REVIEW ARTICLE

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Choice of Fluid Therapy and Bleeding Risk After Cardiac Surgery

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ABNORMAL BLEEDING, defined as diffuse oozing after cardiopulmonary bypass, occurs in more than 10% of patients who undergo cardiac surgery, and between 5% and 7% of all patients will have a postoperative blood loss of more than 2 L within the first 24 hours.[1] Reoperation for bleeding after coronary artery bypass graft (CABG) surgery is required in 2.3% to 8% of patients and is associated with a 4.5-fold increased risk of death.[1,2] Even modest increases in chest drain losses after surgery are associated with an increased risk of death, higher reoperation rates, an increased need for blood products, and prolonged requirements for intensive care.[3,4]

Patients undergoing cardiac surgery use 10% to 25% of the total blood products transfused annually in the United States.[4-6] However, a minority of patients (10%-20%) consume 80% of these blood products. This has led to an increasing desire to identify both modifiable and nonmodifiable risk factors for bleeding.[5,6] Patient-specific factors such as older age; nonwhite ethnicity; greater body surface area; elevated preoperative creatinine levels; preoperative anemia; hereditary coagulopathy; and surgical factors such as urgency of surgery, complexity of surgery, surgeon experience, degree of systemic hypothermia, duration of extracorporeal circulation, and use of an intra-aortic balloon pump are all associated with increased bleeding, blood transfusion requirements, and reoperation rates in cardiac surgery.[2,4,5,7] Frequently, a combination of factors contributes to excessive bleeding in surgical patients, and there now is a growing acceptance of the importance of multimodal strategies to reduce blood loss and requirements for allogeneic blood transfusion.[3,7,8]

Intravenous fluid therapy is a ubiquitous, modifiable component of perioperative cardiac surgical care.[9,10] Cardiac surgical patients receive large volumes of intravenous fluids. On average, these patients are given around 4,000 mL of combined colloid and crystalloid intravenous fluids intraoperatively and around 2,500 mL in the first 24 hours after surgery.[11-14] There is marked heterogeneity in clinical practice and no consensus on the appropriate choice of fluid to use in cardiac surgical patients.[15-17] In part, this is because of a lack of research on the safety and efficacy of intravenous fluids resulting from an era when their introduction into clinical practice did not undergo the same scrutiny as was required for other drugs.[9,18] The absence of robust evidence in specific patient populations, the presence of academic fraud, and the marketing endeavors of manufacturers have resulted in an ongoing debate on the appropriate use of intravenous fluids.[19-21] The purpose of this review article is to focus specifically on the evidence comparing the effect of different intravenous fluids on hemostasis and the risk of bleeding in patients undergoing cardiac surgery.

OVERVIEW OF HEMOSTASIS

Impaired hemostasis is an important contributing factor leading to abnormal bleeding after cardiac surgery.[5,6] Intravenous fluid administration previously was believed only to influence hemostasis through hemodilution; however, there is emerging evidence to suggest that some intravenous fluids may affect hemostasis through a variety of alternative mechanisms, which will be discussed further in each relevant section of this article.

There is a hemostatic balance between coagulation and fibrinolysis, reducing the risk of both bleeding and thrombosis.[22] In vitro, coagulation is arranged into "intrinsic" and "extrinsic" pathways that converge to form a common pathway that activates thrombin and converts fibrinogen to fibrin.[23] This classical enzymatic "waterfall" cascade model was useful in the early understanding of coagulation and still remains useful in the interpretation of laboratory tests—prothrombin time (PT) tests the extrinsic pathway and activated partial thromboplastin time (APTT) tests the intrinsic pathway. During the mid-1990s, a cell-based model of hemostasis was proposed that emphasized the importance of the in vivo cellular components for hemostasis and described the following 3 overlapping phases of coagulation: (1) initiation, the commencement of coagulation on the surface of tissue-factor bearing cells; (2) amplification, activation of platelets and other coagulation factors on the platelets' surface; and (3) propagation, whereby large amounts of thrombin are generated on the surface of platelets, leading to the formation of a fibrin clot.[4,24] Coagulation is limited by

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natural anticoagulants (anti-thrombin III, tissue factor inhibitor, proteins C and S) and plasma protease inhibitors. Fibrin clot degradation occurs through fibrinolysis.[6] This conceptual model provides a better in vivo understanding of hemostasis and correlates with viscoelastic point-of-care testing, such as thromboelastography.[25,26]

