

## Cutting-Edge Strategies in Massive Transfusion in Patients of Obstetric Hemorrhage

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### Abstract

Obstetric hemorrhage is a life-threatening complication which may occur without warning, predictive signs and symptoms, and even in absence of predisposing conditions. It is a major cause of maternal mortality and morbidity almost invariably among all human races. One of the most important strategies in the control of obstetric hemorrhage is hemostatic resuscitation. The speed with which obstetric hemorrhage occurs makes it life-threatening, but thankfully, it can be successfully managed with blood transfusion protocol based management. Resuscitation of massive hemorrhage has shifted towards the earlier administration of higher doses of fresh frozen plasma (FFP) and reducing serious complications and mortality by limiting the conventional use of crystalloids and colloids. In this article, we explored the leading-edge strategy of use of fibrinogen concentrates, cryoprecipitates, Tranexamic acid and prothrombin complex concentrates, apart from fresh frozen plasma as a promising alternative for obstetric resuscitation and for minimizing the risks and complications of obstetric hemorrhage.

**Keywords:** Fibrinogen concentrates; Cryoprecipitates; Tranexamic acid; Prothrombin complex concentrates; Fresh frozen plasma; Recombinant activated factor VII; Hemostatic resuscitation

### Introduction

Hemorrhage is a leading cause of potentially avertable death. Obstetric hemorrhage is one of the most common causes of shock and is a significant contributor to maternal mortality throughout the world. High mortality in obstetric hemorrhagic shock is mainly because of a deadly combination of coagulopathy, acidosis and hypothermia. Massive blood transfusion protocols enable adequate blood circulation and hemostasis and thus prevent high mortality from obstetric hemorrhage. Even though there is no universal definition of massive blood loss, it can nevertheless be described as: i) blood loss exceeding circulating blood volume within a period of 24 h, ii) blood loss of 50% of circulating blood volume within a period of 3 h, iii) blood loss exceeding 150 ml/min, or iv) blood loss that necessitates plasma and platelet transfusion [1]. When critical bleeding occurs, a chief officer – a person in charge, is appointed, who carries out the most important task of medical assessment of the hemodynamic status of a patient and the most likely course of ongoing bleeding, and then declares an emergency. To effectively deal with critical bleeding in obstetric emergencies, effective communication among responsible staff is crucial, especially between obstetricians and nurses in the obstetric ICU, and between blood transfusion services and a blood bank.

### Definition of Massive Blood Transfusion

Massive transfusion is defined, in adults, as replacement of greater than one blood volume in 24 h or greater than 50% of blood volume in

4 h (adult blood volume is approximately 70 ml/kg). In children, it is defined as transfusion of greater than 40 ml/kg (blood volume in children over 1 month old is approximately 80 ml/kg). Thus, the traditional definition of massive transfusion is 20 units' RBCs in 24 h, which corresponds to approximately 1 blood volume in a 70 kg patient [2]. Another definition of massive blood transfusion is the transfusion of 10 units or more units of RBCs in 24 h [3].

Other definitions include use of 50 units of blood components in 24 h; use of 6 units RBCs in 12 h and so on. Thus, there is a high discrepancy in defining massive transfusion which results in great inconsistency in massive transfusion protocols (MTP).

### Massive transfusion protocols (MTPs)

In the past, patients with massive bleeding were initially treated with colloids and crystalloids. Use of blood products was guided by laboratory results. As a result, blood loss continued, due to delay in laboratory turnaround time and dilutional coagulopathy. Latest approach for resuscitation of patients with massive hemorrhage has advanced from reactive, supportive treatment with crystalloid, packed RBCs, and laboratory report based on use of coagulation factors, to an active and urgent use of proactive standardized protocols called MTPs. MTPs are intended towards control of lethal consequences of massive transfusion, namely coagulopathy, acidosis and hypothermia. MTPs are activated by a clinician in response to massive bleeding by and largely it is activated after transfusion of nearly 4 units to 10 units. MTPs have a predefined ratio of RBCs, FFP/cryoprecipitate and platelets units (random donor platelets) in each unit (e.g. 1:1:1 or 2:1:1 ratio) for transfusion [4,5]. Over the last decade, transfusion therapy is targeted towards achieving more balanced transfusion ratios while making efforts to reconstitute the whole blood, which has resulted in

decreased transfusion amounts, reduced complications, and enhanced chances of survival [6-10].

