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Early Use of Fibrinogen in the Treatment of Postpartum Hemorrhage

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CURRENT CONCEPTS IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE

The management of PPH has evolved over the years. Whereas the initial focus was on volume resuscitation with crystalloids followed by transfusion of red cells, attention to coagulation deficits came later, and waited until the first two processes were finished or nearly so[1]. The impetus for this triad of interventions came from the military experiences in the Vietnam War[2,3]. This treatment approach was subsequently adopted by trauma centers in the United States and Europe, but to our knowledge has never been subject to a randomized controlled trial. Recent data from military combat casualties in Afghanistan and Iraq indicate that survival after massive hemorrhage is significantly improved by the introduction of fibrinogen-containing products early in the course of resuscitation efforts[4,5], and early adoption of this approach in the management of PPH has been cautiously reported in the obstetrics literature[6,7]. However, the concept of early use of fibrinogen has not yet been widely adopted by obstetricians.

PATHOPHYSIOLOGY OF COAGULOPATHY

In the normal hemostatic response to tissue injury, thrombin generation, mediated by tissue factor and activated factor VII, is localized to the site of injury. This localization of thrombin to the site of injury leads to formation of a hemostatic plug composed of platelets and cross-linked fibrin[8]. In massive uterine hemorrhage, however, bleeding is associated with extensive clot formation and consumption of fibrinogen. As bleeding continues, these newly formed clots are fibrinogen-poor, and thrombin is able to leak from them and gain access to the systemic circulation where it binds to and depletes antithrombin. The decrease in antithrombin is exacerbated by infusions of crystalloids (Figure 1)[8,9]. The direct consequence of circulating thrombin, unopposed by antithrombin, is disseminated intravascular coagulation (DIC).

DIC is characterized by the intravascular deposition of fibrin. Plasminogen, the precursor molecule of the fibrinolytic system, is bound to fibrin and converted to plasmin, the principle fibrinolytic enzyme. Plasmin attacks circulating fibrinogen as well as fibrin, resulting in hypofibrinogenemia. In addition, the ongoing fibrinolysis generates fibrin and fibrinogen degradation products, which inhibit platelet aggregation as well as fibrin formation. The resulting consumptive coagulopathy is manifest by the depletion of fibrinogen, prothrombin, factors V and VIII, and platelets[9] which invariably results in worsening of bleeding.

Volume resuscitation

In the initial resuscitative efforts of PPH, volume resuscitation with crystalloid and colloid is the easiest and quickest supportive measure to implement and helps rapidly to improve hypovolemia. However, *in vitro* as well as *in vivo* studies show that the degree of dilutional coagulopathy and accompanying decrease in antifibrinolytic factors is proportional to the infused volume[10]. Thrombin generation is also decreased by dilution to a greater extent by crystalloid than by fresh frozen plasma (Figure 1)[8,11]. Data from a German Trauma Registry in 2006 with over 8700 patients (about 30% female) revealed that up to 34% of patients

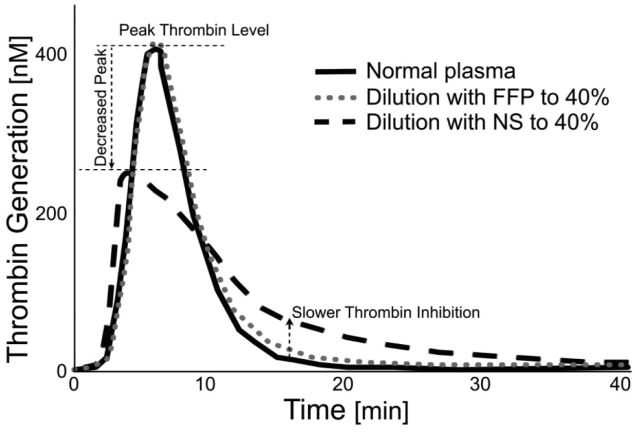

Figure 1 Thrombin generation patterns in platelet-poor plasma before and after dilution to about 40% of baseline. The patterns are similar between baseline and dilution with fresh frozen plasma (FFP). The peak thrombin level is lower (downward arrow) after dilution with normal saline (NS) because of a reduced concentration of procoagulant clotting factor. A concomitant reduction in antithrombin results in sustained thrombin activity (upward arrow). Reproduced from Bolliger *et al.*, 2010[8], with permission

presenting to the emergency room after a traumatic event were coagulopathic at the time of their presentation. Coagulopathy was associated with the extent of prior crystalloid resuscitation; however, up to 10% of patients were already coagulopathic after having received 500 ml or less of IV fluids[12]. Thus, crystalloid resuscitation may exacerbate pre-existing coagulopathy in patients with PPH.

Management of the coagulopathy

Given the circumstances outlined above, most patients with severe PPH have declining levels of fibrinogen as well as other procoagulant factors *early* in the course of bleeding. This has been clearly demonstrated in patients undergoing major surgery[12]. Therefore, as efforts are being made to control the underlying source of bleeding and restore tissue oxygenation by transfusion of red blood cells, the early introduction of fibrinogen and other procoagulants should logically be considered in obstetrics, in accord with it having been advocated so strongly by the military surgeons in today's battlefields.

