VIA MEDICA

REVIEW ARTICLE

Journal of Transfusion Medicine
2014, tom 7, nr 1, 15–19

ISSN 1689–6017

Plasma alternatives in acquired bleeding disorders — factor concentrates

Manuela Gomes, MD

Hemovida, Sociedade Gestora de Serviços de Medicina Transfusional

Abstract

Much has been said and published in the past years about new approaches to coagulation management in acquired bleeding disorders. This is particularily true in the perioperative setting and in trauma induced coagulopathy, which are associated with severe bleeding and massive blood transfusion rates that might have deletirious effects, such as incresead morbidity and mortality.

Our current understanding of hemostasis and new diagnostic tools such as thromboelastography and rotational thromboelastometry (point-of-care tests) offer insight into the in vivo processes ongoing in a bleeding patient. It has been demonstrated that when a patient bleeds, fibrinogen is the first coagulation factor to reach really low levels, insufficient for formation of a clot. Management of massive blood loss may also require the administration of other coagulation factors like those present in Prothrombin complex concentrates (PCC) and plasma.

In resume, the overall use of factor concentrates for management of acquired bleeding disorders has gradually increased during the last several years, mainly that of fibrinogen concentrate. Parallel to this trend we observe the reduction in the number of transfusions of fresh frozen plasma (FFP) and other blood components.

Key words: perioperative bleeding, clotting factor concentrates, point of care tests

J. Transf. Med. 2014; 7: 15–19

Introduction

Much has been said and published in the past years about new approaches to coagulation management in acquired bleeding disorders. This is particularily true in perioperative setting and trauma induced coagulopathy associated with severe bleeding and higher blood transfusion rates [1].

In Portugal as in other countries, these situations are a matter of great concern, particularily because massive blood tranfusions are associated with risks such as increased morbility and mortality [2]. The current trend in the management of coagulopathic patients is therefore to seek alternatives to blood components, in particular clotting factor concentrates.

The aim of this paper is to explain the scientific rationale that justifies the benefits of using factor concentrates in these situstions and to present the state of the art in this situations. Reference to the current situation in Portugal is made throughout the text.

Hemostasis

The Y-shaped cascade model of coagulation was proposed in the 1960s by different groups of investigators after decades of research on the hemostatic mechanism. In this model enzymes cleave proenzymes to generate the next enzyme in the cascade. Finally this leads to the formation of a fibrin network and then to the generation of a stable haemostatic clot (Figure 1).

The coagulation cascade process was split into two pathways: the extrinsic and the intrinsic pathway. Both of them activate factor X to factor Xa;

