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Management of Platelet Disorders and Platelet Transfusions in ICU Patients☆

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ABSTRACT

Thrombocytopenia or receipt of antiplatelet drugs, with or without bleeding, is a common indication for platelet transfusions in the ICU. However, there is almost no evidence base for these practices other than expert opinion. Also common is use of platelet transfusions prior to invasive procedures or surgery in patients with thrombocytopenia. Likewise, there is no high-quality evidence that such practices are efficacious or safe. Recently, it has become clear that, whether causal or not, patients receiving prophylactic platelet transfusions experience high rates of nosocomial infection, thrombosis, organ failure, and mortality, which increase the urgency and need for randomized trials to assess these practices. Investigational methods of improving the safety and efficacy of platelet transfusions include use of alternate strategies such as antifibrinolytics; use of ABO-identical, leukoreduced, and washed platelet transfusions; and improved storage solutions.

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Contents

Platelet disorders are common in critically ill adult and pediatric patients. The most frequently encountered issue is thrombocytopenia. Suspected or actual platelet dysfunction due to disease or, in adult and some pediatric patients, use of antiplatelet drugs and/or heparin is also a commonly seen clinical issue. Severe congenital qualitative or quantitative disorders of platelet function or number, for example, Glanzmann

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thrombasthenia or neonatal alloimmune thrombocytopenia, are uncommon but can be life threatening. Acquired platelet disorders, for example, autoimmune thrombocytopenia (ITP) or thrombotic thrombocytopenic purpura (TTP), are also relatively uncommon. All of these conditions have been recently reviewed by multiple authors [1-3]. We will focus on the treatment rationale for platelet transfusion in critically ill patients.

By far the most common challenge in both pediatric and adult ICU settings is thrombocytopenia due to infection, sepsis, severe liver disease, multiorgan failure, or massive blood loss. Frequent causes of platelet dysfunction in adult patients are use of antiplatelet agents in patients who have experienced or are at high risk of arterial thrombosis. These include such drugs as aspirin, clopidogrel, and antibodies to platelet glycoproteins. This article will touch upon the recent data suggesting that platelet transfusion may be less effective and safe than previously thought in the setting of bleeding while receiving antiplatelet drugs.

There are no specific treatments for most of the abovementioned clinical problems (with the exception of ITP and TTP) except for platelet transfusions. Platelet transfusions traditionally have been liberally used to treat hemorrhage in thrombocytopenic patients and in those receiving antiplatelet drugs. Platelet transfusions are routinely and frequently administered with the expectation of preventing hemorrhage in thrombocytopenic patients who are not bleeding but are about to undergo invasive procedures such as vascular catheter insertion, organ biopsy, and surgery.

Although guidelines exist, almost no high-quality clinical evidence is available concerning the efficacy and safety of platelet transfusions in the setting of critical care. This is particularly true of prophylactic platelet transfusion in nonbleeding patients and, in particular, in those about to undergo an invasive procedure or surgery.

In patients with hematologic malignancies and severe thrombocytopenia, prophylactic platelet transfusions reduce rare, serious bleeding in acute myeloid leukemia (AML) patients during induction therapy yet provide minimal benefit to similar but more stable patients undergoing autologous stem cell transplant [4]. How this information can be extrapolated to ICU patients is not entirely clear. Recent reports, discussed in detail later in this review, question whether prophylactic platelet transfusions to nonbleeding ICU patients, invariably at much higher platelet count thresholds than in AML, provide benefit and with what risks.

Observational Data Concerning the Necessity/Utility of Prophylactic Platelet Transfusions and Therapeutic Platelet Transfusions in Bleeding Patients

In general, there are no randomized controlled trial data supporting use of transfusion of platelets to ICU patients with disorders of platelet number or function, bleeding or not. All guidelines are based upon expert opinion and generally have been contradicted by most observational studies. Patients with disorders of platelet destruction, such as ITP and TTP, usually, in our experience, do not receive platelet transfusions unless actively bleeding. There are reports that platelet transfusions to patients with TTP and heparin-induced thrombocytopenia (but not ITP) are associated with increases in arterial thrombosis [5]. Prophylactic platelet transfusions prior to invasive procedures or surgery have recently been associated, without proof of causation, with a high thrombosis rate (5%) and mortality rate (17%) in the ensuing weeks [6,7]. However, importantly, the mortality rates without platelet transfusion are not well characterized. The degree to which platelet transfusions, which contain highly activated rather than resting state platelets, promote thrombosis [8] is an important knowledge gap in our use of platelet transfusions in general. This is particularly true for ICU patients given these patients' higher baseline risk for both arterial and venous thromboses. These recent reports raise questions of platelet transfusion efficacy and safety not heretofore investigated.

