causes.

Table 1: Previous study details of thrombocytopenia

Study	**Patient population**	**Number of patients**	**Platelet count less than 150 X 10^9/L**	**Platelet count less than 50 X 10^9/L**
Castle et al. (5)	Neonates	807	22%	Nil
Baughman et al.(6)	Patients admitted to medical ICU	162	35.8%	10%
Vanderschueren et al. (4)	Patients admitted to medical ICU	329	41.3%	11%
Strauss et al. (3)	Patients admitted to medical ICU	243	66.7%	5%
Shalansky et al. (7)	Patients admitted to intensive care unit-coronary care unit (ICU-CCU)	362	18.8%	Nil

Akca et al. (8)	Patients admitted to medical ICU	1,449	30%	Nil
Crowther et al. (9)	Patients above 18 years, admitted to ICU	261	46.4%	5%
Brogly et al. (10)	Patients admitted to ICU	822	25%	5%
Stephan et al. (11)	Patients admitted to the surgical ICU	147	35%	17%
Nijsten et al. (12)	Patients admitted to the surgical ICU	885	Only non survivors (13.3%) showed a mean platelet count less than 100 X 10^9	
Hanes et al. (13)	Patients admitted to ICU	63	41%	Nil
Selleng et al. (14)	postcardiac surgery ICU patients	329	21.3%	Nil
Vandijck et al. (15)	ICU patients with nosocomial bloodstream infection	155	43.2%	18%
Sharma et al. (16)	septic shock patients	69	55%	27%
Chakraverty et al. (17)	Patients admitted to ICU	235	38%	Nil

In case of abrupt fall in platelet count within hours of blood transfusion, the passive alloimmunization or bacterial contamination may be the underlying cause for thrombocytopenia. It is important to note the platelet counts at admission as well as counts from preceding hospital or wards, since usually the patients are referred from other wards or other hospitals to the ICU.

Admissions with low platelet counts

At the time of ICU admission, if post major surgery the platelet counts are observed to be in between 50 and 100 x 10^9/L with no observed ongoing overt bleeding than the individuals only require monitoring unless overt bleeding occurs and are usually normal.

In the presence of bleeding from surgery or acute trauma or from retroperitoneal or gastrointestinal hemorrhage, if the platelet counts are observed to be in between 50 and 100 x 10^9/L, there are mainly due to consumption or loss of platelets. In such cases, the management is by intervention like endoscopic vessel occlusion, surgery, rapid reversal effect of anticoagulants or coiling of the vessel to stop the bleeding.

The monitoring of platelet count should be performed regularly and maintained at 80 and 100 x 10^9/L by transfusion of platelets for the prevention of consumptive coagulopathy. Valeri *et al.* (18) suggested that in individuals with microvascular bleeding the hematocrit must be maintained above 30% as low hematocrit may lead to an increase in the tendency of the bleeding (18). CRASH-2 Trial (19) showed that administration of a 1g intravenous dose of tranexamic acid reduced the risk of death from bleeding and mortality.

In patients with no observed signs of bleeding, the cause for a moderate or acute decrease in platelet counts has been observed to be severe infections like endocarditis and sepsis. Neame *et al.* (20) observed that sepsis alone can cause moderate thrombocytopenia, and disseminated intravascular coagulopathy is usually present when the platelet count goes below 50,000/uL. Bone marrow dysplasia, chronic liver disease, and toxic drug effects often lead to a chronic decrease in platelet count. There are fewer common causes that include the platelet consumption related to thrombotic microangiopathic disorders, autoimmune thrombocytopenia, and cardiovascular disease. The most likely cause for the occurrence of acute thrombocytopenia is malaria in endemic areas in severely ill individuals. Thrombocytopenia is often linked to viral infections like Epstein-Barr virus, hepatitis C virus, or human immunodeficiency virus.

In individuals with <20 x 10^9/L platelet count and clinical bleeding, it is necessary to have an intervention. Usually, two therapeutic units of concentrated platelets transfused to the patient are sufficient to control the bleeding and at the same time serve a diagnostic purpose. The determination of platelet count in the first hour of transfusion offers the fastest way to choose the management of the condition further. A blood smear review for the exclusion of fragmented red cells must be performed before transfusion of platelets.

Thrombocytopenia during ICU treatment

If the platelet count is decreasing gradually for several days, the reason may be the worsening of the underlying cause, which may include bacterial or fungal infection-related consumptive coagulopathy and multiorgan failure. Levi et al. (21) have reviewed the treatment and pathogenesis of disseminated intravascular coagulopathy (22). The disturbance of the megakaryocytopoiesis by non-immune causes of the bone marrow forms another important reason for the gradual decrease in the counts of the platelets.