However, there are certain disadvantages linked with MTPs. Since MTPs are not standardized, there exist some controversies regarding the optimum ratios of RBCs: FFPs: Platelets [11-13].

### **Complications following massive blood transfusion**

Complications related to massive blood transfusion include fluid overload, coagulopathy, acidosis, thrombocytopenia, and hyperkalemia. There are also certain complications that are secondary to volume resuscitation. Inadequate resuscitation leads to lactic acidosis, disseminated intravascular coagulopathy, and systemic inflammatory response, and thereby, multi-organ dysfunction.

Overenthusiastic resuscitation may also lead to circulatory overload in patients with hemorrhagic shock, in cases where crystalloids and colloids are used initially and later replaced with blood and blood products. Patients who are transfused with crystalloids and get packed red blood cell replacement may suffer with the dilution of coagulation factors, which ends up in dilutional coagulopathy [14-16]. This may further be complicated by hypothermia and acidosis which further exacerbate coagulation dysfunction, initiating a vicious circle of dilutional coagulopathy.

Some complications result due to large amount of stored blood that is citrate toxicity, which can worsen the acidosis because of the development of hypocalcemia, and hypomagnesemia in the patient. The former may result in myocardial depression.

### **Hemostatic Resuscitation in Obstetric Hemorrhage**

Obstetric hemorrhage remains a leading cause of maternal mortality worldwide. In 2005, hemorrhage was the third leading cause of maternal death due to obstetric complications in the United States [17]. The direct pregnancy related maternal mortality rate in the United States is approximately 7 to 10 women per 100,000 live births and approximately 8% of these deaths are caused by obstetric hemorrhage [18]. Increased rates of cesarean section have resulted in increased occurrence of placental abnormalities that include both placenta previa and accreta, making peripartum hemorrhage as one of the most important potential causes for maternal mortality [19]. The high incidence of obstetric hemorrhage in the developing countries of the world is more likely reflected by its rates for expectant management and the lack of widespread availability of medicines used in obstetric procedures. Lack of availability of blood transfusion services, anesthetic services, and operating abilities also have great implications [20]. Thus, hemorrhage comprises the most common type of shock in obstetric practice.

Obstetric hemorrhage patients require aggressive measures to restore and maintain the circulating blood volume. MTPs are required to treat such patients, which involve multidisciplinary approach, including obstetricians, anesthesiologists, hematologists, and blood bank personnel [21].

Formal assessment of obstetric hemorrhage is made by observing the amount of bleeding and the patient's vital signs initially legs are raised, oxygen is administered, and resuscitation is started with crystalloids. Blood loss of up to 1500 ml in an otherwise healthy patient with obstetric hemorrhage can usually be managed by crystalloid infusion alone in case the cause of bleeding is arrested but it is difficult to assess the exact amount of blood loss. Overenthusiastic

crystalloid resuscitation should be avoided since excessive quantities of crystalloids have been associated with interstitial edema, which can involve vital organs like brain, heart and lungs, leading to grave consequences [22]. Interstitial edema due to an increased hydrostatic pressure may lead to abdominal compartment syndrome, which may also worsen renal perfusion. Also, obstetric hemorrhage patients may have DIC resulting in renal injury and overzealous crystalloid administration in such patients may further aggravate renal damage by inducing interstitial kidney edema with renal vein obliteration [23]. Knowing that chloride induces renal vasoconstriction, administration of chloride rich fluids like 0.9% saline can further deteriorate renal function [24]. A special precaution in obstetric hemorrhage is to allow hypotension with systolic blood pressures between 80 mmHg and 100 mmHg to decrease blood loss before the surgical intervention [25].

Recent studies suggest that acquired fibrinogen deficiency may be the major coagulation abnormality associated with obstetric bleeding which may be compounded by dilutional coagulopathy and hyperfibrinolysis [26,27]. In obstetric hemorrhage, tissue hypoperfusion increases the expression of thrombomodulin on endothelial cells. This receptor interacts with thrombin, leading to activation of the protein C pathway, which irreversibly inhibits factors Va and VIIIa and an increase fibrinolysis by inhibiting plasminogen activator inhibitor 1 [28]. Uterine atony, placental abruption, and placenta accreta also contribute to an increased fibrinolytic activity in obstetric hemorrhage [25].

