Medical Advances in the Treatment of Postpartum Hemorrhage

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Postpartum hemorrhage (PPH) is a leading cause of maternal mortality worldwide. Recent advances in the management of severe bleeding for trauma patients may provide insight into PPH management, but must be applied with caution considering the significant differences between trauma and obstetric patients. In this review, we summarized evidence for current management strategies for patients with major obstetric hemorrhage, including (1) rapid laboratory assessment of coagulopathy, (2) early transfusion of plasma and high plasma-to-red blood cell transfusion ratios in massive PPH, and (3) use of tranexamic acid and fibrinogen concentrates in the setting of PPH complicated by coagulopathy. (Anesth Analg 2014;119:1140–7)

Hemorrhage in the setting of pregnancy is the leading cause of maternal mortality worldwide.[1,2] The leading cause of massive obstetric hemorrhage is uterine atony,[3,4] but obstetric complications such as placental abruption, placenta accreta, and amniotic fluid embolism may also precipitate obstetric hemorrhage, oftentimes complicated by consumptive coagulopathy.[4]

Although knowledge of massive hemorrhage and patient management is expanding, most research has been focused on trauma-associated hemorrhage[5]; fewer studies have focused specifically on the diagnosis and management of postpartum hemorrhage (PPH). Clinicians confronted by PPH have therefore been compelled to turn to the trauma literature to glean insights into transfusion and prohemostatic therapies.[3] However, trauma patients differ from obstetric patients in that they are primarily male. In addition, mechanisms of trauma and obstetric hemorrhage may differ, creating a challenge in applying evidenced-based trauma-management strategies to an obstetric population that possess a fundamentally different hemostatic physiology.[6]

This review aims to summarize medical advances in massive hemorrhage management and their application in the setting of PPH. These advances are broadly categorized into: (1) rapid laboratory assessment of coagulopathy in the setting of PPH, (2) transfusion therapy, and (3) prohemostatic pharmacotherapy as an adjunct to transfusion.

LABORATORY DIAGNOSIS OF COAGULOPATHY

The hemostatic physiology of a pregnant woman is notably different compared with nonpregnant women and men. The hypercoagulable state of pregnancy is marked by increases in fibrinogen concentration, von Willebrand factor, FVII, FVIII, and FIX concentrations, and decreased fibrinolytic and protein S activity.[6] Fibrinogen concentration substantially increases from 28 weeks' gestation to delivery; term pregnancy fibrinogen concentration (350–650 mg/dL) is nearly double that of nonpregnant adults (200–400 mg/dL).[6] D-dimer levels similarly increase throughout pregnancy, with virtually all term-pregnant women showing levels higher than typical threshold levels predictive of thromboembolic disease in nonpregnant individuals. Laboratory monitoring of PPH-related coagulopathy must therefore be interpreted considering these differences and, importantly, validated for an obstetric population.

Several recent studies suggest that fibrinogen is an important predictor of severe PPH.[7,8] Charbit et al.[9] measured clinical and biological variables at the time of administration of second-line uterotonic treatment in 128 patients experiencing PPH. The fibrinogen concentration was the only independent variable that predicted severe PPH, as defined by the presence of 1 or more of the following criteria: (1) hemoglobin decrease >4 g/dL, (2) transfusion of 4 or more packed red blood cell (PRBC) units, (3) invasive rescue procedure such as arterial embolization or ligature, or (4) death. A fibrinogen concentration <2 g/L was predictive of severe PPH, with a positive predictive value of 100% (95% CI: 71–100), whereas fibrinogen concentration >4 g/L predicted a more favorable outcome (negative predictive value of 79% [95% CI: 68–89]).[9] Similarly, in a secondary analysis of the French cluster randomized trial comparing the incidence of severe PPH after randomized implementation of a multifaceted PPH protocol or routine care), the specificity of fibrinogen concentration < 2 g/L for predicting severe PPH was 99.3% (95% CI: 98.4–100.0) and odds ratio for severe PPH was 11.99 (95% CI: 2.56–56.06) for fibrinogen concentration <2 g/L compared with fibrinogen concentration >3 g/L.[10] Gayat et al.[11] prospectively analyzed variables predicting the need for invasive procedures such as arterial ligature or embolization or hysterectomy. A fibrinogen concentration <2 g/L was an independent predicator of need for invasive procedures.[11] Lastly, a retrospective analysis of 456 patients experiencing PPH more than 1500 mL found that fibrinogen concentration correlated

