PERSPECTIVES

CONTEMPORARY APPROACH IN BLEEDING AND TRAUMA COAGULOPATHY MANAGEMENT: FIBRINOGEN AS A MAGIC BULLET

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Abstract

Acute hemorrhage results in blood loss followed by consummation of procoagulants, as well as in circulating clotting factors. In acute bleeding, significant amounts of fibrinogen are lost, therefore both cellular and cascade phase of coagulation could be affected leading to coagulopathy. Fluid resuscitation in bleeding patients leads to dilution coagulopathy lowering the levels of circulating coagulation factors including fibrinogen even more further starting a vicious cycle. Many studies have shown that fibrinogen levels below 1g/l in bleeding patients are associated with bleeding and worse outcome suggesting that fibrinogen levels must be measured in trauma patients serving as a threshold for initiation of fibrinogen replacement therapy. Exogenous fibrinogen as a treatment option in critically bleeding patients with low fibrinogen levels has been shown to decrease transfusion needs. Algorithm-based individualized goal-directed use of fibrinogen resulted in highly significant reduction in transfusion needs, adverse outcomes, in certain studies even mortality, and where investigated - reduced costs, with high safety levels at the same time. It has been well established that low fibrinogen levels in patients who undergo cardiac surgery, liver transplantation surgery, in obstetrics, as well as in trauma patients are associated with higher bleeding risk demanding a proactive approach in early fibrinogen supplementation and replacement in order to a better outcome achievement. Although traditionally fibrinogen replacement and supplementation were performed via administration of fresh frozen plasma or cryoprecipitate, the use of lyophilized fibrinogen (concentrate) has become more prevalent in many countries. Recent reports relating to the efficacy of fibrinogen concentrate, suggest that it is a viable alternative to traditional hemostatic approaches, also being a cost-effective when compared to other replacement options which should be considered in a daily practice as well.

Key Words: *Bleeding; Fibrinogen; Trauma Coagulopathy.*

Introduction

Fibrinogen as a coagulation factor plays a crucial role in both cellular and fluid phase of the coagulation process. In the cellular phase fibrinogen by itself has a pivotal function in platelet activation via Glycoprotein IIb/IIIa, while in the fluid phase it is cleaved by thrombin to monomers of fibrin which polymerize in between resulting in formation of the clot. Since, in bleeding patients plenty of coagulation factors are lost, fibrinogen is most prominently lost, precipitating coagulopathy. Not only coagulation factors, but thrombocytes are lost as well in cases of acute blood loss. Thrombocytes play significant role in the cell phase where they promote thrombin generation on their own surface. So, in cases of thrombocytopenia where thrombin generation is questioned it is more than essential that at least the levels of fibrinogen are within normal ranges in order to avoid hemostasis devastation.

Trauma Coagulopathy, Bleeding and Fibrinogen Supplementation in Clinical Practice: an Evidence-based Review

It has been estimated that around 24-34% of trauma patients develop Trauma Induced Coagulopathy (1) which is described as an inflammatory condition of hemostasis derangement involving hypofibrinogenemia, coagulation factors depletion, increased systemic endothelial activation, platelet dysfunction, increased tPA activity and dysregulation of Protein C function (2). Trauma induced coagulopathy (TIC) is characterized with inability for clot forming due to lack of coagulation factors because of their consumption, shock, acidosis and endothelial damage. According to many guidelines the mainstay in treatment of Trauma Induced Coagulopathy is application of tranexamic acid, fresh frozen plasma, cryoprecipitate and coagulation factors concentrates. Usage of prothrombin complex concentrates and human fibrinogen concentrates have many benefits over fresh frozen plasma and cryoprecipitate supplementation as they offer a bigger and standardized concentration of coagulation factors with lower rate of viral infections transmission, not needing blood type matching. Since clear definition of trauma induced coagulopathy is lacking, difficulties in recognizing this entity could arise. Therefore, on time treatment could be questioned in many cases. Until now the definition for trauma induced coagulopathy was based on clinical aspects like presence of diffuse bleeding from injured and non-injured sites with laboratory findings of prolonged prothrombin time (PT). In reality in many cases PT is not prolonged while still patients are bleeding diffusely leading to a coagulation factors consumption. Nevertheless, treatment should be started immediately in patients who are bleeding despite the absence of laboratory evident disorders in hemostasis. When it comes to laboratory values that could be used in definition of trauma induced coagulopathy, many authors have different opinions making the definition of this condition even more complex and uncertain. Actually, analyzing the results of PT, aPTT and INR were widely used but at different thresholds according to different authors. According to Peltan et al., INR values greater than 1.5 suggest presence of trauma induced coagulopathy, while Frith et al., consider that INR greater than 1.2 should be considered as a threshold for initiation of therapy (1). Another group of authors suggest that extrinsic pathway viscoelastic tests like EXTEM with CA5<40mm and fibrinogen thromboelastometry FIBTEM <9mm are indicating presence of