Management of special cases

The cases of pseudothrombocytopenia should be excluded by assessing the platelet histogram for aggregates and reviewing the smear of the blood. The individuals under GPIIb/IIIa inhibitors form an important case for such evaluation, as the GPIIb/IIIa inhibitors are capable of inducing pseudothrombocytopenia similar to the frequency of true thrombocytopenia. The presence of GPIIb/IIIa inhibitor-induced pseudothrombocytopenia can also be observed in citrated blood, and it becomes essential to exclude the clots of platelets through microscopic blood smear assessment. If the individual received the blood transfusion in the last 2 weeks, then the post-transfusion purpura (23) must be considered. The platelet alloantibodies are the most common cause of the posttransfusion purpura. These alloantibodies are generally against human platelet antigen (HPA)-1a. Those women who were immunized during pregnancy constitute this category. A response is triggered via recent transfusion of the blood from B cells and there is a boost in the antibody levels. The intravenous immunoglobulin G is administered 1 g/kg body weight for the purpose of treatment for two days consecutively.

The platelet anti-HPA-1a alloantibodies, when transmitted via blood or plasma transfusion, cause passive alloimmune thrombocytopenia (24). There is a binding of the antiplatelet antibodies that are transfused to the platelets of the individual, which is removed by the action of the reticuloendothelial system.

Risk of Bleeding

The risk of bleeding is usually increased with the presence of thrombocytopenia. Vanderschueren et al. (4) showed that bleeding was observed in 52.6% of individuals with nadir platelet counts in

comparison to individuals without thrombocytopenia, who showed 4.1% of bleeding cases. The risk of bleeding is not confined to the lowest platelet counts, and in individuals with 50-100 x 109/L platelet counts, it is also enhanced. This points to the role played by additional factor like invasive interventions, hyperfibrinolysis, platelet function defects, and disseminated intravascular coagulopathy. According to Vanderschueren et al. (4), individuals with <30 x 109/L platelet count and bleeding indicate disturbed hemostasis.

Aim and Objectives

The occurrence of thrombocytopenia in ICU patients is common due to the presence of many other comorbidities. There is increased bleeding risk in individuals with severe thrombocytopenia, and with the presence of moderately or mildly low platelet counts, the risk is more profound due to the interference of the normal hemostatic mechanisms.

Thus, the present study aims to assess the prevalence of thrombocytopenia in ICU patients and their underlying causes to choose the appropriate management strategy for these individuals. To achieve this, the following objectives were formulated:-

1. To evaluate the prevalence of thrombocytopenia in ICU patients.
2. To assess the factors associated with thrombocytopenia in ICU patients.

Material and methods

Study population: After obtaining ethical clearance, the study will be conducted in accordance with the ethical guidelines of the Institutional Ethics Committee. All the individuals getting admitted to the ICU and are expected to stay for a minimum of 48 hours will be enrolled. Prior written informed consent will be obtained, and patients with platelet count less than $< 150 \times 10^9$ /L will be excluded from the study. Low platelet counts will be confirmed by peripheral blood smear. The follow-up will be done until the patient is discharged from the ICU or dies.

Data Collection: The parameters such as age of the patient, gender, co-morbidities, and other past as well as present diseases, the category of admission, the diagnosis at ICU, and the drugs used prior to admission for at least up to 2 weeks will be collected and maintained as records. The course of platelet count of a patient through the ICU duration, as well as pre-ICU hospitalization, permits

interpretations regarding the likely causes of thrombocytopenia; hence, wherever available, pre-ICU hospitalization data will also be collected. The acute physiology and chronic health evaluation II score (APACHE II) and sequential organ failure assessment score will also be tabulated. The existence of intravascular catheters, the requirements for transfusion, the drugs to be administered, surgeries, endoscopy, and other therapeutic interventions will be recorded daily. The laboratory data to be collected includes daily full blood counts, serum creatinine, C-reactive protein, serum bilirubin, and coagulation test data.

Definitions for thrombocytopenia: Thrombocytopenia is a frequently observed hematologic aberration amongst patients admitted to the ICU. Based on the reference range, the thrombocytopenia will be defined as the platelet count of less than 150×10^9 /L. The platelet counts will be checked every 24 hours, and thrombocytopenia will be classified as mild if the platelet count goes below 150 ×109 /L, moderate if the platelet count goes below 100 ×109 /L, severe if the platelet count goes below 50 ×109 /L, and very severe if it falls below 20×10^9 /L.
The diagnosis of septic shock will be made in individuals via assumed or documented infections. The presence of disseminated intravascular coagulopathy will be considered when there is an elevation of D-dimers and 25% decrease in markers, namely platelet count within 24 hrs, fibrinogen level, antithrombin, and prothrombin time. Major bleeding episodes will be documented.

Statistical analysis: All statistical analyses will be performed using SPSS software. The Mann-Whitney U test will be used for continuous variables, while Fisher's exact test will be used for categorical variables, in order to compare the group of patients. To determine the odds ratio and confidence interval of the factors associated with thrombocytopenia, the logistic regression analysis will be carried out.

References

(1) Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med 2000;162:347–51. doi:10.1164/ajrccm.162.2.ncc3-00.