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with blood loss ($r = -0.48$, $P < 0.01$), decreasing progressively as blood loss increased.[12]

Standard coagulation screening tests such as the prothrombin time, partial thromboplastin time, and fibrinogen concentration have been mainstays of coagulation testing, but have come under criticism for their slow turnaround times and lack of validation for use in the management of massive hemorrhage. Devices such as thromboelastography (TEG® Haemometics Corp., Braintree, MA) and rotational thromboelastometry (ROTEM®, Tem International GmbH, Münich, Germany) provide an alternative to standard coagulation tests by providing a global assessment of hemostasis in whole blood, reflecting contributions from platelets, soluble coagulation factors, and fibrinogen, as well as assessing fibrinolysis.[13] A Canadian consensus conference on massive transfusion emphasized the importance of rapid serial laboratory assessment and reached unanimous agreement that there was insufficient evidence to support either standard coagulation testing or TEG®/ROTEM as superior tests for this purpose.[14] However, a systematic review of 9 randomized trials comparing TEG®/ROTEM-guided transfusion to usual care in the adult cardiac and liver transplant settings found reduced bleeding and blood component utilization, albeit with no significant evidence of reduced morbidity or mortality, in the TEG®-/ROTEM group.[15]

As low fibrinogen has emerged as a predictor of severe PPH, the need for rapid laboratory identification of hypofibrinogenemia has become evident.[16,17] Obstetric anesthesia guidelines published in the United Kingdom in 2013 identified rapid hematologic analysis as an important support service, and "strongly recommended" the availability of bedside estimation of coagulation status using devices such as TEG® and ROTEM.[16] Interest in TEG®/ROTEM assessment of PPH is driven by its potential for early diagnosis of hypofibrinogenemia and the ability to monitor the impact of fibrinogen repletion therapy.[16,17]

A number of studies have established longitudinal pregnancy and peripartum references values for both TEG® and ROTEM.[18–26] A study of 52 term parturients undergoing elective cesarean delivery examined the correlation between estimated blood loss and TEG® variables using kaolin-activated TEG® (contact activated, yielding information similar to the activated partial thromboplastin time).[13,22] Although no significant correlation was found between precesarean delivery TEG® variables and estimated blood loss, weak correlations were seen in percent change in maximum amplitude (MA) (indicator of clot strength; $r = 0.3$, $P = 0.04$) and postcesarean delivery maximum rate of thrombin generation ($r = 0.31$, $P = 0.02$) and blood loss.[22]

In another study, PPH-induced hypofibrinogenemia was identified by the decrease in FIBTEM (a ROTEM assay reflecting fibrinogen contribution to clot strength) amplitude.[27] FIBTEM amplitude predicted fibrinogen levels within 5 minutes of assay start time and identified its early decrease in hemorrhaging patients.[27] A cutoff value of FIBTEM amplitude at 5 and 6 mm, 5 and 15 minutes after the test onset, respectively, had 100% sensitivity and good specificity (85% and 88%, respectively) to detect fibrinogen concentration <1.5 g/L in PPH.[27] A case–control study of 45 massive obstetric hemorrhages compared 49 nonhemorrhagic deliveries.[28] Significant hemostatic impairment on laboratory and TEG® tests were observed after 2000-mL estimated blood loss. Correlations were noted between fibrinogen and TEG®-MA ($r = 0.70$; $P < 0.0001$) and between estimated blood loss and TEG®-MA, fibrinogen, and antithrombin ($r = -0.53$, $r = -0.77$, $r = -0.78$, respectively; $P < 0.0001$).[28]