Trauma Induced Coagulopathy. In order to be more consensual when speaking about TIC, authors have created a scoring system that stratifies TIC patients into 3 groups according to severity of the condition. This stratification of severity corresponds to a patient with bleeding, shock and one of the following: TIC 1: fibrinogen level <1.5g/L; TIC 2: fibrinogen level <1.5g/L and INR >1.5; TIC 3: fibrinogen level <1.5g/L and INR >1.5 with platelet count <100,000×109/L (1).

Hypofibrinogenemia detected in trauma patients has been identified as an early predictor for massive transfusion, therefore early fibrinogen supplementation has been strongly recommended (3). Since it is well known that hypofibrinogenemia is a parameter who indicates a need for starting a Massive Transfusion Protocol as soon as possible, viscoelastic tests for FIBTEM as a point of care test could have a great impact in early and on time initiation of massive transfusion. Massive transfusion protocol is indicated in patients with bleeding and shock, hemodynamically unstable patients, those with hemoglobin levels lesser than 9g/dl, base deficit greater than -6mmol/l and patients with FIBTEM <10mm. According to most of the recommendations and guidelines, a massive transfusion protocol should start with application of Tranexemic acid as soon as possible. Many studies have proven that application of Tranexemic acid could lower the mortality in trauma patients. According to the CRASH 2 study, application of Tranexemic acid within 8 hours and according to CRASH 3 study application of tranexamic acid within 3 hours of trauma, could significantly lower the risk of death due to bleeding in trauma patients and patients with traumatic brain surgery respectively.

During acute hemorrhage, fibrinogen is the first coagulation factor that reaches critically low levels promoting even more significant bleeding and coagulation factors consumption. Therefore, hypofibrinogenemia has been associated with a poor outcome in trauma patients and was identified as an independent mortality predictor. Fibrinogen is lost very early after trauma happens, leading to coagulopathy, therefore according to most of the recommendations and European trauma guidelines, early supplementation after hospital admission even before laboratory testing has been recommended (1). Fibrinogen supplementation in bleeding patients resulted in significant reduction of transfusion needs, adverse outcomes, and in certain studies it was associated with reduced mortality (4). European trauma guidelines recommend RBC:FFP or RBC:FHC as an initial treatment intervention. Since Fibrinogen Concentrate offers a significantly higher concentration of fibrinogen delivered in a small amount of liquid with significantly less risk for infection transmission, according to the European Expert meeting, it is recommended to be used instead of FFP when treating patients with TIC, delivering to the patient a well-known and fixed concentration of fibrinogen as soon as possible. Supplementation of Fibrinogen either as Fibrinogen Human concentrate or Cryoprecipitate is recommended in bleeding patients with hypofibrinogenemia rather than supplementation with FFP which is not recommended according to the European trauma guidelines. According to the study of Kikura M. et al., patients who have received fibrinogen supplementation either as a cryoprecipitate or fibrinogen concentrate have lower incidence of bleeding 50% versus 75% in the control group who did not receive any type of fibrinogen supplementation. Therefore, 2–3g of fibrinogen replacement reduces the incidence of major bleeding in patients with hypofibrinogenemia during cardiopulmonary bypass in thoracic aortic surgery (5). A meta-analysis that has included 14

randomized controlled trials, where fibrinogen concentrate was given, concluded that the patients that received fibrinogen concentrate have significantly lower mortality rate and lower need of blood transfusion, as well as they have experienced significantly less bleeding. Furthermore, this study has highlighted the fact that no differences in the rate of thrombotic events and myocardial infarction were observed in patients receiving fibrinogen compared to those who did not receive fibrinogen (6). In other words, fibrinogen infusion resulted in an increase in fibrinogen concentration and increased clot stability, while when it was combined with platelet transfusion, shortening of clotting time, increased clot stability and improved platelet aggregation were observed. This result confirms that supplementation of fibrinogen together with platelets improves coagulation and platelet aggregation followed by significantly less bleeding in patients undergoing cardiac surgery (7). Another study has confirmed that administration of fibrinogen has been associated with better clot firmness and lowered need for substitution of blood products as well (8).

