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REVIEW ARTICLE **OPEN ACCESS**

Evolution of the use of Therapeutic Fibrinogen Concentrate in the Massive Bleeding Guidelines

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Abstract:
Fibrinogen concentrate was approved for the first time in the European Union by the German Federal Ministry of Health on January 4th, 1966. Since then, its use has been shown to be effective and well-tolerated in numerous clinical studies with congenital or acquired fibrinogen deficiency. In this review, we analyze the evolution of the indications for the use of fibrinogen concentrate in massive bleeding guidelines in three main clinical scenarios of acquired hypofibrinogenemia, such as cardiac, obstetric, and polytrauma patients.
In cardiac surgery, the administration of fibrinogen has become a noteworthy tool in the management of perioperative haemostasis. The implementation of therapeutic algorithms, together with the use of viscoelastic coagulation tests, has allowed a faster and more personalized diagnosis and treatment of perioperative bleeding. In obstetrics, fibrinogen administration has evolved significantly over the years to a part of the management of massive obstetric haemorrhage, with early administration of fibrinogen now considered important in cases of hypofibrinogenemia during haemorrhage, helping to effectively correct coagulopathy and improve maternal outcomes. Currently, the implementation of protocols based on point-of-care viscoelastic testing has proven to be useful in the management of obstetric haemorrhage. In polytrauma patients with severe bleeding, fibrinogen administration is recommended based on clinical criteria and prior to laboratory test outcomes. After this first approach, guidelines recommend goal-directed coagulation management based on the results of viscoelastic tests and, in their absence, classical laboratory tests are recommended.

Keywords: Fibrinogen, Massive bleeding, Guidelines, Fibrinogen concentrate, Coagulopathy, viscoelastic testing, ABO blood groups.

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1. INTRODUCTION

The first license for the use of fibrinogen concentrate was granted in Brazil in 1963 [1]. Until then, fibrinogen had been debated as a mediator, marker, or predictor of cardiovascular risk [2, 3] since its first isolation in 1879 by Hammarstein, who precipitated and purified it from horse plasma [4].

Historically, the medical management of haemorrhage began in 1667 when the first transfusion to a human being from an animal was performed [5]. It was not until 1818 that an English obstetrician, James Blundell, performed the first transfusion between human beings. This milestone was completed in 1901 with the discovery of the ABO blood groups by the Austro-American immunologist and pathologist Karl Landsteiner, for which he was awarded with the Nobel Prize [6, 7]. Since then, one of the main advances in the management of haemorrhage has

been the shift from using whole blood to using specific blood components. Edwin Joseph Cohn discovered that different components present in blood could be separated through a fractionation process, commonly called Cohn fractionation [8], describing 6 major plasma fractions, where fraction I contained the highest percentage of fibrinogen.

Fibrinogen was first isolated in 1879 by Hammarstein, who precipitated and purified it from horse plasma. Behringwerke started the production of human fibrinogen concentrate in 1956. The first license for the use of fibrinogen concentrate was granted in Brazil in 1963. On January 4th, 1966, fibrinogen concentrate was approved for the first time in the European Union by the German Federal Ministry of Health [9]. However, Behringwerke had started the production of human fibrinogen concentrate earlier in 1956 [10].

There are currently 3 authorized human fibrinogen concentrates in Spain, whose trade names are FibClot®/ (LFB, Les Ulis, France) in 1.5 g presentation, RiaSTAP® P (CSL Behring GmbH, Marburg, Germany) and Fibryga® (Octapharma AG, Lachen, Switzerland), the latter two with 1 g presentations. These concentrates differ in their manufacturing processes, which also explains their different characteristics. FibClot® (LFB, Les Ulis, France), being obtained from cryosobrenadant, contains a purer fibrinogen protein [11] together with other differential characteristics, such as the need for a lower dosage (between 33-40% less depending on the patient's situation), easy reconstitution and lower sodium content which contributes to a higher clot firmness and does not contain albumin to avoid foaming, facilitating and decreasing reconstitution time (Table **1**) [11, 12].

