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New Approaches to Transfusion Therapy for Postpartum Hemorrhage

M. J. Paidas

INTRODUCTION

Blood product replacement, first introduced in 1818, remains the mainstay of life-saving interventions for hemorrhage and in particular postpartum hemorrhage (PPH). Numerous refinements in transfusion therapy have occurred over the past several decades, whereas similar breakthrough advances in blood product replacement have not been forthcoming until quite recently and then prompted initially by the reports of surgeons practicing in battlefields.

Given the alarmingly high rate of maternal mortality, particularly in developing countries, where the maternal mortality rate associated with PPH is 34% and facilities for blood storage are often scarce to non-existent, attempts to simplify blood storage prior to its use are indeed appealing. For example, interest in lyophilization of plasma, essentially creating 'freeze dried plasma' is considerable, and this technique is actively being investigated[1]. If techniques such as these are successful, delivery of critical blood components without the need of present day storage requirements such as refrigeration may prove to be a key intervention in reducing maternal mortality globally. Unlike the futuristic approaches of storage component therapy, one intervention currently receiving intense scrutiny has the potential for transforming transfusion algorithms addressing PPH, namely fibrinogen replacement.

FIBRINOGEN AND POSTPARTUM HEMORRHAGE

Fibrinogen is an acute phase reactant, produced in the liver, and having a plasma concentration of 2.0–3.5 g/l in non-pregnant individuals[2]. In pregnancy, circulating plasma concentrations increase to 5 g/l in the third trimester. Fibrinogen has a half life of 3–5 days in plasma, and is acknowledged to play a fundamental role in hemostasis. Fibrinogen is a precursor of fibrin, which is cross linked to form blood clotting, and is a mediator of platelet aggregation. In normal pregnancy, delivery is characterized by marked increases in the clotting system and fibrinolytic activities[3].

Of relevance to PPH, however, tissue trauma and hypoperfusion both lead to acidosis, which increases fibrinogen consumption and impaired clotting. In particular, hypoperfusion triggers endothelial activation of thrombomodulin, and results in hyperfibrinolysis[4]. Severe PPH is characterized in a variety of manners including transfusion requiring four or more units of blood; estimated blood loss of 50% of circulating blood volume in under 3 h; estimated blood loss of greater than 150 ml/min within 20 min (≥50% blood volume); peripartum decrease in hemoglobin concentration of 4 g/l or more; sudden blood loss of more than 1500 ml (25% of blood volume)[5]. One landmark prospective study with 128 patients comparing severe versus non-severe PPH demonstrated the utility of measuring fibrinogen levels[6]. Univariate analysis revealed significantly lower levels of coagulation parameters fibrinogen, factor V, antithrombin and protein C antigen; and significantly elevated levels of prothrombin time, d-dimer and thrombin–antithrombin complexes. However, when multivariate analysis was performed, only the fibrinogen level remained significant as a marker of severe PPH (defined as a decrease of hemoglobin ≥4 g/l, transfusion ≥4 U packed red blood cells (pRBC), hemostatic intervention, or maternal death). In fact, the risk of severe PPH was 2.63-fold higher for each 1 g/l decrease of fibrinogen. Equally important, the negative predictive value of a fibrinogen concentration greater than 4 g/l was 79% and the positive predictive value of a fibrinogen level of 2 g/l or less was 100%.

In another, albeit retrospective review of 18,501 deliveries with 456 cases of PPH (2.5% of deliveries) with blood loss of at least 1500 ml, fibrinogen levels were found to be the best coagulation parameter correlated with blood loss ($r = 0.48$, $p < 0.01$); moreover, they fell progressively as the volume of PPH increased[7] (Figure 1). The presence of hypofibrinogenemia can be accurately, and rapidly, predicted using thromboelastometry, as demonstrated by the prospective observational study of Huissoud and colleagues[8]. Thrombelastography (TEG) and thrombelastometry (ROTEM) are viscoelastic whole-blood assays evaluating the hemostatic capacity of blood. In the Huissoud study in 37 women with PPH and 54 women without abnormal bleeding, the clotting times at 5 min (CA_5) and 15 min CA_{15}), and the maximum