### **Current trends in hemostatic resuscitation**

Hemostatic resuscitation has emerged as a revolutionary approach and the main idea of this approach is to restrict the administration of crystalloids and encouraging blood products for resuscitation [29]. Physiologically, hemodynamic compensatory mechanisms maintain vital organ perfusion till about 30% total blood volume loss [30]. Since it is difficult to gauge the amount of blood loss in obstetric hemorrhage, using blood products becomes the keystone of hemostatic resuscitation. Thus, the MTPs play a vital role in hemostatic resuscitation. MTPs provides early access to red blood cells, plasma, and platelets (6:4:1) for patients experiencing severe obstetric hemorrhage [31].

### **Fresh frozen plasma (FFP) and platelets**

Earlier, previously healthy women (with no preexisting disorder of hemostasis) with obstetric hemorrhage required an initial blood work – a coagulation screen and platelet count. After getting laboratory reports, the ratio of packed RBCs (PRBCs), platelets and FFP to be administered was decided. Nowadays, rapid transfusion of PRBCs in a 1:1:1 ratio with FFP and platelets is carried out to replenish the lost oxygen carrying capacity as well as circulating volume [32,33]. A rapid infusion set with an integrated warmer or a pressure cuff may be used to increase the infusion rate. Complications like dilutional coagulopathy, interstitial edema, and renal complications can be thus minimized in these patients. A recent clinical trial found no indication of adverse reactions related to increased ratios of FFP:PRBC [34].

A number of studies advocate the addition of 1 U of FFP for every 5 U of PRBCs for patients who require continued transfusion. Thrombocytopenia is likely after 1.52 times the blood volume has been replaced. The aim is to keep the platelet count more than  $50 \times 10^9/L$  by using platelet transfusion. Each unit of platelets increases the platelet count by approximately  $10 \times 10^9/L$  (Platelets are usually given in packs

of 56 U). If bleeding continues and the platelet count is less than  $50 \times 10^9/L$ , 10 U to 12 U is administered initially. Ideally, the patient should have a platelet count  $>50 \times 10^9/L$ , fibrinogen  $>50e100$  mg/dL, temperature  $>32^\circ C$  (pH $>7.2$ ), and normal ionized calcium, prior to administration [35].

### Use of recombinant activated factor VII (rFVIIa)

Recombinant activated factor VII (rFVIIa) was originally used in the treatment of hemorrhage in patients with hemophilia A or hemophilia B in whom alloantibodies were formed against factors VIII or IX after replacement therapy [36]. Usage of Recombinant Activated factor VII in cases of obstetric bleeding has made notable advances in the last more than one decade since it was first used by Moscardo et al. [37], who reported the original case in 2001. However, in a study, researchers found that there is a larger risk of arterial thrombosis in patients who receive recombinant activated factor VII [38].

It seems that routine use of factor VIIa in massive blood transfusion in obstetric hemorrhage can hardly be justified, mainly because of its adverse effects, high cost and lack of survival benefits.

### Role of fibrinogen and cryoprecipitates

In the United States, most of the fibrinogen replacement is done in the form of cryoprecipitates. Fibrinogen levels are generally higher in pregnancy (they reach up to 500 mg/dl), and therefore, low levels of fibrinogen characterize a more severe coagulopathy compared with non-pregnant individuals [39]. In case of obstetrical hemorrhage, a serum fibrinogen level below 200 mg/dl had a positive predictive value for progression to severe hemorrhage [40].