(2) Drews RE. Critical issues in hematology: Anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. Clin Chest Med 2003;24:607–22. doi:10.1016/S0272-5231(03)00100-X.

(3) Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: Bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002;30:1765–71. doi:10.1097/00003246-200208000-00015.

(4) Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000;28:1871–6. doi:10.1097/00003246-200006000-00031.

(5) Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. J Pediatr 1986;108:749–55. doi:10.1016/S0022-3476(86)81059-9.

(6) Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the intensive care unit. Chest 1993;104:1243–7. doi:10.1378/chest.104.4.1243.

(7) Shalansky SJ, Verma AK, Levine M, Spinelli JJ, Dodek PM. Risk markers for thrombocytopenia in critically ill patients: A prospective analysis. Pharmacotherapy 2002. doi:10.1592/phco.22.11.803.33634.

(8) Akca S, Haji-Michael P, De Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. Crit Care Med 2002;30:753–6. doi:10.1097/00003246-200204000-00005.

(9) Crowther MA, Cook DJ, Meade MO, Griffith LE, Guyatt GH, Arnold DM, et al. Thrombocytopenia in medical-surgical critically ill patients: Prevalence, incidence, and

risk factors. J. Crit. Care, vol. 20, 2005, p. 348–53. doi:10.1016/j.jcrc.2005.09.008.

(10) Brogly N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. J Infect 2007;55:136–40. doi:10.1016/j.jinf.2007.01.011.

(11) Stephan F, Hollande J, Richard O, Clieffi AU, Maicr-Redclspcrgcr M, Flahault A. Thrombocytopenia in a surgical ICU. Chest 1999;115:1363–70. doi:10.1378/chest.115.5.1363.

(12) Nijsten MWN, Ten Duis HJ, Zijlstra JG, Porte RJ, Zwaveling JH, Paling JC, et al. Blunted rise in platelet count in critically ill patients is associated with worse outcome. Crit Care Med 2000;28:3843–6. doi:10.1097/00003246-200012000-00017.

(13) Hanes SD, Quarks DA, Boucher BA. Incidence and risk factors of thrombocytopenia in critically ill trauma patients. Ann Pharmacother 1997;31:285–9. doi:10.1177/106002809703100302.

(14) Selleng S, Selleng K, Wollert HG, Muellejans B, Lietz T, Warkentin TE, et al. Heparin-induced thrombocytopenia in patients requiring prolonged intensive care unit treatment after cardiopulmonary bypass. J Thromb Haemost 2008;6:428–35. doi:10.1111/j.1538-7836.2007.02870.x.

(15) Vandijck DM, Blot SI, De Waele JJ, Hoste EA, Vandewoude KH, Decruyenaere JM. Thrombocytopenia and outcome in critically ill patients with bloodstream infection. Hear Lung J Acute Crit Care 2010;39:21–6. doi:10.1016/j.hrtlng.2009.07.005.

(16) Sharma B, Sharma M, Majumder M, Steier W, Sangal A, Kalawar M. Thrombocytopenia in septic shock patients - A prospective observational study of incidence, risk factors and correlation with clinical outcome. Anaesth Intensive Care 2007;35:874–80. doi:10.1177/0310057x0703500604.

(17) Chakraverty R, Davidson S, Peggs K, Stross P, Garrard C, Littlewood TJ. The incidence and cause of coagulopathies in an intensive care population. Br J Haematol 1996;93:460–3. doi:10.1046/j.1365-2141.1996.5101050.x.

(18) Valeri CR, Cassidy G, Pivacek LE, Ragno G, Lieberthal W, Crowley JP, et al. Anemia-induced increase in the bleeding time: Implications for treatment of nonsurgical blood loss. Transfusion 2001;41:977–83. doi:10.1046/j.1537-2995.2001.41080977.x.

(19) Olldashi F, Kerçi M, Zhurda T, Ruçi K, Banushi A, Traverso MS, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet 2010;376:23–32. doi:10.1016/S0140-6736(10)60835-5.

(20) Neame P, Kelton J, Walker I, Stewart I, Nossel H, Hirsh J. Thrombocytopenia in septicemia: the role of disseminated intravascular coagulation. Blood 1980;56:88–92. doi:10.1182/blood.v56.1.88.bloodjournal56188.

(21) Levi M, Löwenberg EC. Thrombocytopenia in critically ill patients. Semin Thromb Hemost 2008;34:417–24. doi:10.1055/s-0028-1092871.

(22) Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol 2009;145:24–33. doi:10.1111/j.1365-2141.2009.07600.x.

(23) Waters AH. Post-transfusion purpura. Blood Rev 1989;3:83–7. doi:10.1016/0268-960X(89)90002-7.

(24) Warkentin TE, Smith JW, Hayward CP, Ali AM, Kelton JG. Thrombocytopenia caused by passive transfusion of anti-glycoprotein Ia/IIa alloantibody (anti-HPA-5b). Blood 1992;79:2480–4.