Usefulness of Fibrinogen Concentrate in Critical Obstetric Hemorrhage:
Up to Date with a Systematic Review

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Among the various coagulation-related factors, fibrinogen levels are the first to decrease below critical levels during massive hemorrhage. Therefore, in obstetric hemorrhage, the lost fibrinogen should be replaced at an early stage to restore hemostatic blood levels. Recently, the use of fibrinogen concentrates for critical obstetric hemorrhage has been increasing in Japan, and its efficacy in Japanese patients is similar to that reported in patients from other countries. According to the survey conducted by the Japanese Society of Obstetrics and Gynecology on the use of fibrinogen concentrates, a median dose of 3 g is generally administered, and if the effect is inadequate, additional doses are administered. The Japanese Clinical Practice Guide for Critical Obstetrical Hemorrhage (2017 revision) states that blood transfusion should be initiated as soon as possible and recommends the prompt administration of fresh-frozen plasma and red blood cells because obstetric hemorrhage can easily result in disseminated intravascular coagulation. Moreover, the use of fibrinogens is also recommended for severe hemorrhage cases.

Evaluation of the efficacy of fibrinogen concentrates in severe cases, such as a placebo-controlled, randomized and double blind study, cannot be carried out because it is unethical. However, since it is clear that fibrinogen concentrates have a high potential for reducing maternal mortality, there is an urgent need to expand the indications for fibrinogen concentrate administration.

Key words: critical obstetric bleeding, disseminated intravascular coagulation, fibrinogen, fibrinogen concentrates

Introduction

In 2019, the transfusion guidelines for patients with massive bleeding were published, in which the important clinical issues regarding transfusion and hemostatic therapy for patients with massive bleeding were identified, and a systematic review of the literature (more than 5,000 research papers) was performed to evaluate the current evidence and address clinical questions (CQ) regarding “fibrinogen concentrate,” “massive transfusion protocol (MTP),” “prothrombin complex concentrate (PCC) and recombinant activated factor VII (rFVIIa),” and “antifibrinolytic therapy.” In the guidelines, the evidence for each CQ was summarized according to 4 fields (cardiovascular surgery, injury, obstetrics, and other), and recommendations were evaluated and graded according to the Minds Manual for Guideline Development 2014. The administration of fibrinogen concentrate or cryoprecipitate is useful for treating patients with massive bleeding in the fields of cardiovascular surgery, injury, and obstetrics, and it was proposed that treatment should be considered when the...
plasma fibrinogen level is 150–200 mg/dl.

Japanese Clinical Practice Guide for Critical Obstetrical Hemorrhage 2017

In 2010, the guidelines for the management of critical bleeding in obstetrics were developed by 5 scientific societies and have been widely used in clinical practice. Six years later, as there was a need for revision because of the gap from the present situation, the guidelines were revised by the 5 scientific societies, based on the advancements in perinatal care and availability of new evidence, and then published as the guidelines for management of critical bleeding in obstetrics 2017. The major points of revision were as follows:

(i) "fibrinogen level of 150 mg/dl or lower" was added to the shock index (SI) which is calculated as heart rate divided by systolic blood pressure and (ii) consideration of the use of cryoprecipitate or fibrinogen concentrate (FC) prepared in the hospital when bleeding is persistent, although this is an off-label use. Although the target fibrinogen level was set based on the findings from observational studies, there is no clear evidence from randomized controlled trials regarding the fibrinogen level required for adequate hemostasis by replenishing the clotting factors and target fibrinogen level in the management of critical bleeding in obstetrics; thus, further studies are required.

The guidelines include a flow chart outlining the steps. The revised points are as follows:

1. With regard to the box "Blood loss 1 l or more or SI of 1 or higher," SI was emphasized and blood loss was placed in parenthesis to prevent underestimation of the initial response.

2. With respect to the actions for "Intrapartum abnormal hemorrhage," not only the hemoglobin test but also tests for platelet and clotting function were included. In addition, oxygen administration, intravertine balloon tamponade, and tranexamic acid administration (see below) were included.

3. In addition to an SI of 1.5 or higher or obstetric DIC score of 8 or higher, the "fibrinogen level of 150 mg/dl or lower" was added in parenthesis.

4. The phrase "declaration of" was added to "Critical bleeding in obstetrics," and the actions were revised. The appointment of the commander and hemostatic methods (uterine compression suture and interventional radiology) were added, assuming that these actions are implemented in high-level medical institutions.