clot firmness were significantly lower in the PPH group than in controls (p <0.0001). These parameters were strongly correlated with fibrinogen levels in both groups (r = 0.84–0.87, p <0.0001) (Figure 2, Table 1). A recent Cochrane systematic review concerning the use of thrombelastography or thromboelastometry to guide transfusion therapy, although not specific to pregnancy, found a significant reduction in blood loss favoring the use of TEG/ROTEM (85 ml; 95% CI 29.4–140.7) and in the proportion of patients receiving freshly frozen plasma and platelets (relative risk (RR) 0.39, 95% CI 0.27–0.57)[9]. Table 2 lists the classification of thrombelastography and thrombelastometry parameters[10].

FIBRINOGEN REPLACEMENT THERAPY

Fibrinogen concentrate has been used to correct hypofibrinogenemia in the setting of obstetric hemorrhage. Bell and colleagues reported the use of fibrinogen concentrate to treat six cases of obstetric hemorrhage in conjunction with other blood components including platelets, fresh frozen plasma and pRBC[11]. In their experience, coagulation parameters normalized rapidly and hemorrhage improved. Table 3 highlights the differences in the volume of fibrinogen replacement products[11]. Table 4 provides characteristics of the available fibrinogen replacement products[2].

A randomized, double blind, placebo controlled trial is underway to assess the utility of fibrinogen replacement in the setting of PPH (Fibrinogen Concentrate as Initial Treatment for PPH: A Randomised Clinically Controlled Trial (FIB-PPH, Copenhagen, Denmark, ClinicalTrials.gov Identifier: NCT01359878). The aim of the study is to determine

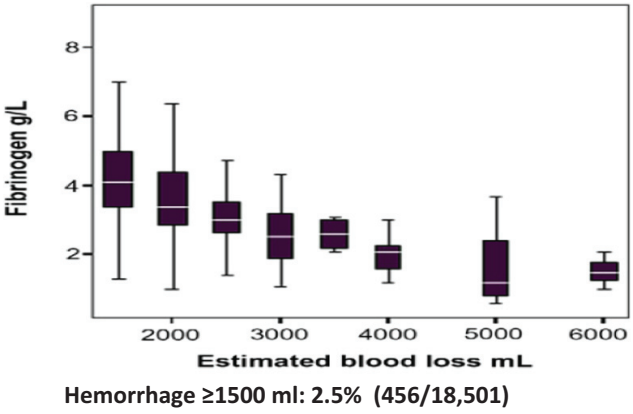

Figure 1 Fibrinogen levels in postpartum hemorrhage. From de Lloyd *et al.*, 2011[7], with permission

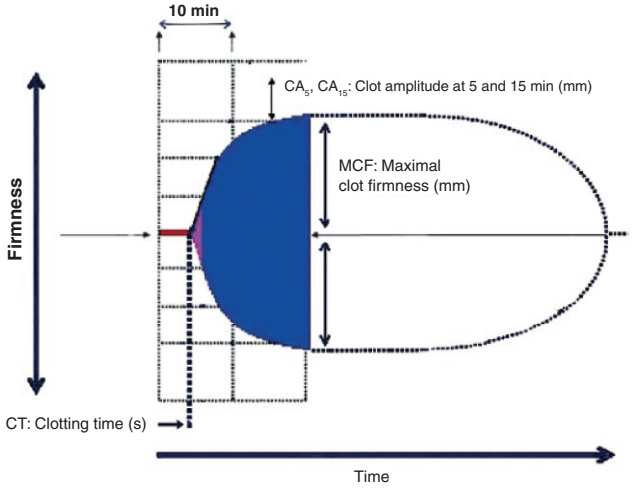

Figure 2 Assessment of fibrinogen level in PPH by thromboelastography: fib-tem® test. From Huissoud *et al.*, 2009[8], with permission

Table 1 Cut off values for CA_5 fib-tem® in PPH. From Huissoud *et al.*, 2009[9], with permission