Fibrinogen is vital in clotting cascade by serving as the substrate for thrombin to generate fibrin and also by interacting with the glycoprotein IIb/IIIa on the platelet surface [41]. To achieve specific fibrinogen levels is now considered an important target during massive transfusion. Cryoprecipitate provides a more concentrated form of fibrinogen and other clotting factors (VIII, XIII, von Willebrand factor) and is faster to prepare in the blood bank. It is commonly given 10 U in doses, which is expected to raise the serum fibrinogen by 100 mg/dl [42]. It is also helpful immediately before any surgical intervention in patients with abnormal coagulation test results. The use of heparin and anti-fibrinolytic therapy is not recommended in women with DIC of obstetric origin. The goal is to maintain a fibrinogen level of at least 150 mg/dl to 200 mg/dl during obstetrical hemorrhage.

Each unit of cryoprecipitate will increase the serum fibrinogen by 10 mg/dl. Cryoprecipitate contains a higher concentration of fibrinogen than FFP. However, like FFP, it always carries a risk of viral transmission. Another disadvantage is the large amount of time required to thaw cryoprecipitate.

Fibrinogen concentrate, which is produced from pooled human plasma using the Cohn/Oncley cryoprecipitation procedure, has emerged as an effective agent in recent years since the concentration of fibrinogen in it is standardized, the product is stored as a lyophilized powder at room temperature, and can be reconstituted concretely and in less time with sterile water and infusion volumes are low, allowing for rapid administration avoiding delays in thawing and cross matching [43]. The safety profile of fibrinogen concentrate is better because viral inactivation and removal of multiple antigens and antibodies is part of the manufacturing process, and hence, risk of viral transmission is greatly reduced [44].

The most widely used fibrinogen concentrate is Hemocomplettan [45]. A number of clinical studies show that this fibrinogen concentrate is able to improve clotting and lower blood loss during obstetric hemorrhage [46,47].

Thus, administration of fibrinogen supplementation can be a safe, quick and effective measure of controlling obstetric hemorrhage.

### Tranexamic acid (TA)

Tranexamic acid (TA) is another anti-fibrinolytic agent which is widely used for prevention and treatment of obstetric hemorrhage. Various clinical trials have shown that TA can decrease blood loss more than 500 ml, and this impact was more marked in vaginal deliveries. In obstetric hemorrhage the use of TA has been seen to be associated only with mild side effects like diarrhea, nausea and vomiting, and so far, there is no evidence that could suggest the correlation between the use of TA and increased risk of thrombotic events [48].

Studies have shown a reduction of blood loss in peripartal hemorrhage with the use of TA [49]. Some studies have also described that there has been significant reduction of postpartal hemorrhage with high doses of TA [50]. The use of tranexamic acid is advised in cases of refractory atonic bleeding or persistent trauma-related bleeding [51].

### Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) seems to have a significant role in achieving hemostasis in patients with obstetric hemorrhage. PCC is a combination of clotting factors II, VII, IX and X, and protein C and S, prepared from fresh-frozen plasma. It has come to be widely used in prophylaxis and treatment of patients with hemorrhage who have vitamin K deficiency, congenital deficiency of clotting factors and liver disease [52]. It is also used as an alternative to fresh frozen plasma in case of massive hemorrhage due to overdose of anti-coagulants. Previously PCC was also used in obstetric hemorrhage patients where acquired and congenital deficiencies of clotting factors were resolved [53,54].

A very recent study has shown that in patients with vitamin K antagonists-related intra-cranial hemorrhage PCC is superior to FFP with respect to normalization of international normalized ratio (INR), and thus, smaller hematoma expansion results [55].

However, in patients with obstetric hemorrhage, role of PCC is not quite proven, and, therefore, it should not be used as base treatment alternative, in patients with normal clotting factors assay but in patient's non-responsive to massive blood transfusion protocols, it may be used as an alternative if all other options have been exhausted.

### Conclusion

Poor quantification of blood loss, lack of step-wise progression and poor utilization of blood products are issues of utmost importance in cases of obstetric hemorrhage. MTPs prevent mortality from hemorrhagic shocks, with their precision improving day-by-day by involving a multidisciplinary approach – which provides for timely identification and proper intervention, as well as prompt administration of blood products. In obstetric hemorrhage, emergence of novel strategies like use of TA, fibrinogen concentrates and prothrombin complex concentrates have not only improved the safety profile but also reduced the mortality rates. MTPs need to be revised

continuously so as to enable the implementation of a well-accepted approach to a clinical problem of paramount significance and thereby improving outcomes, striving towards perfection.

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