Collins et al.[29] investigated the utility of FIBTEM amplitude and fibrinogen concentration measured by the Clauss method to predict the progression of PPH. They recruited 356 consecutive patients with a 1000 to 1500 mL bleeding and measured the progression of hemorrhage on transfusion, invasive procedures, and bleeding volume. FIBTEM amplitude was an independent predictor of a bleeding volume more than 2500 mL, red blood cell (RBC) transfusion, and duration of need for intensive care.[29]

It should be noted that TEG® and ROTEM testing are the only laboratory methods that can rapidly identify excessive fibrinolysis. Although evidence is lacking to support empiric therapy with antifibrinolytic agents in PPH, early detection of hyperfibrinolysis by TEG® or ROTEM in the setting of PPH supports their targeted use and highlights the utility of these tests in PPH.

Hydroxyethyl starch (HES) colloid solutions have been observed to impact in vivo coagulation and laboratory assessment of coagulation. Thirty percent hemodilution using HES in 20 cystectomy patients resulted in significantly decreased maximum clot firmness on ROTEM.[30] Significantly reduced clot reaction time and kinetic time by TEG® were observed in 16 patients undergoing cesarean delivery after a 1500 mL bolus of HES compared with lactated Ringer's solution.[31] Notably, in November 2013, the United States Food and Drug Administration issued a boxed warning on HES solutions in some clinical settings, citing data showing increased mortality and/or renal injury when HES was used in critically ill patients. The boxed warning also warned of increased bleeding in the setting of cardiopulmonary bypass.[32]

For centers that do not have access to TEG® or ROTEM, standard coagulation testing may be tailored for improved turnaround time. Chandler et al. reported the development of an emergency hemostasis panel composed of prothrombin time, fibrinogen concentration, platelet count, and hemoglobin concentration; this panel replaced "stat" orders for a complete blood count and coagulation screen. By making alterations in sample handling and calibration ranges, the mean (SD) turnaround time for result reporting was reduced from 35 ± 37 minutes to 14 ± 3 minutes, a time much more suitable for rapid diagnosis of hypofibrinogenemia in PPH.[33,34]

TRANSFUSION MANAGEMENT

Advances in transfusion management of massive hemorrhage have historically been driven by trauma research. The last decade has seen a number of retrospective studies in both military and civilian trauma settings reporting correlations between earlier and higher plasma-to-RBC transfusion ratios with improved survival and outcomes.[35–39] In 2013, the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study reported the results of 1245 adult trauma subjects who survived at least 30 minutes

and received at least 1 unit of PRBC in the first hour after admission, and at least 3 total units of blood products in the first 24 hours after admission. An increased plasma:RBC ratio was independently associated with improved 6-hour mortality (adjusted hazard ratio 0.31, 95% CI: 0.16–0.58, $P < 0.001$).[40] However, not all studies have found such favorable outcomes, and interpretation of observational study results is complicated by survivor bias, among other concerns.[41–43] Randomized trials, such as the recently completed Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial (ClinicalTrials.gov identifier: NCT01545232), are important for determining answers to questions on optimal blood product transfusion ratios in trauma resuscitation.

