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EVIDENCE BASED BEST PRACTICES IN PLATELET TRANSFUSION - A REVIEW

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ABSTRACT Economic viability of separation of blood into its components has resulted in augmenting their demand with a concomitant increased wastage due to limitations of shelf life. Transfusion of blood and its components, though essential in therapy, is wrought with inherent risks of infections and reactions, which may be life-threatening. Adherence to transfusion protocols will prevent indiscriminate use. This review aims to provide a holistic appraisal of the current evidence and best practices related to platelet transfusion.

KEYWORDS : platelet transfusion

Introduction

Platelets are the first responders to vascular injury and are, hence, integral to haemorrhage control. The clotting response is initiated, at both the cellular and the molecular levels. This process is a sequentially controlled and calibrated activity involving pro-haemostatic and anti-haemostatic responses. Cessation of bleeding or amelioration of its risk, due to thrombocytopenia or thrombasthenia, is the primary purpose of platelet transfusion,

An increasingly senescent population, higher incidence of onco-haematological disorders and rising trend of cell transplantation has manifested in a year-on-year increment in the demand of stored platelets. The population of people >70 years in the United Kingdom in 2012 was 7.5 million which will likely double by 2046[1]. Presently, 67% of all platelet transfusions are in patients with haematological malignancies, 7-10% in cardiac surgery and 5-9% in intensive care units[2,3]. The augmented demand has outpaced the donor base. This combined with ambiguities regarding:

1. optimal prophylactic dose to prevent thrombocytopenic bleeding,
2. threshold mandating transfusion,
3. uncertainty of superiority of prophylactic over therapeutic transfusion.

The average life span of platelets is 8-10 days which is pre-determined by the megakaryocyte due to the absence of a nucleus. About 1/5 of the total number of platelets are regenerated in a day. The shelf life of stored platelets averages 5-7 days. Accumulation of bio-reactive substances due to extended storage is possible but its clinical relevance is uncertain[4].

The risk potential for haemorrhage and appreciation of the reversibility of cause form the cornerstone in the management of thrombocytic derangement. Auto-immunity, haematological malignancy, myelofibrosis, infectious diseases, chemotherapy/radiotherapy, anti-platelet medications, are some entities from myriad causes afflicting thrombocytes. Thrombocytopenia may be consequent to myeloid suppression or increased platelet destruction. Thrombasthenia could be congenital or iatrogenic.

The Risks

Preventive rather than therapeutic platelet transfusions, from either pooled random donors (RDP) or single donor (SDP), has been the tradition. An unit of RDP contains at least $55X10^9$ platelets suspended in 40-70 mL of plasma, whereas, an unit of SDP contains $300X10^9$ platelets suspended in 200-300 mL of plasma[5,6]. The incidence of haemolytic reactions and transfusion related acute lung injury (TRALI) is higher in patients receiving ABO unmatched transfusions due to the larger amounts of plasma content in SDP[7,8,9]. SDP, however, carries a lower risk of transmission of infections due to lesser donor exposures. ABO cross-match with leukoreduction drastically mitigate the incidence of alloimmunisation, transfusion refractoriness and cytomegalovirus infection[10,11,12]. The flip side of leukoreduced platelets is the higher cost and wastage of 25% platelets.

Assessment of response

The only markers to assess the efficacy of therapeutic transfusions are through quantifying the amount and rate of bleeding. Prophylactic transfusion is even more complex, where the only indicator being a rise in the platelet counts along with the absence of bleeding.

Usually, platelet transfusion is prescribed in a dose of 5-6 units of RDP or a single unit of SDP. Each unit of RDP will raise the platelet count by $5X10^9$/L while SDP will raise it by $30–50X10^9$ /L. Response to transfusion is assessed by obtaining platelet count after 10–60 minutes post-transfusion and calculating the corrected count increment (CCI) using the formula:

$$CCI = \frac{(\text{post-transfusion count} - \text{pre-transfusion count}) \times BSA^*}{\text{Total number of platelets transfused}}$$

BSA = body surface area

CCI values >7.5 at 60 minutes after transfusion or >4.5 at 20-24 hours is acceptable as an indicator of therapeutic efficacy. Failure to achieve acceptable CCI on two successive transfusions indicates refractoriness, whose cause must be identified[13].

Prophylactic vs Therapeutic

Erstwhile considerations regarding platelet transfusion were largely anecdotal. The current evidence base reveals its association with multi-organ failure[14], TRALI[15], sepsis[16], and, earlier recurrence of leukaemia[17]. Further, platelet transfusion is fraught with immuno-modulation, pro-inflammatory and pro-thrombotic processes[17,18,19,20,21]. The safety and benefit of fewer transfusions of lower doses are now well established. Serious haemorrhage is the most unambiguous indication for platelet therapy. The therapeutic strategy is defined as using platelet transfusion only with evidence of bleeding and thrombocytopenia or thrombasthenia, the converse is prophylactic strategy[22].