Tranexamic acid

Tranexamic acid exerts hemostatic effects by inhibiting the activity of plasmin and preventing fibrin degradation. The use of tranexamic acid was added during the revision of the guidelines for the management of critical bleeding in obstetrics. This was based on the CRASH-2 trial, which examined the effects of tranexamic acid on injury, and the WOMAN study, which examined the effects on obstetric hemorrhage. The CRASH-2 trial reported that the administration of tranexamic acid (1 g, for 10 minutes) within 3 hours after injury and its additional administration (1 g, for 8 hours) reduced mortality and blood loss. The WOMAN study reported that the intravenous administration of tranexamic acid (1 g) within 3 hours and its additional administration (1 g) in cases of persistent bleeding reduced maternal mortality due to bleeding. However, the administration of tranexamic acid did not reduce the need for surgical treatment, such as intrauterine balloon tamponade, uterine artery embolization, removal of the placenta, and arterial ligation, and the risk of hysterectomy, indicating that the drug is not a panacea and does not replace the need for surgical hemostasis; therefore, familiarity with surgical therapy is desirable.

Uterine balloon tamponade

Uterine balloon tamponade was described by Bakri in 1992 as a method for controlling bleeding from the placental attachment site in patients with placenta accreta. At present, it is widely used as an effective hemostatic method that is readily and easily available for patients with uterine bleeding after vaginal delivery. We have used balloon tamponade for compression hemostasis in our patients, including those undergoing caesarean section. In 2011, we reported that uterine balloon insertion induced uterine contraction in patients undergoing balloon tamponade using acoustic radiation force impulse elastography. We believe that this method is effective for the management of...
bleeding after caesarean section as well. During balloon tamponade, it is important to administer uterotonic drugs, monitor vital signs (particularly, SI), and observe for any signs of external bleeding at sites around the balloon. There is a reported case of blood retention in the uterine cavity due to clogging of the drainage port of the Bakri balloon, leading to shock and hysterectomy. Therefore, careful monitoring of the vital signs is essential even after balloon insertion. In 2020, we developed and commercialized a new hemostatic balloon in collaboration with Atom Medical (Figure-1). This balloon is unique in that a guide wire is used and allows the rapid response to bleeding during caesarean section or after vaginal delivery. It is expected that the balloon will be widely used in Japan.

**Current status of the use of FC in Japan**

We conducted a nationwide survey to investigate the current status of the use of FC in patients with massive obstetric hemorrhage and provide basic data for the analysis of the usefulness of FC in women with acquired hypofibrinogenemia.

Of the 667 institutions that responded to the survey, 44 (6.6%) responded that FC was used during the period from April 2008 to March 2013, and a total of 101 patients were included in the analysis. A total of 99 (98.0%) patients survived. The causative pathologies were placental abruption in 34, atonic bleeding in 20, amniotic embolism in 12, placenta accreta in 10, cervical laceration/uterine rupture in 8, placenta previa in 4, and others in 13 patients. The median obstetric DIC score was 12 (1–35), and the blood loss at that time was 3,235 (0–9,800) ml. FC was administered once in 84 patients, twice in 16 patients, and four times in 1 patient. The dose per administration was 3 (1–15) g. The fibrinogen levels before and after the initial administration of FC were 74 (20–228) mg/dl and 187 (50–386) mg/dl, respectively, and the increase in the fibrinogen level per 1 g of FC was 32.9 ± 34.5 mg/dl/g Fib. An analysis of the increase according to disease category showed that the fibrinogen level after the initial administration of FC was less than 150 mg/dl only in the amniotic embolism group, and the increase in the fibrinogen level per 1 g of FC was the lowest in the atonic bleeding group.

The increase in the fibrinogen level per 1 g of FC was less than 10 mg/dl in 9 patients who were considered poor responders; 5 of the 9 patients required a second administration, and the fibrinogen level exceeded 150 mg/dl after the last administration in most of them. Maternal death was noted for 2 patients. Their death was due to soft birth canal laceration and uterine type amniotic fluid embolism, respectively. The final fibrinogen level was 150 mg/dl or lower in the two patients who died. In addition, all institutions requested that FC be covered by insurance.

**Current status of the used FC in other countries**

In Japan, coagulation disorder associated with massive hemorrhage can be treated with FFP; however, cryoprecipitate and FC have not been approved for use in treatment. On the other hand, in Western countries, cryoprecipitate and FC are
commonly used in clinical practice. In particular, FC is approved in Germany, the Netherlands, and Austria, among other countries, and administration of FC is recommended in guidelines in Western and other countries.\(^\text{10-16}\)

Administration of FC tends to be recommended in overseas guidelines because FFP and cryoprecipitate have the following problems: 1) compatibility of blood for transfusion is determined by the blood type; 2) there is a risk of viral transmission due to a lack of safety measures against viral infections\(^\text{17}\); 3) massive administration is required to effectively correct the fibrinogen level and may lead to excess of fluid\(^\text{18}\); 4) there is a risk of transfusion-related acute lung injury\(^\text{19}\); and 5) melting operation is needed before transfusion.

In addition, domestic and international studies have reported the usefulness of FC for the treatment of patients with hypofibrinogenemia associated with massive bleeding.\(^\text{20-25}\)

**A systematic review of the effectiveness of FC for critical obstetric hemorrhage**

We conducted a comprehensive screening of articles published up to May 2017.