Influence of Extracorporeal Circulation on Hemostasis

The use of extracorporeal circulation during cardiac surgery has been reported to be associated with an increased risk of bleeding after surgery.[27-34] Extracorporeal circulation leads to a unique combination of acquired pathophysiologic hemostatic abnormalities that can be grouped into hemodilution, activation, and consumption processes.[1] The use of an asanguineous priming fluid in the extracorporeal circulation results in decreases in coagulation factors and platelet count due to hemodilution.[1,4,6] The marked activation of coagulation proteins, tissue factor, and fibrinolysis that occurs in patients undergoing cardiac surgery with extracorporeal circulation is due largely to the continuous contact of blood on the nonbiocompatible surfaces within the bypass circuit.[1,23] The activation processes trigger thrombin-, plasmin-, and inflammatory-mediated consumption of coagulation factors and platelets. Values for coagulation factors (II, V, VII, VIII, IX, and X) and the platelet count can remain lower than preoperative levels for up to 48 hours and 14 days, respectively, after surgery with extracorporeal circulation.[1]

TYPES OF INTRAVENOUS FLUIDS

Intravenous fluids are classified into 2 broad groups: crystalloid fluids and colloid fluids, both of which contribute to hemostatic abnormalities by hemodilution. However, each intravenous fluid has a unique physiochemical profile and pharmacodynamic properties that may affect coagulation beyond that of hemodilution.[35]

Crystalloids

Crystalloid fluids are a heterogeneous group of aqueous solutions containing different concentrations of inorganic ions and small organic molecules.[36] Crystalloid fluids have evolved since first being used during the cholera epidemic in the 1830s, and they now commonly are classified according to their main solute (eg, sodium chloride, glucose) or tonicity compared with human plasma (isotonic, hypotonic, hypertonic).[37] The different electrolyte composition of each crystalloid fluid contributes to the ability of the infused fluid to remain within the intravascular space and potentially lead to tissue edema and fluid overload.[10,38,39] There recently has been a push to further distinguish crystalloid fluids into physiologically balanced/buffered or physiologically unbalanced/unbuffered fluids. Balanced crystalloid fluids more closely resemble the physicochemical properties of extracellular fluid and may have different biologic properties.[9] However, no studies have assessed the comparative effectiveness of using balanced crystalloids versus unbalanced crystalloids for volume expansion or pump priming in cardiac surgery patients.

Unbalanced/Unbuffered Crystalloids

Unbalanced crystalloid fluid mainly refers to 0.9% saline; however, by definition it also can include dextrose- and mannitol-based fluids.[40] Worldwide, 0.9% saline is the most commonly prescribed, cheapest, and most well-researched intravenous fluid available.[9,41] Despite being commonly referred to as "normal saline," 0.9% saline is not normal physiologically and has a supraphysiologic concentration of chloride. It also has a strong ion difference of zero, and as a result, its administration in appreciable volumes may lead to hyperchloremic metabolic acidosis.[42,43] The clinical consequences of using 0.9% saline are uncertain; however, there is emerging evidence suggesting that 0.9% saline is associated with increased risk of acute kidney injury, dialysis use, and mortality in critical ill patients.[41,43-46]

The few studies that specifically have investigated the influence on bleeding risk and blood transfusion requirements in patients who have received unbalanced crystalloids versus balanced crystalloid fluids have been performed only in noncardiac surgical populations.[46,47] A recent meta-analysis of 6 randomized controlled trials (RCTs), including 255 patients undergoing noncardiac surgery (vascular, orthopedic, renal transplant, and colorectal surgery), reported no difference in postoperative blood loss in patients who had received 0.9% saline compared with those who had received Ringer's lactate fluid (a balanced crystalloid).[47] The investigators reported that in a subgroup analysis of 3 studies containing 120 "high-risk" patients (defined by the investigators as patients with a reported blood loss of at least 800 mL), lower blood loss volumes were found in patients who received Ringer's lactate fluid (relative risk, 0.42; 95% confidence interval [CI], 0.06-0.78). Although it is plausible that clinically significant differences in hemostasis between balanced and unbalanced fluid may only manifest after large-volume crystalloid fluid infusion (mean volumes of more than 5,000 mL in the 3 studies included in the subgroup analysis), it also may be possible that patients who bled more received more intravenous fluids; therefore, this post hoc analysis needs to be interpreted with caution.[43,48,49] Three studies (n = 156 patients) in this meta-analysis reported the volume of transfusion and showed that patients who received Ringer's lactate or Ringer's acetate required lower red blood cell transfusion volumes compared with those who received 0.9% saline (relative risk, 0.42; 95% CI, 0.11-0.73). All the RCTs included in this meta-analysis had a small sample (fewer than 70 patients), were conducted within a heterogeneous group of surgical patients, and had differing intravenous fluid regimens; therefore, results may not be generalizable to cardiac surgery patients.

Results from recent observational studies and experimental data have suggested that the use of 0.9% saline may be associated with increased blood transfusion requirements, blood loss, and coagulopathy compared with balanced crystalloids. A large (926 patients in the balanced crystalloids group *v* 2,778 patients in the 0.9% saline group) propensity-matched observational study of patients undergoing major abdominal surgery reported higher requirements for blood transfusion (11.5% *v* 1.8%, $p < 0.001$) and a significantly increased number of units transfused in patients who had received only