The Transfusion

The cause of thrombocytopenia or thrombasthenia with an understanding of its nature, i.e., acute or chronic and its

reversibility must be elucidated before considering platelet transfusion. Platelet transfusion is based on consideration of not only its numerical value but also by the threat of grave bleeding. A well-defined strategy needs to be formulated for platelet therapy considering the risk-benefit ratio. Appropriate treatment of pre-existing thrombocytopenia, discontinuation of anticoagulants and antiplatelets, use of adjuvant medications like antifibrinolytics and desmopressin, use of other clotting factors in cases requiring massive blood transfusions must be exhibited prior to platelet use,

Haematological malignancies account for the largest database providing the threshold and dosing pattern for platelet transfusion. It also helps resolve the debate over prophylactic versus therapeutic platelet transfusion. Transfusion in these patients has been, historically, prophylactic since the risk of significant bleeding is rare. Serious spontaneous bleeds in the presence of a coherent vascular status do not occur with thrombocytopenia of $>5X10^9/L$[23,24]. This correlates with the estimated wastage of $7.1X10^9/L$ platelets per diem as the critical number of thrombocytes necessary for vascular integrity[25]. The trigger threshold in such clinically stable patients is, hence, suggested to be $\geq 10 X 10^3/L$[26,27,28].

Timely thrombocyte count is frequently not possible with co-existent coagulopathy. Platelets may be administered if thrombocytopenia is considered a contributory factor in the coagulopathy. However, if thrombocytopenia is due to exaggerated platelet destruction, as occurs with heparin-induced thrombocytopenia (HIT), haemolytic uremic syndrome (HUS), idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP), prophylactic platelet transfusion is seldom indicated [29]. It is not only ineffective but may also induce arterial thrombosis[13,32].

Scientific data concerning the threshold and dose for platelet transfusion in the critically ill does not exist. One randomised controlled trial done on dengue haemorrhagic fever patients concluded that prophylactic platelet transfusion did not prevent bleeding but increased the incidence of complications[30]. Recommendations extracted from the literature[31] concerning acute leukaemia patients are:

1. platelet count should be maintained $\geq 20X0^9/L$ in the critically ill patient with fever, sepsis, or coagulopathy,
2. maintain platelet count $\geq 50 X 10^9/L$ in the presence of significant bleeding.

Patients with chronic myeloid failure due to myelodysplastic syndrome or aplastic anaemia rarely have significant bleeding despite platelet counts of $\leq 5X10^9/L$. The indication is therefore surrounded in ambiguity. The British Committee for Standards in Haematology (BCSH) recommends maintenance of a platelet count $>10 X 10^9/L$ in patients without fever, coagulopathy or other risk factors of serious bleeding. A lower threshold of $5 X 10^9/L$ for initiating prophylactic transfusion, or even withholding it, is recommended in select stable patients[13,32].

There is no data regarding the threshold for platelet transfusion and its safe count before subjecting surgical patients to procedures. Recommendations are drawn from retrospective case studies and expert consensus statements. Most consider a platelet count $\geq 50 X 10^9/L$ to be safe for most scenarios[13,32,33]. These include gastroscopy and biopsy, insertion of indwelling lines, trans-bronchial biopsy, liver biopsy, laparotomy, and similar procedures. However, for neurosurgical and ocular operative interventions a platelet count $>100 X 10^9/L$ is recommended[13,32]. Platelet counts $> 50X10^9/L$ is recommended to be safe for lumbar puncture since the incidence of traumatic tap or risk of haematoma are high at platelet counts $< 20 X 10^9/L$[33,34]. Published recommendation for epidural catheter insertion range from >50-80X19^9/L thrombocytes[13,32,35,36].

Post-partum haemostasis is primarily a mechanical phenomenon. Labouring parturients undergoing vaginal delivery can be safely managed with a platelet count $>50X10^9/L$[37]. Patients requiring massive blood transfusion need platelet transfusions too. Their platelet count must be maintained $>50 X 10^9/L$. However, if the patient has polytrauma or a neuraxial injury including traumatic brain injury, the established recommendation is to achieve and maintain a platelet count $>100X10^9/L$[13,31,38,39].

Unexplained platelet dysfunction is a frequent manifestation after cardio-pulmonary bypass (CPB). Increased microvascular bleeding is a manifestation of a platelet disorder – thrombocytopenia or thrombasthenia. Platelet transfusion is recommended in these patients after exclusion of other surgical causes of bleeding. Prophylactic platelet transfusion following CPB is not indicated[13,32], which therefore, needs to be done according to a formulated therapeutic strategy.

Thrombasthenia may be acquired or congenital with the acquired being the commoner of the two. Antiplatelets, anticoagulants, and renal disease are the most dominant causes. Platelet count in these circumstances is usually a poor guide to therapy. The decision to transfuse platelets is based on clinical indicators. The BCSH[13] recommends the following to avoid platelet transfusion:-

1. Stop all antiplatelet medications,
2. Consider desmopressin for patients on aspirin,
3. Consider desmopressin for patients desmopressin for patients with congenital disorders, uremia and other acquired causes of platelet dysfunction,
4. In patients with renal failure, correct haematocrit to >0.30, use desmopressin and dialysis.
5. Transfuse platelets after the above strategy fails.

Conclusion

Changing traditional practices is formidable without convincing evidence to demonstrate that they were needless or even pernicious. With the ever-increasing demand of platelets, it is daunting to ensure continuous availability while minimising wastage. This becomes even more challenging in remote geographies. Adoption of a restrictive strategy towards prophylactic transfusion is an evidence-based approach. Thus, restricting the use of prophylactic transfusions at platelet counts $>10 X 10^9/L$, or, before invasive procedures at counts $>50 X 10^9/L$, will go a long way in reducing the requirement of platelets and preventing avoidable transfusion-associated complications. Usually, a single unit of SDP suffices to raise the platelet count to acceptable limits. Administering more than this must be viewed critically on account of its potential to precipitate pro-thrombotic and pro-inflammatory complications. Serious bleeding can very rarely be explained principally by thrombocytopenia at platelet counts between 50-100 $X 10^9/L$ alone.

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