Evidence suggests that fibrinogen concentrate has a good margin of safety in providing a standardized dose of fibrinogen [12, 13]. Its use has been shown to be effective and well tolerated in numerous clinical studies with congenital or acquired fibrinogen deficiency, including surgical patients, polytrauma, liver transplantation, and obstetrics [14-17]. These data have been corroborated by systematic reviews that further confirm that administration of fibrinogen concentrate may reduce the incidence of allogeneic red blood cell transfusion in these clinical scenarios [18, 19].

However, many of the studies currently published are of low quality and highly biased in the main variables analyzed, such as the incidence of transfusions or without being able to eliminate controversies related to the appropriate fibrinogen threshold for starting treatment with fibrinogen concentrate [1, 20]. In this regard, Ranucci and the team, in their editorial, pointed to the discrepancy between licensing, guidelines, and clinical use as open questions and gaps in knowledge that need to be addressed [20].

The main objective of this review was to analyze the evolution of the different indications for the use of fibrinogen concentrate in the massive bleeding guidelines up to the present day in the three main clinical scenarios of acquired hypofibrinogenemia according to their characteristic pathophysiology, such as obstetric patients, cardiac surgery, and polytrauma. At the time of writing this paper, an update of the 1993 systematic review was underway [18, 21].

Table 1. Differences in the biochemical composition of three plasma-derived human fibrinogen concentrates [11-13].

-	FibClot® (LFB, Les Ulis, France)	RiaSTAP® P (CSL Behring GmbH, Marburg, Germany)	Fibryga® (Octapharma AG, Lachen, Switzerland)
Presentation	1,5 gr	1 gr	1 gr
Manufacturing process	Cryosobrenadant	Cryoprecipitate	Cryoprecipitate
Sodium content	46 mg Na/g	164 mg Na/g	132 mg Na/g
Albumin content (mg Albúmina/3 gr Fg)	0,7	1449	21
Dose adults > 40 kg	(Desired level-Basal Level) x 0,043 x Kg weight	(Desired level-Basal level) x 0,058 x Kg weight	(Desired level-Basal level) x 0,056 x Kg weight
Dose emergency No basal levels	50 mgr/kg	70 mgr/kg	60 mgr/kg

1.1. Fibrinogen and Cardiac Surgery

According to the American series, 50% of cardiac surgery patients receive blood components, which accounts for 10-15% of the consumption of blood bank stores. Due to Patient Blood Managenent strategies, transfusion trends have changed since 2011 towards a lower transfusion rate, although in this surgical specialty, the decrease is lower than in other surgeries [22].

Fibrinogen deficiency during cardiac surgery favours bleeding and blood transfusion and has been associated with the need for immediate postoperative reoperation, which worsens morbidity and mortality outcomes [23, 24]. Cardiopulmonary bypass (CPB)- associated coagulopathy is multifactorial and rarely due to inadequate reversal of systemic heparin alone. The components of the bypass circuit induce systemic inflammation and multiple disturbances of the coagulation and fibrinolytic systems [25]. Low pre-operative fibrinogen levels (less than 3g/l), prolonged perfusion times, and re-interventions will favour the development of hypofibrinogenemia intraoperatively and postoperatively [26].

In recent years, the importance of viscoelastic tests in the diagnosis of coagulopathy and the determination of hypofibrinogenaemia have been emphasized due to their reliability and the possibility of obtaining early results in the operating theatre [26, 27]. Studies in cardiac surgery have shown a decrease in bleeding, a decrease in the need for transfusion in patients, an increase in the use of prohaemostatic drugs, and a decrease in surgical haemostasis time, from the start of CPB to thoracic closure following the implementation of thromboelastography [28].

Replenishment of low fibrinogen levels with fibrinogen concentrate has been shown to be effective in the treatment of surgical bleeding and in perioperative bleeding prophylaxis in a large number of studies, reducing the need for transfusion, without further complications of thrombosis associated with those presented by cryoprecipitates and more effectively than placebo and plasma [29-32]. However, other authors like Bielecen *et al*. [33] did not show significant differences in the amount of intraoperative blood loss after administration of fibrinogen concentrate, compared with placebo in patients with intraoperative bleeding during high-risk cardiac surgery.