Platelet Transfusion Efficacy in Bleeding Patients

Patients with disorders of platelet production, such as patients with acute leukemia who have received myelotoxic chemotherapy, may benefit from prophylactic transfusions, but this is the only setting where there are favorable randomized trial data [4]. There are no data at all, other than anecdotal personal experience, whether platelet transfusions effectively treat bleeding in actively hemorrhaging patients with disorders of platelet number or function, regardless of the mechanism of thrombocytopenia. It may be that alternative approaches, such as antifibrinolytics, would be equally or more effective. Assessment of the effectiveness of platelet transfusions in actively hemorrhaging patients and the efficacy when given prophylactically prior to invasive procedures and surgery are long-standing knowledge gaps in the management of ICU patients and patients in general. That said, it is almost impossible to withhold platelet transfusions from severely bleeding patients when the platelet count is <10-50 $\times$ 10^9/L.

However, it is reasonable to consider, based upon decades of clinical experience, that bleeding which does not improve with a single platelet transfusion is rarely benefited by a second transfusion and essentially never improved by a third. The use of massive transfusion protocols is perhaps an exception. The dictum that when the usual approach does not work, try something else (surgical correction of a lesion, antifibrinolytics, intravascular interventions, etc) is not evidence based but a perennial favorite of experienced physicians. There is a growing interest in treatments guided in real time by rapid whole blood hemostasis metrics derived from thromboelastography, but randomized trials are lacking.

Platelet Transfusions as Prophylaxis Against Hemorrhage in Patients Requiring Vascular Access

One of the most common uses of prophylactic platelet transfusions is in thrombocytopenic patients needing vascular access, usually via central venous catheters. There are extensive observational data documenting that bleeding, with or without transfusion, rarely occurs except through technical misadventure. In one study of 567 patients requiring tunneled central venous catheter insertions with platelet counts <50 $\times$ 10^9L or international normalized ratios (INRs) of greater than 1.5, there were no bleeding complications in these patients as opposed to 3 bleeding complications in the entire study population of 3170 patients (0.095%). All 3 bleeding episodes occurred in patients with normal or less severe abnormalities of platelet count or INR [9]. INR was not a good predictor of bleeding in these patients. Patients with platelet counts 25-50 $\times$ 10^9/L received no platelet transfusions in this study. Peripherally inserted central catheters led to no major bleeding in 143 insertions [10]. Moderate abnormalities in hemostatic screening tests (INR of 1.1-2.0) and/or platelet count (50-150 000/μL) have not proven reliably predictive for hemorrhage. Normal to nearly normal or, in liver disease, balanced hemostasis may be present even with abnormal test results and/or low platelet count [20].

In other studies, the incidence of major/serious bleeding with central line insertions was 0 of 1737 procedures [11], 1 in 658 (due to an accidental artery puncture) [12], 0 of 330 [13], 1 in 76 [14], 0 in 259 [15], and 2 of 388 [16]. These data encompass 4 major bleeding episodes in 3448 procedures, demonstrating that serious bleeding is quite rare. About 1 in 1000 patients bled. All of these patients had laboratory hemostasis testing abnormalities, often both a decreased platelet number and coagulation test results out of the normal range (INR, partial thromboplastin time, etc) and often without any attempt to correct these laboratory abnormalities with transfusions. If the rate of thrombosis after platelet transfusion in similar patients (those undergoing central line insertion, liver biopsy, etc) approximates the 5% in one small preliminary study [6] and these events are cause and effect, the use of prophylactic platelets may carry a 50-fold higher rate of thrombosis than the baseline risk of bleeding reported in the literature.

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