Significantly fewer studies have focused specifically on transfusion management in obstetric patients,[44–46] and expert panels have urged caution in applying observational transfusion data from trauma patients to obstetric patients.[47] A 4-year retrospective cohort study of 142 patients with PPH initially treated with prostaglandins compared subjects who required interventional procedures (such as arterial embolization or hysterectomy) with those whose hemorrhage was controlled by prostaglandins alone. A plasma:RBC ratio more than 1:2 was associated with a lower risk of requiring interventional procedures (odds ratio: 1.25, 95% CI: 1.07–1.47, $P = 0.008$).[48] Another single-center study reviewed outcomes in patients after implementation of their obstetric massive transfusion protocol.[49] The protocol stipulated initial blood product delivery consisting of 6 units PRBC, 4 units fresh frozen plasma, and 1 apheresis platelet unit, with subsequent transfusions determined by laboratory-driven algorithms.[49] Although the authors concluded that the obstetric massive transfusion protocol provided rapid and early access to PRBCs, plasma, and platelets for patients experiencing unanticipated or severe PPH, further studies are warranted to establish whether this translates into improved clinical outcomes.[49]

Recent data suggest an alternate/additional mechanism for the salutary role of plasma transfusion in trauma resuscitation. These studies examined the impact of hemorrhagic shock and plasma transfusion upon the endothelial glycocalyx, a glycoprotein complex that lines the endothelium and helps maintain its barrier function.[50] A prospective study in adult trauma patients found that high circulating syndecan-1, a marker of endothelial glycocalyx degradation, was an independent marker for mortality (odds ratio of 30-day mortality compared with low circulating syndecan-1: 1.01 [95% CI: 1.00–10.2], $P = 0.0430$). In a rat model of hemorrhagic shock, electron microscopy of mesenteric postcapillary venules showed partial restoration of the endothelial glycocalyx after plasma resuscitation, but no restoration after resuscitation with lactated Ringer's solution.[51] A 2012 prospective study observed that 5.2% of 77 trauma patients showed evidence of autoheparinization (heparinization due to shed constituents of the endothelial glycocalyx), and that these patients had significantly higher injury severity scores, syndecan-1 levels, and greater RBC transfusion rates.[52]

These studies are important explorations of potential therapeutic benefits of plasma transfusion beyond simple repletion of coagulation factors; more clinical studies are necessary to determine the impact of plasma on the endothelium in trauma patients. The endothelium in pregnant females shows increased shedding of endothelial glycocalyx markers (such as syndecan-1) compared with nonpregnant females, with even more pronounced shedding observed in pregnancy-induced endothelial disorders such as hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome.[53,54] Whether the endothelial glycocalyx plays a role in the pathophysiology of PPH and whether plasma transfusion modifies the function of the endothelial glycocalyx in this setting are currently not known. However, these studies are hypotheses generating and highlight the need to study the obstetric population separately from nonpregnant patients with massive hemorrhage.

TRANSFUSION PROTOCOLS

There is virtually unanimous agreement from professional societies on the need of multidisciplinary hemorrhage protocols for management of both trauma and PPH.[17] Such protocols ensure rapid availability of prepared blood products and a concomitant reduction in the time to transfusion and resuscitation.[55,56] Obstetric hemorrhage protocols have been recommended by the American College of Obstetrics and Gynecology, the UK Confidential Enquiry into Maternal and Child Health, the European Society of Anaesthesiology, the French National College of Gynaecologists and Obstetricians, and The Joint Commission in the United States. Stepwise, escalating interventions in these protocols combine obstetric, surgical, and medical interventions aimed at preventing PPH progression.[17,57–61] The California Maternal Quality Care Collaborative collated best practices from published and nonpublished obstetric hemorrhage protocols; notable elements of these protocols include (1) rapid release of "obstetric hemorrhage packs" to include RBCs, plasma, platelets, and cryoprecipitate; (2) availability of a local expert (hematologist or transfusion medicine physician) for consultation; (3) scripted responses for team members, which are periodically practiced and rehearsed; and (4) laboratory assessment of hematology and coagulation variables to be performed at regular intervals (e.g., every 30 minutes) until the hemorrhage is controlled.[62] Reduced maternal morbidity and mortality have been reported after implementation of obstetric hemorrhage protocols.[63,64]

