

The Rationale Use of Platelet Transfusion in Dengue Fever

Introduction

Dengue fever and dengue hemorrhagic fever have emerged as a global public health problem in recent decades.

Platelet concentrates due to their short shelf life are frequently in limited supply. Hence, appropriate use of blood is required to ensure the availability of blood for patients in whom it is really indicated, as well as to avoid unnecessary exposure of the patients to the risk of transfusion reactions and transmission of blood borne infection. We shall summarize the studies conducted in Singapore to evaluate the appropriateness of platelet transfusion in dengue patients with thrombocytopenia.

The Relationship between Platelet Counts and Hemorrhage in Dengue Fever

The mechanisms of hemorrhage in dengue are multi-factorial and incompletely understood¹. Studies have demonstrated that the presence or degree of thrombocytopenia alone is not associated with increased bleeding risks in dengue. In a prospective analysis of children with Dengue Shock Syndrome (DSS)², only modest increase in prothrombin time (PT) and partial thromboplastin time (PTT) was noted. The plasma concentration of anticoagulants protein C, S and antithrombin III were noted to decrease with increasing severity of shock, likely due to increased capillary leakage. Increased levels of thrombomodulin, tissue factor and plasminogen activator inhibitor type 1 (PAI-1) were observed, with thrombomodulin levels increasing with severity of shock, and PAI-1 levels increasing with severity of bleeding. Direct activation of fibrinolysis by the dengue virus has been implicated, a process that distinguishes hemorrhage in dengue from that seen in classic disseminated intravascular coagulopathy.

The presence of fever is viewed as an additional risk factor for bleeding in the presence of severe thrombocytopenia. Severe thrombocytopenia in dengue occurs around the tail end of the febrile period.

The lack of association between bleeding severity and degree of thrombocytopenia has been demonstrated in other examples.

1. A prospective analysis in which bleeding scores were not related to platelet counts, suggesting instead that vascular alteration and platelet activation seen in dengue infection a separate, underlying process was responsible for bleeding as well as thrombocytopenia.
2. In a retrospective cohort analysis of 256 patients admitted to hospital with dengue in

¹ Ann Acad Med Singapore 2011;40:539-45

² Wills BA, Oragui EE, Stephens AC, Daramola OA, Dung NM, Loan HT, et al. Coagulation abnormalities in dengue hemorrhagic Fever: serial investigations in 167 Vietnamese children with Dengue shock syndrome. Clin Infect Dis 2002;35:277-85.

Singapore, the incidence of clinical bleeding was 6% among patients with platelet count >150 x 10⁹/L, 12% among patients with platelet count of 100–149 x 10⁹/L, 11% among patients with platelet count of 80–99 x 10⁹/L, 10% among patients with platelet count of 50–79 x 10⁹/L, 11% among patients with platelet count of 20–49 x 10⁹/L, 13% among patients with platelet count of 10–19 x 10⁹/L, and 0% among patients with platelet count <10 x 10⁹/L (*P* = 0.22), demonstrating **no significant relationship between clinical bleeding and platelet counts.**

Plateletcount (x 10 ⁹ /L)	>150	100–149	80–99	50–79	20–49	10–19	<10
clinicalbleeding	6%	12%	11%	10%	11%	13%	0%

Prophylactic Platelet Transfusions in Dengue

- No significant difference in occurrence of hemorrhage between prophylactic platelet transfusions and no platelet transfusion group

In an analysis of pediatric DSS, patients who received prophylactic platelet transfusions were compared with an equal number who did not. There was no significant difference in occurrence of hemorrhage between the two groups (*P* = 0.136); however, length of hospitalization and development of pulmonary edema were significantly higher in the prophylactic platelet transfusion group (*P* <0.05).
- Significant bleeding occurred in both transfused and non-transfused patients

In a retrospective cohort analysis of 256 patients with DF in Singapore whose platelet counts were <20 x 10⁹/L without major bleeding, 188 patients received prophylactic platelet transfusion. Clinically significant bleeding occurred in transfused (1/188) and non-transfused (2/68) patients, with no significant difference in rates of bleeding (*P* = 0.17).
- Quantifiable increases in platelet counts are transient

In dengue, even more so than in other conditions where prophylactic platelet transfusions are administered, the quantifiable increases and improvements in platelet counts and other coagulation parameters are transient at best. In DSS patients who underwent prophylactic platelet transfusion, platelet counts, prothrombin time ratio (PTR), and PTT returned to pre-transfusion values in less than 5 hours, demonstrating the lack of sustained haemostatic benefit of prophylactic platelet transfusions in DF, which translates into lack of clinical efficacy as an intervention which happens to target a parameter - platelet counts - which is not the implicated culprit of major bleeding in dengue.

Risks of Platelet Transfusion

Platelet transfusion carries with it a variety of risks including alloimmunisation with resulting refractoriness, allergic reactions, febrile non-hemolytic reactions, transfusion associated acute lung injury, viral, bacterial and parasitic infections.²²⁻²⁹ Platelets carry

an additional non-negligible risk of bacterial contamination due to the fact that its storage is done at room temperature for up to 5 days compared with other blood products which are stored in the blood bank refrigerator or frozen. It is estimated that 1 in 1000 to 3000 platelet units are contaminated with bacteria, resulting in life-threatening incidents in 1 of 100,000 recipients and immediate fatal outcomes in 1 of 500,000 recipients.²²

The presence of leukocytes in platelet preparations is largely responsible for the febrile, non-hemolytic, transfusion reactions via the generation of cytokines, occurring in 30% to 40% of platelet transfusion recipients.

Alloimmunisation may result in refractoriness to platelet transfusion in the future, when it may be really necessary. Platelet transfusion can also cause significant hypotension in patient on angiotensin converting enzyme inhibitors by generation of large amounts of bradykinin by filtration of platelet concentrates through a negatively charged filter.

Conclusion

Based on the evidence summarized herein, Annals Academy of Medicine Singapore propose that prophylactic platelet transfusion in dengue patients may be safely withheld for platelet counts as low as $5 \times 10^9/L$ in the absence of additional bleeding risk factors such as prolonged high fever (as seen in dengue patients with severe hepatitis and secondary bacterial infections), sepsis, vascular compromise, anatomic aberrations, significant coagulopathy, uncorrected hemodynamic instability, DHF and severe dengue.

They propose that, in the absence of such additional bleeding risk factors, platelet transfusion in dengue should be reserved for patients with major bleeding (Grade 2 and above in WHO bleeding scale). Careful observation without platelet transfusion is warranted in stable dengue patients with only minor 'dry' bleeding such as petechiae, ecchymoses and minor 'wet' bleeding such as mucosal oozing (WHO bleeding scale Grade 1). Factors that contribute to increased risk of bleeding such as those mentioned above may warrant higher platelet transfusion triggers based on astute clinical judgment.

Therefore, we proposed:

1. Prophylactic platelet transfusion in stable dengue patients without additional bleeding risk factors may be avoided without compromising patient safety;
2. Prophylactic platelet transfusion in dengue patients may be safely withheld for platelet counts as low as $5 \times 10^9/L$ in the absence of additional bleeding risk factors;
3. Attempting to increase platelet counts via transfusion in the absence of major bleeding has not conferred protective benefits from bleeding in dengue. Early recognition of dengue with prompt correction of hemodynamic parameters remains the cornerstone of avoiding hemorrhage and ensuring good clinical outcomes.

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Reference

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