Fibrinogen levels (g/l)	*Fib-tem cut-off values* (mm)	*Sensitivity % (95% CI)*	*Specificity % (95% CI)*	*PPV % (95% CI)*	*NPV % (95% CI)*	*AUC*
Fibrinogen <2	CA_5 = 6	100 (100–100)	87 (77–96)	50 (36–64)	100 (100–100)	0.97
Fibrinogen <1.5	CA_5 = 5	100 (100–100)	85 (76–95)	30 (17–43)	100 (100–100)	0.96
Fibrinogen <1	CA_5 = 4	100 (100–100)	86 (76–96)	13 (3–22)	100 (100–100)	0.96
Fibrinogen <2	CA_{15} = 8	100 (100–100)	84 (75–94)	46 (32–60)	100 (100–100)	0.96
Fibrinogen <1.5	CA_{15} = 6	100 (100–100)	88 (78–97)	33 (20–46)	100 (100–100)	0.97
Fibrinogen <1	CA_{15} = 5	100 (100–100)	88 (79–97)	14 (5–24)	100 (100–100)	0.97

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value

Table 2 Classification of thromboelastometry (TEG) and thromboelastography (ROTEM). From Armstrong *et al.*, 2011[10], with permission

Curve parameter	*Definition*	*ROTEM® abbreviation*	*TEG® abbreviation*	*Clinical application*
Clotting time (s)	Time from start of test until the start of clot formation (2 mm amplitude of deflection)	CT	r	Assesses activation of coagulation – primarily clotting factors
Clot formation time (s)	Time from beginning of clot formation to amplitude of 20 mm	CFT	k	Assesses rate of clot development
Alpha angle (°)	The angle of a tangent to the curve at 2 mm amplitude		α	Assesses both rate and strength of clot formation
Maximum clot firmness (mm)	Maximal amplitude of the curve	MCF	MA	Assesses contribution of fibrinogen and platelets to the clot
Amplitude at set times (mm)	Amplitude of the curve at 5, 10, 15 and 20 min	A5,A10	A30,60	Assesses of rate of clot formation

whether early treatment with fibrinogen concentrate (Haemocomplettan®, CSL Behring 2 g IV) compared to saline (100 ml) can reduce the incidence of blood transfusion in PPH. The study is planned to finish October 2013, after evaluating 245 patients from four hospitals in Denmark over a 2 year period. The primary outcome of the study is the incidence of transfusion with allogenic transfusion blood products during hospitalization or until 6 weeks postintervention. The secondary outcomes include the following:

(1) Severe PPH as shiown by decrease in hemoglobin more than 2.5 mmol/l, transfusion of 4 pRBC or more, or hemostatic intervention (embolization, surgical arterial ligation or hysterectomy, death);

(2) Estimated blood loss during hospitalization or until 6 weeks postintervention;

(3) Total amount of transfused blood products during hospitalization or until 6 weeks postintervention;

(4) Rebleeding during hospitalization or until 6 weeks postintervention (bleeding reoccurring after primary hemostasis) and requiring surgical procedures or intervention;

(5) Hemoglobin less than 3.6 mmol/l during hospitalization or until 6 weeks postintervention;

(6) Side-effects: including thromboembolic complications (safety measures/potential known side-effects) or until 6 weeks postintervention.

Inclusion criteria for the trial consist of informed consent from patient; women who develop PPH as bleeding from uterus and/or the birth canal within 24 h postpartum; age 18 years or older; if vaginal birth indication of either estimated blood loss of 500 ml or more and indication of manual removal of placenta or indication of manual exploration of uterus due to continuous bleeding after birth of placenta in the operating theater with anesthetic assistance; and if birth by cesarean section, perioperative blood loss of 1000 ml or more. The study exclusion criteria consist of patients with known inherited deficiencies of coagulation; patients in antithrombotic treatment antepartum due to increased risk of thrombosis; pregnancy with prepregnancy weight less than 45 kg; and patients who refuse to receive blood transfusion. Thromboelastography will be evaluated in the trial using the TEG/Functional Fibrinogen/Rapid-TEG, at baseline; immediately after intervention, and 4 hours and 24 hours after intervention. The baseline test is blinded to the providers, while the remainder are clinically available to the care providers. Fibrinogen levels, d-dimer, international normalized ratio (INR), platelet count, and antithrombin will be assessed as well. This trial will provide necessary data to formulate clinical guidelines regarding the use of fibrinogen replacement in the setting of PPH.

