Transfusion Medicine Reviews 31 (2017) 223–229

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Recognition and Management of Hemostatic Disorders in Critically Ill Patients Needing to Undergo an Invasive Procedure

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ARTICLE INFO

Available online 15 June 2017

Keywords:
Coagulopathy
Critical illness
Fresh-frozen plasma
Platelet transfusion
Interventions

ABSTRACT

Abnormal laboratory coagulation test results are frequently documented in critically ill patients, and these patients often also need to undergo invasive procedures. Clinicians have an understandable desire to minimize any perceived heightened risk of bleeding complications in those patients who require invasive procedures. In this setting, prophylactic administration of platelets or plasma is commonplace. This review explores the nature of these sequential statements and the degree to which these statements are supported by evidence. We discuss the complexity of managing the low risk of procedure-related bleeding in a setting where coagulation tests fail to reliably predict this risk. The role of prophylactic transfusion of platelets and plasma and correction of medication-induced coagulopathy is also reviewed. New strategies are required to improve the evidence base, including novel methodological approaches or the use of a clinical scoring system.

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http://dx.doi.org/10.1016/j.tmrv.2017.05.008
0887-7963/

The nature of critical illness by definition implies a heightened risk for adverse outcomes, including bleeding and thrombosis [1]. Indeed, the pro-bleeding and procoagulant states are not mutually exclusive, and complex patterns of hemostasis with both bleeding and thrombotic events co-exist [2]. Any interventions to reduce a risk of bleeding must be appropriately weighed against treatment risks, which in the context of transfusion include adverse events such as volume overload, transfusion-related acute lung injury, and transfusion-transmitted infections.

Much of the common practice of preprocedural platelet and plasma transfusion can be summarized as a series of "beliefs": (1) that patients with abnormal laboratory test results are at greater risk for significant bleeding after a procedure, (2) that laboratory tests predict bleeding risk, (3) that interventions such as plasma or platelet transfusion will modify and reduce bleeding risk, and (4) that the risks of transfusion will not exceed the benefits of transfusion. These beliefs have been perpetuated to varying degrees in clinical guidelines and recommendations, which may promote specific laboratory thresholds for prophylactic transfusions, despite generally low levels of supporting evidence.

By way of illustration, in the United Kingdom, in 2009, 2 patient-based scenarios were sent in a survey to all 2700 members of the national intensive care professional society. Scenario 1 was a non-bleeding septic patient with coagulopathy; scenario 2 was a non-bleeding critically ill patient with hepatic cirrhosis and coagulopathy. Responses were sought in relation to fresh-frozen plasma (FFP) prophylaxis before central venous cannulation. For scenario 1, 52% of respondents stated that they would never routinely administer prophylactic FFP if the patient was not bleeding or undergoing an intervention, but this decreased to 9% when central venous cannulation was planned ($P < .01$). There was wide variation in the "trigger" international normalized ratio (INR) value which would prompt them to give transfusions, the most common range being 2.0 to 2.4. For scenario 2, responses were very similar. More than 80% of clinicians stated that they would routinely treat coagulopathy before lumbar puncture, epidural catheterization, intracranial pressure (ICP) monitoring, and tracheostomy; and 54% before chest drain insertion [3]. These responses clearly illustrate a common attitude in favor of prophylaxis.

In this review, we will address the recognition and management of hemostatic disorders in critical care. We will cover the ability of tests to identify increased bleeding risk, the frequency and bleeding risks of invasive procedures in critical care, and the evidence supporting the likelihood of interventions to modify bleeding risk. Then, we will summarize outstanding research questions.

Definitions and Frequency of Coagulopathy and Thrombocytopenia in Critical Illness

The definition of *coagulopathy* is "a condition in which the blood's ability to clot is impaired" [4]. The definition may have very different meaning when considered as impaired clot formation in vitro vs impaired clot formation in vivo. The term *disordered hemostasis* or *coagulopathy* is often applied in clinical practice to patients who have abnormalities in conventional laboratory test results, most frequently the platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT), or the INR.