1. **Participants and Method**
   - **Population**
     - Women with a major obstetric hemorrhage defined as a blood loss volume of \(\geq 1,000\) mL within 24 hours of delivery
     - Women with severe postpartum hemorrhage defined as a blood loss volume of \(\geq 1,000\) mL within 24 hours of delivery
     - Hemorrhage of approximately \(1,000\) mL and ongoing bleeding with placental abruption, placenta accreta, placenta increta, placenta percreta, placenta previa, or uterine rupture
   - **Intervention**
     - Fibrinogen concentrate transfusion of any dose within 24 hours of delivery
   - **Outcome measures**
     - Maternal mortality, successful achievement of hemostasis, change in fibrinogen level, change in DIC score, total amount of blood loss, total amount of allogeneic blood product transfused, bleeding recurrence within 24 hours, incidence of thrombosis, incidence of allergic reaction, incidence of pulmonary edema, and proportion of women requiring invasive procedures (i.e., return to theatre, uterine brace sutures, uterine tamponade balloons, radiological intervention, and hysterectomy).

   - **Study design**
     - Case-control, cohort, and cross-sectional studies and case series (>5 cases).

   - **Methods of systematic review**
     - The efficacy and safety of FC for women with severe postpartum hemorrhage were clarified on the basis of the data from randomized controlled trials or case-control, cross-sectional, or cohort studies. Severe postpartum hemorrhage was defined as a blood loss volume of \(\geq 1,000\) mL within the first 24 hours of vaginal or after cesarean delivery.

2. **Search strategy**
   - The CENTRAL, CINAL, PubMed, EMBASE, BNI, and MEDLINE databases and any other accessible relevant databases were used for the literature search.
   - The following search terms were used: hemorrhage, postpartum hemorrhage, severe bleed, massive bleed, maternal bleed, blood loss, hypofibrinogenemia fibrinogen, fibrinogen concentrate, transfusion, infusion, treatment, human, women, maternal, postpartum, and perinatal.

3. **Data analysis**
   - A meta-analysis of the studies with similar outcomes was performed to measure effects. For the outcomes presented as dichotomous data, the odds ratios (ORs) were used; for the continuous outcomes, the weighted mean difference or standardized mean difference (SMD) was used. The results are presented with their 95% confidence intervals (CIs). The data were analyzed using Review Manager (RevMan 5.3.5). P values of \(<0.05\) were considered statistically significant.

4. **Results**
   - A total of 921 articles were identified through the comprehensive literature search, of which 38 were included after screening of the titles and abstracts.
Eight articles were selected for qualitative synthesis after full-text screening, of which 3 articles with relevant subjects were analyzed (Figure-2).

1) For patients who presented with bleeding volumes of \( \geq 2.5 \text{ l} \) and required a transfusion of \( \geq 5 \) units of red blood cells, the administration of FC was more strongly associated with an increased blood fibrinogen level than that of cryoprecipitate. All the subjects had hypofibrinogenemia (fibrinogen level < 200 mg/dl).  

2) In transfusion therapy for postpartum hemorrhage with a bleeding volume of \( \geq 1.5 \text{ l} \), combined use of FC significantly reduced the total transfusion volume. All the subjects had hypofibrinogenemia (fibrinogen level < 200 mg/dl).  

3) In a retrospective case-control study at a single tertiary medical care institution, the administration of FC increased the blood fibrinogen level dose dependently and reduced the fresh-frozen plasma (FFP)/red cell concentrate (RCC) ratio and required FFP volume in patients with excessive bleeding and hypofibrinogenemia (fibrinogen level <150 mg/dl) in the obstetrics department. In addition, the administration of FC reduced the incidence of pulmonary edema, a complication of massive FFP administration. An analysis according to pathological condition revealed that the administration of FC significantly reduced the required FFP volume even in patients with placental abruption who were expected to require transfusion of < 10 units of RCC.  

### Conclusion

In clinical practice, some patients cannot achieve target levels of fibrinogen after administration of FC, and treatment is difficult in such cases. Potential reasons for the limited increase of fibrinogen level include lack of replenishment, progression of DIC (with consumption exceeding replenishment), and hemostasis failure (recurrent decline after bleeding despite the replenishment). It is also possible that multiple factors may contribute to the condition. Therefore, it is important to maintain the fibrinogen level above 150 mg/dl with appropriate monitoring.  

It is reported that a massive transfusion protocol developed by anesthesiologists contributed to improved safety in labor and delivery by providing...
a system for management of bleeding during emergency caesarean section and postpartum hemorrhage. It is expected that the establishment of such a system may reduce maternal death in Japan as well. For example, when transferring a patient with postpartum hemorrhage from a primary institution (where FFP is not immediately available) to a high-level medical institution, administration of FC at the primary institution may improve the prognosis thereafter. We therefore believe that sharing knowledge regarding the use of FC and establishment of the necessary support system are important.

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Conflict of interest

None.

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