It has been reported that fibrinogen supplementation reduces the need for blood products transfusions by 53% (9). Regarding fibrinogen supplementation, German and British guidelines recommend fibrinogen supplementation in patients with fibrinogen levels lower than 1.5g/l in dose of 3-4g. According to the European consensus, human fibrinogen concentrate is recommended as the first line therapy in bleeding patients with hypofibrinogenemia. They recommend that fibrinogen should be administered even in bleeding patients in which fibrinogen levels are above the threshold value. Many societies have published recommendations for application of Prothrombin Complex Concentrate (PCC) in trauma patients where criteria for TIC are met in order to support thrombin generation and stability. Since in the very early stages of hemorrhage thrombin generation is not impaired, rather potentiated, therefore application of PCC should not be the first goal during the treatment of TIC, but hypofibrinogenemia should be firstly corrected instead. Preoperative levels of fibrinogen strongly corelate with the amount of bleeding as well as with the need for blood transfusion. According to this study patients who undergo spinal surgery with preoperative levels of fibrinogen lower than 1.9g/l will bleed significantly more than those with higher preoperative levels of fibrinogen (10). Another study confirmed that lower levels of fibrinogen in the preoperative setting in patients who undergo spinal fusion surgery could identify the patients with increased bleeding risk (11). Therefore, preoperative testing of fibrinogen levels in patients undergoing major surgery could reveal if the patient is prone to bleeding and its possible benefit of early supplementation of fibrinogen. Since lower fibrinogen levels were found to be associated with bleeding in patients who undergo liver transplantation, preoperative measurement of fibrinogen should be assessed in order to recognize those patients where fibrinogen administration will be beneficial (12).

Traditionally, fibrinogen supplementation was done with application of fresh frozen plasma (FFP) and/or cryoprecipitate, where FFP contains 2.0 to 4.5g/L of fibrinogen while cryoprecipitate contains 15 to 17g/L (13). Human fibrinogen concentrate is made from pooled human plasma and can be found in single‑use vials containing 900 to 1300mg lyophilized fibrinogen concentrate powder for reconstitution. Human fibrinogen concentrate should be applied with an infusion rate of 10-15min for 1g of Fibrinogen compared to the FFP and Cryoprecipitate which need at least 30 minutes for thawing.

Cost effectiveness of fibrinogen concentrate has been questioned recently, since the price of the human fibrinogen concentrate is higher than the price of cryoprecipitate as a source of fibrinogen. Beyond the price of a single dose of Fibrinogen concentrate in comparison to Cryoprecipitate, there are multiple interventions, transfusions and care that when taken all at once can make the cost of fibrinogen concentrate versus cryoprecipitate more objective and real. Apparently, the question about the cost and effectiveness of fibrinogen concentrate versus usage of cryoprecipitate as an alternative source of fibrinogen, was examined in the study of Abrahamyan L. where 495 patients were included and randomized in 2 groups receiving Fibrinogen concentrate versus Cryoprecipitate due to cardiac surgery. In both groups number of transfusions in the first 24 hours and in the 7 postoperative days, as well as total cost of health care services and hospital stay were measured. According to the results of the study, in the group where Fibrinogen concentrate was given, lower amount of transfusions were met in comparison to cryoprecipitate group in both times at 24 hours as well as at the 7th day (14). They have found that the cost for transfusions in the first 7 days was lower in the fibrinogen group with 2.280$ versus 2.770$ in the group of patients receiving cryoprecipitate. The cost of hospital treatment at day 28th was lower in the fibrinogen group than in the cryoprecipitate group with total amount of 38.180$ versus 38.790$. Therefore, application of fibrinogen concentrate in hypofibrinogenemic patients is more suitable and cost effective when compared to cryoprecipitate delivering fixed and predictable dose of fibrinogen in more safe form with lowered risk for infection transmission which is not the case with cryoprecipitate where the amount of fibrinogen delivered to the patient is not predictable neither standardized while transmission of infections is still possible (14). Human fibrinogen concentrate has many advantages over cryoprecipitate when treating hypofibrinogenemia. Actually, HFC is lyophilized and stored at a room temperature or refrigerated versus cryoprecipitate which is frozen needing more time for preparation due to proper thawing. Cryoprecipitate has a shelf life of 1 year while HFC has 3 years of shelf life (15). When we talk about near patient storage, rapid preparation and injection, human fibrinogen concentrate is superior to cryoprecipitate. Most importantly HFC is a pathogen reduced composition versus cryoprecipitate, where pathogen reduction and inactivation could be questioned. Fibrinogen content is another important task worth discussing because HFC is a preparation that offers uniform fibrinogen content to be delivered to the patient, which is not the case when cryoprecipitate is given considering that fibrinogen content could be highly variable and unpredictable. Pureness is another advantage of HFC regarding the process of preparation where fibrinogen is highly purified, while numerous impurities could be met in cryoprecipitate preparation which contains many other factors that could interfere with hemostasis. Actually, cryoprecipitate contains significant amount of factor XIII which could be very beneficial in bleeding control, but other factors, such as Factor VIII, platelet microparticles and vWF could elevate the risk for thrombosis. Regarding the risk for thrombosis in cardiac patients the FIBRES study has shown that usage of HFC in bleeding patients is associated with lower rate of arterial and venous thrombotic events when compared to cryoprecipitate. In another study in patients undergoing abdominal surgery, it was found that the patients who received HFC had 0% of thrombotic events versus 30% when patients were receiving Cryoprecipitate. Another difference between HFC and cryoprecipitate is that HFC acts on the process of fibrin polymerization while cryoprecipitate interferes in all phases of hemostasis which may be considered as an advantage

