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Review Article

A systematic review of massive transfusion protocol in obstetrics

Hiroaki Tanaka [a, *], Shigetaka Matsunaga [b], Tomoyuki Yamashita [c], Toshiyuki Okutomi [d], Atsushi Sakurai [e], Akihiko Sekizawa [f], Junichi Hasegawa [g], Katsuo Terui [h], Yasutaka Miyake [i], Jun Murotsuki [j], Tomoaki Ikeda [a]

[a] Department of Obstetrics and Gynecology, Mie University School of Medicine, Mie, Japan
[b] Department of Obstetrics and Gynecology, Saitama Medical Center, Saitama, Japan
[c] Department of Acute Medicine, Japanese Red Cross Medical Center, Japan
[d] Department of Anesthesiology, Kitasato University, Sagamihara, Japan
[e] Department of Acute Medicine, Nihon University Hospital, Tokyo, Japan
[f] Department of Obstetrics and Gynecology, Showa University School of Medicine, Tokyo, Japan
[g] Department of Obstetrics and Gynecology, Marianna University School of Medicine, Kawasaki, Japan
[h] Department of Anesthesiology, Saitama Medical Center, Saitama, Japan
[i] Department of Acute Medicine, Teikyo University, Tokyo, Japan
[j] Department of Obstetrics, Miyagi Children's Hospital, Miyagi, Japan

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ABSTRACT

Post-partum obstetric haemorrhage is a leading cause of mortality among Japanese women, generally treated with haemostatic measures followed by supplementary transfusion. Commonly used in the setting of severe trauma, massive transfusion protocols (MTPs), preparations of red blood cell concentrate (RBC) and fresh frozen plasma (FFP) with additional supplements, have proved effective in decreasing patient mortality following major obstetric bleeding events. Although promising, the optimal configuration of RBC and FFP utilized for obstetric bleeding needs to be verified. Here, we conducted a systematic literature review to define the optimal ratio of RBC to FFP for transfusion therapy during instances of obstetric bleeding. Our analysis extracted four retrospective, observational studies, all demonstrating that an FFP/RBC ratio of $\geq$1 was associated with improved patient outcomes following obstetric haemorrhage. We therefore conclude that, from the standpoint of haemostatic resuscitation, an FFP/RBC ratio of $\geq$1 is a necessary condition for optimal clinical management during MTP administration in the field of obstetrics. Hence, we further propose an optimized MTP strategy to be utilized in the setting of severe obstetric bleeding.

Introduction

Obstetric bleeding is the leading cause of maternal mortality in Japan [1]. In addition to clinical strategies designed to achieve haemostasis, transfusions are a critical component in the management of severe bleeding events. Currently, a massive transfusion protocol (MTP) is the recommended therapeutic transfusion strategy for the clinical management of severe trauma. Generally utilized following a major bleeding event, an MTP is defined by the administration of fixed proportions of red blood cell concentrate (RBC), fresh frozen plasma (FFP), and platelet concentrates (PC) to the patient. As accessibility to these various blood-derived preparations differs across countries, a diverse array of MTPs exists, supplemented with various adjuncts including cryoprecipitate, fibrinogen concentrate, and recombinant factor VIII. Additionally, it is common for individual institutions to establish in-house ratios for administration of the respective blood-derived preparations.

While these factors make systematic reviews challenging [2–6], previous investigation reported significantly reduced mortality in patients receiving MTPs containing suitable coagulation factor supplements [7]. Although early and sufficient coagulation factor supplementation can improve patient outcomes, tissue injury due to coagulopathy in these patients has already occurred prior to MTP administration [8]. Interestingly, this report further demonstrated that MTPs were significantly more effective when containing an

* Corresponding author. Department of Obstetrics and Gynecology, Mie University School of Medicine, 2-174, Edobashi, Tsu, Mie, Japan. Fax: +81059 231 5202.
E-mail address: h_tanaka@med.miyazaki-u.ac.jp (H. Tanaka).

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FFP/RBC ratio of 1.0 or greater [7]. As the pathology of obstetric bleeding mirrors that of severe trauma, an MTP with FFP/RBC ratios resembling the preparations utilized for trauma may be useful for obstetric bleeding. Therefore, in the present investigation, we have conducted a systematic literature review regarding the ratio of RBC to FFP utilized in transfusion therapies for obstetric bleeding to verify the optimal MTP configuration for obstetric bleeding. We further propose a novel treatment strategy for massive obstetric bleeding.