In cardiac surgery, analyzed clinical guidelines recommend the administration of fibrinogen in cases in which the patient has a level of less than 1.5 g/L. However, some articles are somewhat more generous, recommending it below 2.0 g/L. Of particular relevance is the amount of factor XIII that each commercial preparation of the fibrinogen complex contains. RiaSTAP® P (CSL Behring GmbH, Marburg, Germany) has been studied to have an amount equal to human plasma, whereas the factor XIII activity in FibClot® (LFB, Les Ulis, France) is 1.8 times higher than in plasma [11, 12]. As FXIII has a high half-life of 11-14 days, it is possible that a higher activity contributes to some extent to clot stabilization.

In the last decade, recommendations for the use of fibrinogen in cardiac surgery have evolved significantly. Initially, fibrinogen was administered empirically in critical bleeding situations, and even clinical trials were presented with the prophylactic use of fibrinogen in cardiac surgery to reduce the risk of bleeding and transfusion [34-36].

Over time, evidence has shifted the recommendations for the use of fibrinogen towards targeted therapy based on specific diagnostic tests, especially with the generalization of viscoelastic tests, such as Point of Care, allowing goal-directed treatment. This is reflected in the Spanish guidelines, updated in 2023 with the HEMOMAS-II Consensus Document [37], which emphasizes the importance of individualization of treatment, recommending the use of fibrinogen based on the assessment of coagulopathy by viscoelastic testing. European guidelines have followed a similar way. In 2018, the European Society for Cardiothoracic Surgery and Cardiothoracic Anesthesia [38] advised against the use of fibrinogen prophylactically (class III B recommendation) but did recommend it in patients with bleeding and with hypofibrinogenemia below 1.5 g/L to reduce postoperative bleeding and transfusion (class IIB). On the other hand, the European Society of Intensive Care Medicine [39] has published recommendations that advise against early empirical use of fibrinogen in patients with massive non-traumatic haemorrhage, due to the low quality of the available evidence. However, in cases of bleeding with hypofibrinogenemia diagnosed either by viscoelastic test or by serum levels of less than 1.5 g/L, they recommend its replacement with a grade of evidence 1B (Fig. **1**).

In the United States of America, the administration of fibrinogen concentrate in cardiac surgery is considered off-label use, with cryoprecipitate being more commonly used. The clinical guidelines of the Society of Cardiovascular Anaesthesia also advise against prophylactic treatment with fibrinogen replacement products, but recommend it in cardiac surgery patients with low fibrinogen levels and bleeding at the end of CPB. Correction can be with cryoprecipitate or fibrinogen concentrate [40, 41].