Abnormalities of these conventional coagulation tests among critical care patients are common. In a prospective multicenter study (ISOC-1) of consecutive patients admitted to a UK general intensive care units (ICUs), around 30% of patients had, or developed, a prolonged INR (defined as an INR > 1.5). Most INR abnormalities appeared minor (1.5-2.6) and short-lived (single episode), with ~70% of highest INR values in the range from 1.6 to 2.5. Patients with INR prolongation in this study were more likely to have sepsis, be older, be female, and have higher Acute Physiology and Chronic Health Evaluation II scores, chronic liver disease, and dialysis-dependent renal failure [5]. Moderate thrombocytopenia ($<50 \times 10^9$/L) during stay in the ICU is also common and reported to range from around 5% to 20% [6,7]. Recent audit data (unpublished) from Oxford University Hospitals NHS Foundation Trust indicate that 19% of patients admitted to ICU have a nadir platelet count less than 100×10^9/L.

Assessment of Procedure-Related Bleeding Risk in Critically Ill Patients With Abnormal Laboratory Coagulation Test Results

The Limitations of Conventional Coagulation Tests and Platelet Counts to Predict Bleeding Risk

The laboratory tests of aPTT and PT were developed to investigate coagulation factor deficiencies in patients with a known bleeding history and suspected inherited disorders. Both PT and aPTT may be abnormal for reasons not associated with bleeding risk, including variation of coagulation factor levels or as part of an acute-phase response; for example, an increase in factor VIII can induce a shortening of aPTT. Coagulation results also vary in their sensitivity to reduced levels of different coagulation factor levels. For example, the aPTT will be significantly prolonged with only small reductions in the levels of factors XII and IX, and the PT has been shown to be sensitive to mild deficiencies of *multiple* pro-coagulants, as is often seen in clinical practice, which appears of very questionable clinical significance [8]. Altogether, their clinical value in predicting procedure-related bleeding risk in critically ill patients appears very limited, certainly at the ranges of abnormalities most commonly seen in critically ill patients (INR 1.5-2.0) [9,10].

Some physicians base decisions to transfuse products on a certain INR threshold, typically greater than 1.5 times the control. The INR is based on PT and was developed to monitor vitamin K antagonist (VKA) therapy by standardizing results to account for different sensitivities of thromboplastins in the laboratory. In patients with liver disease, over the INR range of 1.3 to 1.9 inclusive, mean factor levels ranged from 31% to 65% (factor II), 40% to 70% (factor V), and 22% to 60% (factor VII) [11]. In critically ill patients with INR values ranging from 1.5 to 2.2, factor levels were in similar ranges [12]. All of these levels are consistent with adequate concentrations of factors to support hemostasis in most clinical settings. Therefore, the INR was developed for monitoring stable patients taking VKAs and was never validated as a measure of bleeding risk for patients with critical illness.

Isolated counts of platelets are considered to have a limited role to predict bleeding in patients with hematologic malignancies, where much of the platelet clinical research has been undertaken. Friedmann et al [13] reported a large retrospective review of thrombocytopenic patients and found no relationship between first or lowest platelet count of the day and the risk of severe hemorrhage. Similar findings showing a poor relationship between morning platelet count and bleeding was shown by the Platelet Dose (PLADO) study, a randomized controlled trial in which patients undergoing stem cell transplantation or chemotherapy for malignancy were randomized to low dose (1.1×10^{11} platelets/m^2 body surface area), medium dose (2.2×10^{11}/m^2), or high dose (4.4×10^{11}/m^2) platelet transfusion when their morning platelet count was 10×10^9/L or less [14]. Thrombocytopenia is well recognized to be associated with mortality and hospital stay in critically ill patients, and there are only limited data on the nature of bleeding risk at different platelet count thresholds [15].

There are many causes of thrombocytopenia in critically ill patients, and the pathophysiology reflects alterations in platelet production, consumption/utilization, and pooling in the spleen and liver [16]. An increased risk of bleeding may be compounded by comorbidities, sepsis and inflammatory disorders, renal and liver failure, and the use of multiple medications [4,17]. Increased platelet consumption may occur with or without overt disseminated intravascular coagulation [18]. Conditions in critically ill patients may also cause platelet dysfunction [19], which will not be captured by isolated platelet counts. Platelet dysfunction may be a major factor in bleeding risk despite platelet counts greater than 50×10^9/L [20], but measures of platelet function do not exist in routine care. Taken together, one can see the limitations of guidelines that reference isolated tests of platelet count as a surrogate marker of