Materials and methods

PubMed and MEDLINE online journal databases were queried regarding articles detailing the clinical effectiveness of MTP published from October 31, 2005, to October 31, 2015. Three key phrases were utilized to query these databases: postpartum haemorrhage; obstetric haemorrhage; and massive transfusion. Only articles written in English were selected. All matching articles were independently screened by two experts. For inclusion into analysis, identified manuscripts were required to fulfil the following criteria:

1. The study background, objectives, and subjects of the analysis are clearly defined.
2. Specific transfusion therapy utilized for obstetric-related bleeding is described.
3. Methods for solving the problem at hand are clearly demonstrated in the introduction.
4. Clear demonstrations of specific hypotheses regarding each clinical variable as well as functions for deriving the clinical measurement method from theoretical models.
   None of the presented data contradict the conclusions of the study.
5. Properties, definitions, and sources of reported data are clearly demonstrated.
6. The presented data forms the basis of reliable arguments.
7. Sufficient data are reported to characterize the specific bleeding event.
8. The methods are utilised to sufficiently test the validity of the presented hypotheses.
9. A sufficient discussion of the reported data is proposed.
10. The discussion itself was determined to be valid. Specifically, no logical errors are made when presenting final conclusions.
11. Presented and referenced facts are clearly distinguishable from speculation.

All adopted articles were standardized based on PICO (population, intervention, comparison, outcome) criteria and subsequently evaluated. Further, articles were deemed to be within the field of obstetrics when at least 50% of included patients presented with obstetric diseases.

Results

Database queries utilizing the 3 key phrases described above yielded a total of 18,899 articles. Interestingly, our search did not identify any systematic reviews, meta-analyses or reports regarding randomized, controlled trials (RCT). Following our criteria-based screening protocol, only four original articles and four guidelines were extracted. Patient outcomes in these original articles included reduced transfusion volume, decreased patient morality rate, and acute lung injury (ALI). Interestingly, our database query returned no reports investigating protocol effectiveness relative to control patient populations. Although no control populations were analysed, the following five retrospective observational studies were identified by our search, all investigating the FFP/RBC ratio (FFP/RBC) in the setting of massive obstetric bleeding (Table 1).

Bonnet et al. analysed the FFP/RBC ratio in 38 cases of maternal death caused by massive obstetric bleeding. Specifically, the authors analysed the temporal administration of both FFP and RBC for patients with postpartum haemorrhage to determine peak transfusion times for both preparations. Interestingly, the report indicated that FFP/RBC rose above 1 at 12 h following haemorrhage onset [9]. Specifically, the FFP:RBC ratio in 4 out of 5 patient groups are less than 1; median FFP:RBC ratio was 0.6 (range 0–2) [9]. Further, the authors reported that blood test results of patients with coagulopathies normalised after the performance of an MTP.

Matsunaga et al. investigated 196 cases of massive obstetric bleeding necessitating aggressive coagulation factor supplementation. The study determined that when the transfusion therapy was performed to meet specific haemostatic targets, the calculated FFP/RBC ratio was 1.3 when converted from whole blood [10].

In a cohort of 181 patients in the United Kingdom, Green et al. analysed the amount of blood products utilized in instances of massive obstetric bleeding requiring transfusion therapy. In the United Kingdom, cryoprecipitate is readily available. Therefore, if cryoprecipitate is considered as five units of FFP, then the amount of FFP utilized in these patients exceeded the amount of RBC administered, essentially shifting the FFP/RBC ratio to values of 1 or greater [11].

Gutierrez et al. defined their MTP protocol as a package consisting of six units of O-negative RBC, four units of plasma (either liquid AB plasma or thawed type-specific plasma), and one apheresis platelet (PLT) unit. Favourable haematologic indices were observed post-resuscitation [12].

Tanaka et al. examined 54 patients (22 suffering mortality) with uterine artery embolization, hysterectomy, and a FFP/RBC transfusion regimen following amniotic fluid embolism complicated by coagulopathy. Interestingly, the FFP/RBC ratio was 1 or greater in transfusions administered to 40.9% of patients (9/22 patients) who died as well as 90.6% of patients (29/32 patients) surviving embolism. This finding was associated with significantly improved rates of post-embolism survival following transfusion with a FFP/RBC ratio $\geq$1 (odds ratio: 28.32; 95% confidence interval: 4.26–188.37). No significant differences were observed with respect to either uterine artery embolization or hysterectomy between the groups [13].

Four guidelines for obstetric bleeding

1. American College of Obstetrician and Gynecologists (ACOG) [14,15]

The article entitled “Preventing Maternal Death: 10 Clinical Diamonds” does not describe a specific MTP [9]. However, one of the “Clinical Diamonds” listed, informed by severe trauma treatment strategies, does recommends the generic introduction of an MTP [2,3]. Moreover, when massive transfusions are required this guideline further recommends early and aggressive transfusion at an RBC:FFP:PC ratio of 1:1:1. It concludes that therapy following an MTP may potentially facilitate the resolution of coagulopathies, hypothermia, and acidosis, all conditions that significantly increase the likelihood of patient mortality. Although not definitively proven for obstetric bleeding, similarities between the clinical courses of traumatic and obstetric bleeding lead this guideline to conclude that transfusions following an MTP utilised during traumatic bleeding could be effective in the setting of obstetric bleeding.