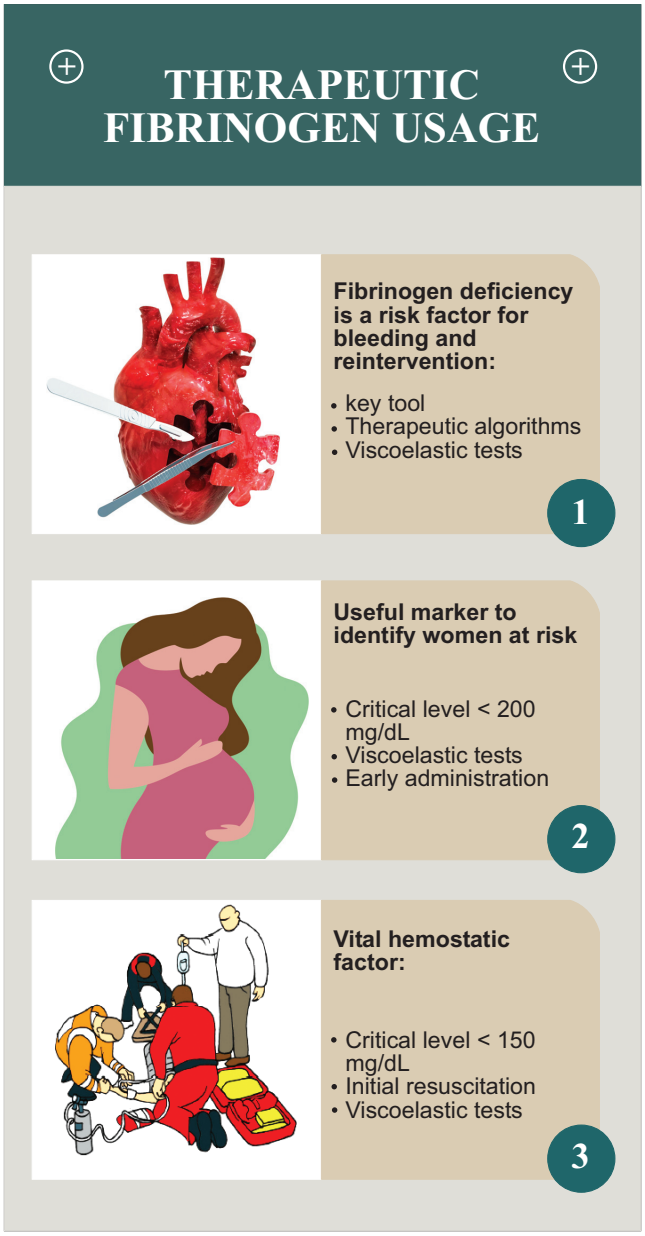

Fig. (1). Therapeutic fibrinogen concentrate usage. From Original Dra. Fornet.

1.2. Fibrinogen in Obstetrics

Postpartum haemorrhage (PPH) is defined as blood

loss of over 500 ml following a vaginal delivery or over 1000 ml after a cesarean section delivery. Postpartum hemorrhage (PPH) is the leading cause of maternal mortality in the world, affecting approximately 14 million women each year and causing some 70,000 deaths annually, which represents one in every four maternal deaths. In Spain, according to the registry carried out by the Spanish Obstetric Safety Group (GESO), the maternal mortality registered in 2022 reached 9 deaths per 100,000 births, tripling the official figure provided by the National Institute of Statistics (INE) to the WHO of 3.26 deaths. PPH was responsible for 11% of all maternal deaths [42].

Fibrinogen plays an essential role in obstetrics because of its pivotal role in blood clotting [43]. Fibrinogen concentrations are higher in pregnant women compared to non-pregnant women. These concentrations increase gradually throughout pregnancy, peaking in the third trimester [44], probably secondary to the increase in oestrogen 43. During delivery, the placenta separates from the uterus, which can lead to bleeding. Fibrinogen is needed to form blood clots and stop bleeding at the site of the detached placenta, which helps prevent excessive blood loss and its potential complications. However, fibrinogen concentration tends to decrease after delivery [45, 46], possibly as a result of increased intravascular fibrin deposition and increased fibrinogen consumption [47] associated with hemorrhage. This mechanism may also explain the observed increased risk of venous thromboembolism during the puerperium [48].

Current evidence suggests that the cut-off fibrinogen concentration to maintain adequate haemostasis is 200mg/dL [49] (Fig. **1**), and some authors have expressed reservations about the use of fresh frozen plasma (FFP) (which has an approximate fibrinogen concentration of 200mg/dL) or cryoprecipitate which can reach up to 400mg per unit 43 for fibrinogen replacement, due to the potential for circulatory overload, immune reactions or transmission of infection [50]. As a result, the use of fibrinogen concentrates has become increasingly common [51, 52].

There is a clear association between low fibrinogen levels and an increased risk of severe postpartum haemorrhage [47, 53-58]. However, establishing direct causality may be more complex [59] as low fibrinogen levels can be both a cause and a consequence of postpartum haemorrhage. The association suggests that fibrinogen may be a useful marker to identify women at risk of postpartum haemorrhagic complications. Wikkelsø *et al*. in 2013 [18] investigated the efficacy and safety of fibrinogen concentrate in patients with bleeding disorders. Although administration of fibrinogen concentrate decreased the need for allogeneic transfusion, all studies reviewed had methodological shortcomings. The same authors conducted the “FIB-PPH Trial” [60] in 2012, a clinical trial investigating the use of fibrinogen in the early stage of postpartum haemorrhage. Contrary to the initial expectation, this study did not show any benefit from the administration of concentrates as compared with placebo in reducing the requirements for red blood cell transfusion. However, we have to consider that Wikkelsø *et al*. [60] administered a fixed dose of fibrinogen concentrates when the blood loss estimation reached 1500 ml without any biological measurement of the plasma fibrinogen levels, and only 2.2% of their patients had a level of fibrinogen <2 g litre−1. Additionally, we have to consider that 15% of the bleeding population in this study could not be randomized in the trial because they were bleeding heavily, informed consent could not be obtained, and this subgroup of patients would have benefited most from the fibrinogen concentrate administration [61].