Fibrinogen therapy is a promising intervention for PPH. Key questions which remain unanswered regarding PPH are outlined below. What is the trigger for fibrinogen replacement? Will it be used for prophylaxis or treatment, or both? Where does fibrinogen fit in postpartum prevention and/or treatment

Table 3 Comparison of cost and quantity of fresh frozen plasma (FFP), fibrinogen concentrate and cryoprecipitate required to raise plasma fibrinogen concentration by 1 g/l in a 70-kg adult. From Bell *et al.*, 2010[11], with permission

Blood product	*Predicted quantity required to increase plasma fibrinogen concentration by 1 g/l* (ml)	*Cost to increase plasma fibrinogen concentration by 1 g/l*
FFP[6]	4 units (1000 ml)	£384
Cryoprecipitate[6]	13 units (260 ml)	£478
Fibrinogen concentrate[8]	2 g (100 ml)	£440

Quantities may vary according to ongoing consumption or dilution of fibrinogen. Prices obtained from the University Hospital of Wales Blood Bank, 2008

Table 4 Comparison of attributes of fresh frozen plasma (FFP), cryoprecipitate and fibrinogen concentrate. From Rahe-Meyer and Sørensen, 2011[2], with permission

Attribute	*Fibrinogen concentrate*	*Cryoprecipitate*	*Human plasma*
Constituents	Pure preparation of fibrinogen (few other constituents)	Contains clotting factors VIII and XIII as well as fibrinogen Also contains von Willebrand factor	Contains all clotting factors and numerous other proteins
Safety and transmission of pathogens	Viral inactivation, therefore minimal risk of pathogen transmission No unwanted clotting factors Low thombogenic potential	No viral inactivation, therefore potential risk of pathogen transmission Transfusion of large quantities can raise levels of several coagulation factors Thrombotic risk established	No viral inactivation (except commercially produced plasma products), therefore potential risk of pathogen transmission Risk of transfusion-related reactions (e.g. TRALI) and hypervolemia
Dosing: control and consistency	Well-defined quantity of fibrinogen Accurate and consistent dosing Low infusion volume	Variable fibrinogen levels, which are donor dependent Accurate dosing not possible Low infusion volume, albeit larger than fibrinogen concentrate	Variable fibrinogen levels, which are donor dependent Accurate dosing not possible Only modest increase in fibrinogen is possible High infusion volume
Administration	Rapidly reconstituted – administered with minimal delay (5 min) No cross-matching required	Must first be thawed, delaying administration (45 min) Cross-matching is required	Must first be thawed, delaying administration (45 min) High volume: time-consuming infusion Donor-recipient AB compatibility is required

TRALI, transfusion-related lung injury

algorithm? What is the optimal dose? Should fibrinogen replacement be given before severe PPH, for example, based upon evidence of hypofibrinogenemia? The safety of fibrinogen therapy must be established, specifically related to risks of infection, thrombosis and risks with concomitant agents.

Finally, antifibrinolytic therapy has been well described in the setting of PPH prevention, as summarized in the Cochrane systematic review, which included two randomized controlled trials[12]. Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or cesarean section in the dosage of 1 g or 0.5 g intravenously (two studies, 453 women, RR 0.51, 95% CI 0.36–0.72). There were no serious side-effects reported in women who received tranexamic acid. Tranexamic acid is currently being evaluated in a very large, multicenter, international, randomized controlled trial, called the World Maternal Antifibrinolytic Trial, or WOMAN Trial. This trial is sponsored by the London School of Hygiene and Tropical Medicine will enroll 15,000 women who will be randomized to 1–2 g of tranexamic acid intravenously versus saline. The inclusion criteria are an estimated blood loss of 500 ml or more after vaginal delivery or 1000 ml or more after cesarean delivery. The primary outcome is hysterectomy or death. Secondary outcome measures are other surgical interventions, transfusions, thromboembolism and other relevant medical events[13].

CONCLUSION

In summary, soon obstetric care providers will no longer need to rely solely on the experience of clinical trials involving transfusion therapy in other specialties to guide management and tailor treatments according to the unique needs of our patients. This fact in itself represents a breakthrough in PPH management. Advances in blood component storage offer the opportunity ultimately to provide more patients with life-saving therapies in catastrophic PPH.

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