Why fibrinogen first?

From the information presented above, one can appreciate that a *significant decrease in procoagulant factors and fibrinogen is present early in the course of PPH*. Furthermore, the data suggest that a decrease in fibrinogen is an early predictor of the severity of PPH[13]. Assessing this information together, the early use of fibrinogen-containing products should be prioritized in the current management of PPH. Bolliger *et al.*[9] recommend a fibrinogen target of at least 200 mg/dl. This is particularly important when one considers the normal lag time between receipt of the request for and delivery of blood products from the blood bank or fibrinogen concentrate from the pharmacy. *Waiting until fibrinogen levels are less than 100 mg/dl prior to transfusing fails to take this delay into account and runs the risk of jeopardizing patient survival.*

Fibrinogen replacement: cryoprecipitate or fibrinogen concentrate?

While both cryoprecipitate and fibrinogen concentrate are capable of correcting hypofibrinogenemia, the choice of product requires careful consideration, based on patient characteristics and availability of material. Table 1 examines a number of features of each product. RiaSTAP® is a fibrinogen concentrate which is currently approved in the US for the treatment of bleeding in congenital fibrinogen deficiency. Compared to cryoprecipitate, this fibrinogen concentrate is more potent, has less risk of infection transmission and is easier to administer. On the other hand, it is more expensive, might be more thrombogenic and is not FDA-approved for the management of PPH. However, it might be preferred over cryoprecipitate in a massively bleeding patient because it is capable of rapidly and predictably increasing the fibrinogen level. A randomized, controlled trial that will examine the safety and efficacy of fibrinogen concentrate for PPH is underway in Denmark[14].

Table 1 Comparison of cryoprecipitate and fibrinogen concentrate (RiaSTAP®)

Characteristic	*Cryoprecipitate*	*Fibrinogen concentrate*
Fibrinogen content	≥150 mg in 1 bag	900–1300 mg in 1 vial
Fibrinogen concentration	Variable from bag to bag; usual dose up to 10 bags	Indicated on label; predictable response
Viral inactivation/ removal	None	Enveloped and non-enveloped viruses*
Administration	Requires thawing, slow IV infusion	Rapid reconstitution and IV infusion
Storage	Bags must be kept frozen	Room temperature with shelf-life of 30 months
Allergy	Chills, fever, pruritus, anaphylaxis	Chills, fever, pruritus, anaphylaxis
Thrombosis	Yes	Yes

*HIV, West Nile virus, herpes simplex virus-1, hepatitis A virus, surrogates for hepatitis C virus and B19 parvovirus

Monitoring therapy

As previously noted, waiting for the results of coagulation tests prior to infusing blood products might jeopardize the survival of a patient with severe PPH. Recent work indicates that the thromboelastograph (TEG) can assist in the selection of blood products for massively bleeding patients[15,16]. The TEG can be acquired in the emergency room, operating room, or intensive care unit to guide the selection of blood products. De Loughery suggests that fresh frozen plasma (FFP) is indicated if the TEG reaction time is prolonged, fibrinogen if the kinetics are impaired, platelets if the maximum amplitude is reduced, and inhibitors of fibrinolysis if the lysis index is increased[17]. Whether the TEG will improve the management of PPH awaits prospective studies.

Battlefield evidence

Retrospective data from casualties in army combat support hospitals in Iraq show a significant survival advantage with the introduction of fibrinogen-containing products – FFP or cryoprecipitate – early in the course of a massive transfusion protocol. A review of 246, predominantly male, battlefield-injured patients treated at a combat support hospital in Iraq revealed that patients who received a higher ratio of plasma to red blood cell transfusions had a significantly higher rate of survival. In the group with the lowest plasma to red blood cell transfusion, mortality was 65% compared to 19% ($p < 0.001$) in the group with the highest plasma to red blood cell transfusion.[18] Evaluation of a similar population looking at the ratio of fibrinogen to red cells transfused noted a comparable improvement in survival in those having received a higher ratio of fibrinogen to red cells transfused[5].

Additionally, in patients who did not receive massive transfusion (defined as ≤10 units of red blood cells), transfusion of FFP was independently associated with increased survival[19]. Findings that replicate these results have also been described in transfused civilian trauma patients[20]. It is important to note, however, that although none of these data are from prospective trials, their findings are nevertheless compelling and require attention from the obstetric community as well as the development of trials to evaluate these protocols prospectively in patients with PPH.

A need for a change from tradition

As with many things in medicine, change is slow and difficult. Nevertheless, there is an urgent need for a change in the tradition of late use of fibrinogen in management of PPH. Such changes ideally should be generated on the basis of investigations which concern themselves with patients who have PPH. Although some authors have recently recognized the importance of addressing coagulopathy and incorporating some of the findings from military data into their recommendations[21,22], the numbers are small. It is hoped that this chapter and others in this volume will spur readers to re-examine the management of severe PPH.

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