Although the association between low fibrinogen levels and PPH is clear, establishing a cause-effect relationship and recommending the widespread use of fibrinogen concentrates as a prophylactic or therapeutic measure requires further research. In this way, Deleu F *et al*. [62] showed that the use of fibrinogen concentrate in severe postpartum hemorrhage needing red blood cell transfusion during active bleeding was not associated with improved maternal outcomes. However, the evolution of massive bleeding management guidelines reflects a greater recognition of the importance of fibrinogen in obstetrics and a more personalized and evidence-based approach to improve maternal outcomes [63]. In Spain, the 2023 HEMOMAS-II document is a clear example of this trend, updating previous recommendations with a rigorous and evidence-based methodology, including the review of guidelines and relevant scientific literature. This document highlights the importance of early identification of patients who could benefit from massive transfusion protocols and the administration of fibrinogen as part of the comprehensive management of massive haemorrhage [37].

At the European level, guidelines have followed a similar pathway, integrating fibrinogen administration into protocols for the management of massive obstetric haemorrhage. The adoption of viscoelastic tests for real-time monitoring of coagulation has allowed better assessment of hypofibrinogenemia [64] and, thus, more accurate administration of fibrinogen [65]. In America, guidelines have also incorporated significant changes, recognizing the importance of fibrinogen in obstetric haemorrhage and promoting its early use in cases of severe bleeding. The trend has been towards more proactive management of coagulopathy, with a focus on prevention and early intervention to improve clinical outcomes. The convergence of these guidelines reflects an international consensus on the relevance of fibrinogen in obstetrics and its crucial role in improving maternal safety. As research continues to advance, future guidelines are likely to further refine recommendations on the use of fibrinogen, with the goal of optimising outcomes for mothers and their babies [66].

1.3. Fibrinogen in Trauma Surgery

Haemorrhage is the second leading cause of death in trauma patients and accounts for almost 50% of all trauma deaths in the first 24 hours [67].

Within the management of haemorrhage, blood volume

replacement with red cell concentrates (CH) or crystalloid or colloid solutions causes dilution of coagulation factors and platelets, leading to the establishment of a coagulopathy known as “dilutional coagulopathy” [68]. Furthermore, polytrauma-associated haemorrhages are associated with another type of coagulation disorder called “trauma-induced coagulopathy”, which encompasses a number of haemostatic disorders, including hypofibrinogenemia and hyperfibrinolysis, impaired platelet function and endothelial activation [69, 70].

The application of massive transfusion protocols based on standardized ratios of FFP, platelets, and CH has been associated with improved survival in trauma patients, and international guidelines have included them in their recommendations for years. However, transfusion of blood components can lead to complications, such as acute respiratory distress syndrome, transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), pathogen transmission, and adverse immunological reactions. Recent association studies indicate that the use of multiple blood components reduces long-term survival [71, 72].

Fibrinogen is a vital haemostatic factor that, in the context of tissue or vascular injury, converts to its active form, fibrin, to form a stable clot. Of all the clotting factors, fibrinogen is found in plasma in the highest concentration and has been shown to be the most and earliest affected by trauma-induced coagulopathy. Decreased plasma fibrinogen concentration has been shown to be associated with worse outcomes, while survival increases with its replenishment. Mitra *et al*. [73] identified that in critically hemorrhaging patients requiring massive transfusion, several factors as independent predictors of mortality are included, such as hypothermia, thrombocytopenia, increased INR, prolonged partial thromboplastin time, low fibrinogen level, low pH, and low bicarbonate levels. Stinger *et al*. [74] detected hypofibrinogenemia in 73% of patients with a haemoglobin less than 10 g/dl on admission and in 63% of those with a base excess of less than -6 mmol/L. Rourke *et al*. [75] also observed hypofibrinogenemia in 41% of patients with associated hypotension on admission to the hospital. This study showed that in addition to hypotension, the severity of shock and injury in polytrauma patients was also associated with low fibrinogen levels.