or disadvantage too, depending of the case. Cryoprecipitate after thawing has a significantly shorter life span of 4-6 hours when compared to HFC after reconstitution which life span is 24 hours (15). Order to needle time has been discussed as well, which is considered to be 30min when HFC is given to the patients versus 2.7 hours after trauma in the group of patients who had received cryoprecipitate, which is significantly longer time and according to many authors is considered very late because those patients have already received in average 8 units of blood or blood products (15). Real disadvantage of HFC over cryoprecipitate is the higher price that could be an issue in a low-income country. In the study of Ayaganov et al., 88 patients undergoing cardiac surgery were randomized to receive Cryoprecipitate or HFC in order to manage bleeding, so 48 hours after administering either of the preparations, no significant differences between plasma concentration of fibrinogen were observed while treatment of patients with Cryoprecipitate was significantly more expensive with 1505$ versus 631$ in comparison to the group where HFC was administered showing again that HFC is non inferior to Cryoprecipitate when treating bleeding patients but is significantly cheaper (16). Another study have examined the effectiveness of HFC versus Cryoprecipitate in neonates undergoing cardiac surgery where no significant differences in clot degradation were observed while significantly less blood transfusions, bleeding and thrombosis after CPB were observed in HFC group (17). Regarding the acutely bleeding trauma patients, administering HFC in comparison to Cryoprecipitate was found to be associated with lower need for blood and blood products transfusions and shorter ICU and In-hospital length of stay while no differences in complications and mortality was observed between both groups (18). Moreover, the effect of HFC application in patients with trauma induced coagulopathy was recently examined in RETIC study ("Reversal of Trauma-induced Coagulopathy using First-line Coagulation Factor Concentrates or Fresh-Frozen Plasma") where patients were randomized to receive HFC as a first line therapy either other sources of coagulation factors as FFP or PCC. The results have shown that HFC given in patients with Fibrinogen levels greater than 1.0g/l in dose of 63mg/kg only once sufficiently has corrected the plasma levels of fibrinogen as well as ROTEM results, while those patients with fibrinogen levels lower than 1.0g/l needed doubled dose of HFC or approximately 126mg/kg to achieve normalization of plasmatic fibrinogen levels as well as ROTEM testing results (19). According to the RETIC study, early achievement of plasmatic fibrinogen concentration greater than 2.0g/l is associated with better clot firmness, significantly lower rates of massive transfusion and has prevented lowering of platelet count followed by lowered rate of platelet transfusion. This study has concluded that despite the body weight, initial fibrinogen levels have significant impact when proper dosing of HFC is questioned in order to prevent massive blood loss (19).

Conclusion

Many of the above-cited studies have highlighted the advantages of HFC when used in special occasions where objective indication exists. According to all previously mentioned, we can conclude that Human Fibrinogen Concentrate is a safe source of fixed concentration of purified fibrinogen offering predictable correction of plasmatic fibrinogen concentration when dosed properly without any significant prothrombotic events even in patients undergoing cardiovascular interventions. Advantages of HFC over other alternative sources of fibrinogen, such as Cryoprecipitate and Fresh Frozen Plasma, have been clearly discussed making HFC the

most reliable source of Fibrinogen in clinical practice. The significance of on-time fibrinogen supplementation in bleeding patients and those experiencing TIC has been entitled in all guidelines and European Trauma Consensuses recommending the usage of HFC as a first line therapy in order to prevent massive transfusion and many other bleeding associated complications.

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