PHARMACOLOGIC TREATMENT OF PPH-INDUCED COAGULOPATHY

Antifibrinolytic Therapy

Antifibrinolytic agents strengthen fibrin clots by inhibiting enzymatic fibrinolysis. Tranexamic acid is a synthetic lysine derivative that blocks the degradation of fibrin clots by plasmin and has been shown to have a moderate but significant effect on blood loss reduction in perioperative settings without significant adverse effects.[65–67] The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial randomized more than 20,000 adult trauma patients to receive empiric tranexamic acid within 8 hours of injury or placebo.[68] The study not only found a significant decrease in all-cause mortality (14.5% vs 16%, relative risk: 0.91, 95% CI: 0.85–0.97, $P = 0.0035$) as

well as mortality due to hemorrhage (4.9% vs 5.7%) in the tranexamic acid group, but importantly showed no significant increase in thromboembolic complications in subjects receiving tranexamic acid.[68]

The rationale for tranexamic acid use in PPH management was described in a meta-analysis by Ferrer et al.[69] Prospective randomized studies demonstrate a mild reduction in estimated blood loss when tranexamic acid is administered prophylactically before elective cesarean delivery or routine vaginal delivery.[70–76] Although there was a statistically significant difference in the estimated blood loss between the tranexamic acid and placebo group, the difference was small and not clinically significant. The exception was 1 study in which tranexamic acid was used in anemic parturients; blood transfusion sparing was demonstrated.[76]

One randomized, controlled, open-label study examined the efficiency of a high dose (4 g) bolus of tranexamic acid administered early in the management of PPH.[77] A small reduction of measured blood loss and duration of bleeding was observed.[77] Total blood loss at 6 hours was significantly lower in the tranexamic acid group compared with control (170 mL vs 221 mL; $P = 0.041$), but this difference is of questionable clinical significance. In the first 6 hours after bleeding onset, no differences between the groups were observed in the number of RBC units transfused, although significantly fewer total units of blood were administered in the interval from delivery to 42 days postpartum in the tranexamic acid group. A significantly higher incidence of nonsevere adverse effects such as visual disturbances and nausea was noted in the tranexamic acid group (23% vs 6%; $P = 0.03$).[77]

The available data on tranexamic acid for the treatment of PPH, while encouraging, do not address questions on safety and efficacy of empiric tranexamic acid use at the time of hemorrhage recognition. The risk of tranexamic acid-associated thrombotic events during pregnancy and postpartum was investigated in a retrospective study published in 1993. Among 2102 pregnant women with various bleeding disorders, 256 were treated with tranexamic acid and 1846 women did not receive tranexamic acid (controls).[78] Two patients in the tranexamic acid group had pulmonary embolism (1 had cesarean delivery). Three patients in the control group, all with cesarean delivery, had deep vein thrombosis and 1 had pulmonary embolism. The authors concluded that tranexamic acid was not associated with thromboembolic complications.[78] An ongoing, international, randomized, placebo-controlled trial enrolling 20,000 patients with PPH (the WOMAN trial) is investigating the impact of tranexamic acid on a composite end point of maternal death or hysterectomy.[79]

Both the World Health Organization and the European Society of Anaesthesiology guidelines recommend tranexamic acid treatment as part of PPH management.[1,17] Nevertheless, the role of tranexamic acid to prevent or treat PPH-associated coagulopathy has yet to be evaluated in large randomized studies adequately powered to assess safety, and its impact on maternal outcomes has yet to be determined. There are wide variations in dosing regimens; the optimal dose with respect to efficacy and safety remains to be determined.[65–67,69] Further studies focusing on the dose–response for hemostasis and fibrinolysis in the PPH setting are needed.