Therefore, in recent years, in addition to considering fibrinogen as a fundamental parameter in all polytrauma patients, there has also been a change in the bleeding guidelines regarding the indications for fibrinogen administration in polytrauma patients with haemorrhage [76-78]. The latest European guidelines of 2023 recommend initial treatment of coagulation disorders in patients with massive haemorrhage by administration of fibrinogen or cryoprecipitate during initial resuscitation, even before obtaining the results of laboratory tests, with a grade 1C recommendation. Therefore, 2g of fibrinogen is proposed to be administered on admission based on clinical criteria: systolic pressure <100mmHg, lactate >5 mmol/L, base excess <-6 or haemoglobin <9g/dL [79].

We should also consider that fibrinogen concentrate is inactivated against viruses (differences in the number of viral inactivation steps among fibrinogen concentrates as stated in the summaries of product characteristics) and therefore poses less of a threat of introducing pathogens into the patient, and the risk of TRALI is greatly reduced, as fibrinogen concentrate is potentially free of antibodies. Finally, fibrinogen concentrate offers the possibility of replacing fibrinogen at a much higher concentration than cryoprecipitate and FFP. Thus, the administration of FFP is discouraged whenever FFP is available due to the large amount of FFP volume required to raise fibrinogen levels above 1.5 - 2 g/L [71, 72].

After this first approach to the polytrauma patient, in recent decades, all guidelines recommend goal-directed coagulation management based on the results of viscoelastic tests and in their absence by classical laboratory tests [76-78]. The threshold has evolved over the years, and while in the past the threshold was established if fibrinogen values were critically low (<1g/L), today it is recommended to replenish fibrinogen if its plasma concentration is less than 1.5g/L with a grade 1C recommendation (Fig. **2**) [37, 78-80].

Regarding the recommended dose of fibrinogen, initial supplementation with 3-4 g is generally recommended. The HEMOMAS Consensus Document [37] advises individualising the dose of fibrinogen according to the severity of the haemorrhage, as well as the initial plasma concentration of fibrinogen. Thus, if plasma fibrinogen values are used as a guide, the following formula should be used: fibrinogen dose (g) = desired fibrinogen increment (g/L x plasma volume (L)). Assuming a plasma volume of 0.04 L/kg, this formula shows that for each gram of fibrinogen administered, plasma fibrinogen increases by 0.25-0.28g/L on average [75]. However, when fibrinogen replacement is guided by rotational thromboelastography, the dose is calculated as follows: fibrinogen dose (g) = target FIBTEM-MFC(mm)-actual FIBTEM-MFC(mm) × weight (kg)/140.

CONCLUSION

We can, therefore, conclude that fibrinogen deficiency acquired during CPB is common and is an important risk factor for bleeding and reoperation. An analysis of the literature published in recent years shows that the administration of fibrinogen in cardiac surgery has evolved significantly and has become a noteworthy tool in the management of perioperative haemostasis. The implementation of therapeutic algorithms and the use of viscoelastic coagulation tests have allowed a faster and more personalized diagnosis and treatment of perioperative bleeding, providing information on a patient’s coagulation status in 10 - 15 minutes, compared with the classical laboratory tests (activated partial thromboplastin time and prothrombin time).

In obstetrics, fibrinogen administration has evolved significantly over the years from a poorly understood measure to a part of the management of massive obstetric haemorrhage, with early administration of fibrinogen now considered important in cases of hypofibrinogenemia

during haemorrhage, helping to correct coagulopathy and improve maternal outcomes effectively. Furthermore, advances in the understanding of the physiology of pregnancy and coagulopathy have led to the implementation of protocols based on point-of-care viscoelastic testing, which have proven to be useful in the management of obstetric haemorrhage.

In the initial resuscitation of a polytrauma patient with severe bleeding, prior to obtaining laboratory test results, fibrinogen administration is recommended based on clinical criteria. After this first approach, guidelines recommend goal-directed coagulation management based on the results of viscoelastic tests and in their absence by classical laboratory tests, with the current threshold for fibrinogen replenishment being less than 1.5 g/dL. Furthermore, compared to FFP, it is recommended to replenish with fibrinogen concentrates whenever available.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

CPB = Cardiopulmonary Bypass

PPH = Post Partum Haemorraghe

TRALI = Transfussion Relataed Lung Injury

TACU = Transfussion Associated Circulatory Overload

FFP = Fresh Frozen Plasma

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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