Address for correspondence: Manuela Gomes, e-mail: amdrgv@gmail.com

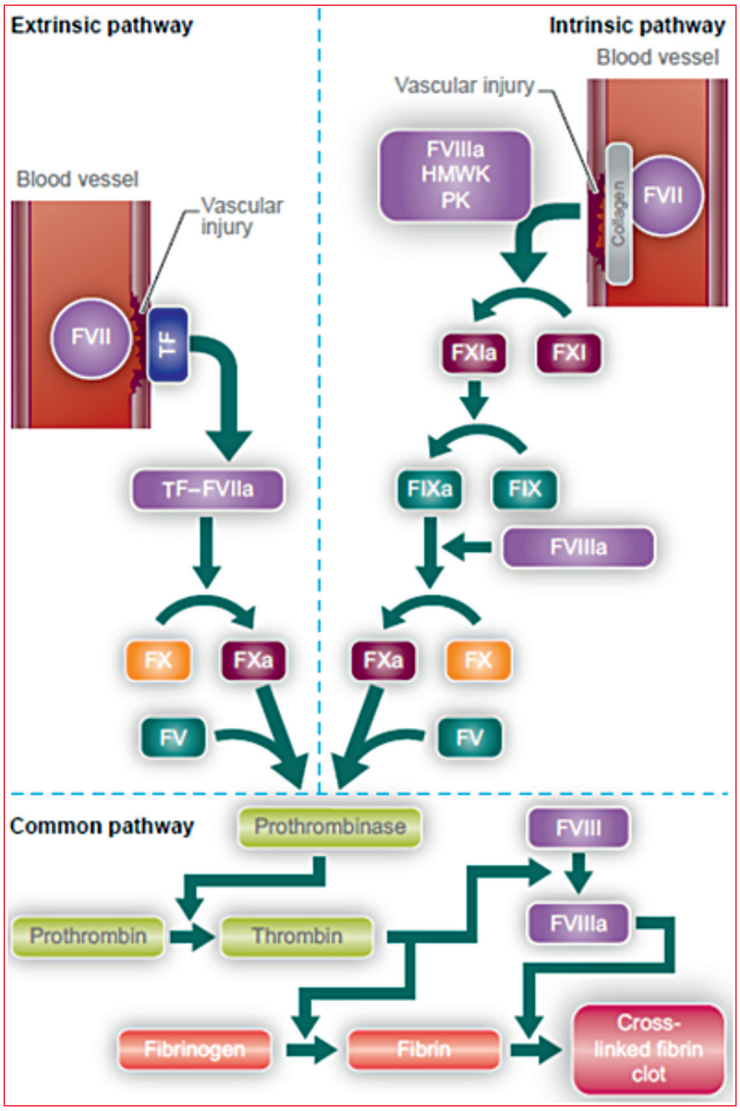

Figure 1. The coagulation cascade in its classical Y-shape (adapted by: Gailani D. & Renn T. 2007; Mackman N. 2007; Tortora G.J., Derrickson B. 2006; Synapse B.V. 2009; Keularts I.M. 2001; Monroe D.M. & Hoffman 2005)

the latter in turn activates prothrombin to thrombin, which then cleaves fibrinogen to form fibrin [3].

The cascade model is extremely helpful for the understanding of the coagulation enzymatic steps and provides an adequate explanation of the sequence of events in a static system where blood does not interact with vascular wall or cell surfaces. This model may also suggest that the extrinsic and intrinsic pathways operate independently whereas clinical manifestations in patients with congenital factor deficiencies contradict this concept [3]. The coagulation cascade model therefore does not adequately explain the mechanisms leading to hemostasis *in vivo*.

The currently developed model of hemostasis replaces the classical model of coagulation cascade and takes into account the vital role of blood components such as platelets and microparticles in blood coagulation processes, because the speed at which enzymatic reactions proceed are to a large extent affected by the presence of a viable cell membrane. The generation of thrombin, which is essential for this process, occurs directly on the activated platelet surface, and both pathways are parallel generators of FXa. The cell-based model of coagulation provides four distinct phases: initiation, amplification, propagation and stabilization [3]. In primary hemostasis which immediately follows vascular injury, collagen and other substrates