Fibrinogen Repletion

With the recognized correlation of severe PPH with hypofibrinogenemia,[7–12] the correction of hypofibrinogenemia as a potential therapeutic target has gained attention.[8,80–82] Although plasma contains small amounts of fibrinogen, cryoprecipitate and fibrinogen concentrates are preferable products for treatment of hypofibrinogenemia due to their higher fibrinogen concentration per infused volume.[8,17,83] Purified, pasteurized fibrinogen concentrate (Clottafact® LFB Les Ullis, France; RiaSTAP® CSL Behring Marburg, Germany) is currently used in many countries for the treatment of congenital and/or acquired hypofibrinogenemia.

Fibrinogen concentrates have notable differences compared with cryoprecipitate: (1) they are pathogen-reduced, whereas cryoprecipitate most often is not and (2) they can be administered within 10–15 minutes; cryoprecipitate requires 30 minutes or more for thawing and pooling.[8] However, cryoprecipitate is a heterogeneous mixture of prohemostatic proteins such as von Willebrand factor, FVIII, and FXIII; these procoagulants are present in minimal concentrations in fibrinogen concentrates.[83] No randomized trial data are available comparing fibrinogen concentrate and cryoprecipitate for treatment of hypofibrinogenemia associated with PPH. A single-center retrospective study in Ireland compared patients with major obstetric hemorrhage managed with cryoprecipitate ($n = 14$) to patients managed with fibrinogen concentrate ($n = 20$).[84] This study reviewed the impact of a practice change after the Irish Blood Transfusion Service replaced cryoprecipitate with fibrinogen concentrate in 2009 due to concerns over transfusion-transmitted infection. Both groups received similar amounts of fibrinogen repletion, with no significant difference in posttreatment fibrinogen concentration between cryoprecipitate and fibrinogen concentrate; no thrombotic events were noted in either group at discharge.[84]

The European Society for Anaesthesiology 2013 guidelines for severe perioperative bleeding recommends use of fibrinogen concentrate for significant bleeding and known or suspected hypofibrinogenemia.[17] However, there is a low level of evidence for its use in the obstetric setting and no data from randomized controlled trials are available regarding complications such as thromboembolism.[85–89] A retrospective review of 43 patients receiving fibrinogen concentrate for acquired hypofibrinogenemia included 12 cases of obstetric hemorrhage.[81] On the basis of the decreased transfusion requirements and on the significantly increased plasma fibrinogen concentration after fibrinogen concentrate infusion, the authors recommend early fibrinogen replacement in massive bleeding. Another case series described the use of fibrinogen concentrate in 6 cases of obstetric hemorrhage administered in conjunction with platelets, plasma, PRBCs, uterotonics, and obstetric intervention.[85] A single-center study in Japan reported 18 obstetric hemorrhage cases complicated by coagulopathy treated with fibrinogen concentrate; fibrinogen concentration increased approximately 40 mg/L per gram fibrinogen concentrate. No adverse events were noted, and in all cases, the hemorrhage improved.[87]

As with antifibrinolytic therapy, randomized trials are needed to validate the efficacy and safety of fibrinogen concentrate in treating PPH-related coagulopathy. A randomized trial (FIB-PPH) in Denmark has recently completed enrolling subjects in a randomized trial of women with PPH to receive fibrinogen concentrate 2 g or placebo; the primary outcome was rate of transfusion.[89] The results of this trial are highly anticipated and may provide significant evidence for the use of fibrinogen concentrate in the obstetric setting.[89]

CONCLUSIONS

This review discusses several strategies that may decrease maternal morbidity and mortality from PPH. A clear multidisciplinary protocol for obstetric hemorrhage management (including laboratory assessment, transfusion support, and use of adjuvant therapies) is recommended for improving rapid diagnosis and targeted therapy of PPH-induced coagulopathy. Although transfusion support and pharmacologic treatment are mainstays of PPH management, the low grade of most of the studies may induce bias and further study is needed to better define the role of these strategies in the obstetric population. The paucity of research on obstetric hemorrhage should serve as a call for increased efforts investigating maternal hemostasis during delivery and effective, safe interventions in PPH.

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