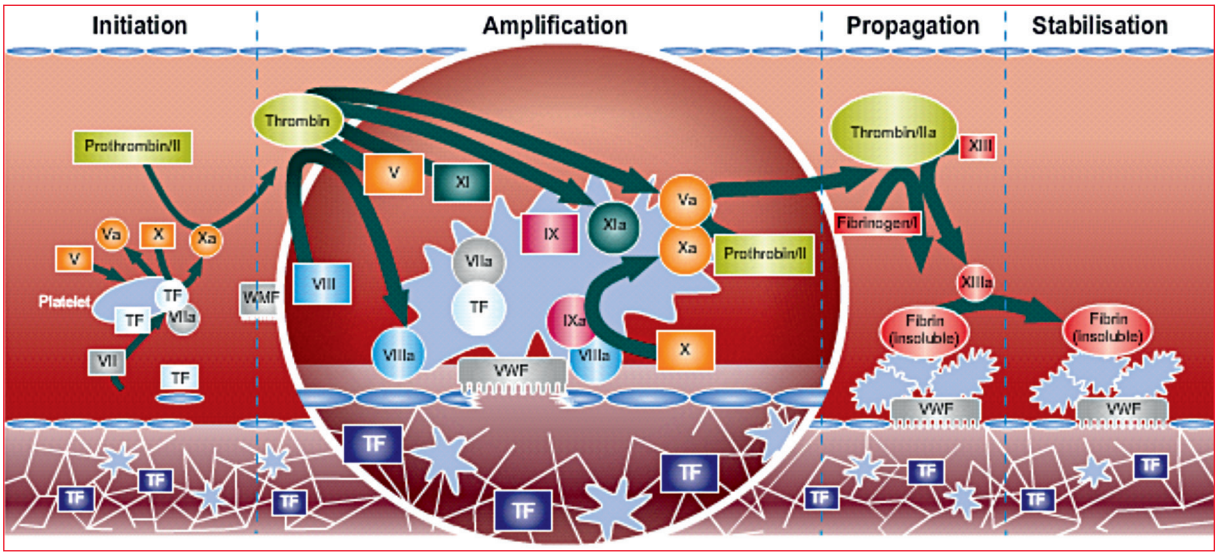

Figure 2. The cell based model of coagulation. Both figures where kindly supplied by CSL Behring

are exposed to blood flow and platelets adhere to them, through von Willebrand factor (VWF), which binds both to collagen and to specific receptor on the platelet surface. During adhesion, platelets become activated, they change shape, undergo degranulation, spread over the damaged endothelium and release several substances, which recruit more platelets to the growing mass and promote aggregation [4].

The cell-based model of coagulation focuses on the interaction between coagulation factors and the cell surface of activated platelets. Through the four phases of secondary hemostasis thrombin is progressively generated until the phase of propagation is reached. Now the bleeding patient has sufficient amount of thrombin to convert fibrinogen into fibrin, but it is FXIII that leads to the formation of a really mechanically stable clot through cross linking and stabilization. Finally, the bleeding is arrested and the process of wound healing begins (Figure 2).

Given the above facts one may speculate that requirements for transfusion in a bleeding patient may be different and specific for the moment. The so called bedside point of care tests like thromboelastography and rotational thromboelastometry [5] facilitate prompt and accurate/ /adequate diagnosis for such specific requirements in situation of trauma [6], in the operating room setting [7] or the Intensive Care Unit. These concepts came in a time with the growing awareness of risks associated with the transfusion of blood components in both health-care professionals and patients. Therefore it can be said that during the last decades the understanding of the haemostatic system has undergone major revisions, and the therapeutic choices have also shifted to specific plasma factor concentrates. The above is true for many countries in Europe including Portugal where the use of clotting factor concentrates mainly that of fibrinogen concentrate and prothrombin complex concentrate has increased during the last several years. The parallel trend observed is a reduction in the number of transfusions of Fresh Frozen Plasma (FFP) and other blood components.

Clotting factor concentrates

Fibrinogen

Fibrinogen is a 340 KDa glycoprotein, synthesized in the liver and present in blood plasma at a concentration of 2.0 to 4.5 g/L as measured by the Clauss method [8]. In a bleeding patient, the levels of fibrinogen depend on the balance between syntheses, use, and consumption [9]. It has been systematically demonstrated that when a patient bleeds, this is the first factor to reach really low levels, inadequate for the formation of a clot.

One of the first randomized placebo controlled clinical trials was designed by Fenger-Erikson for patients who underwent radical cystectomy (fibrinogen versus placebo). Although the number of study participants was low, it was sufficient enough to show that the number of blood components transfused was significantly lower in the fibrinogen group [10]. Several recent studies have shown fibrinogen to be beneficial in various clinical situations

such as cardiovascular and vascular surgery, obstetric complications, trauma, hepatic surgery, etc.

A quite recent placebo controlled double blind study designed by Rahe-Mayer which included 61 patients submitted to aortic surgery has proved that the number of allogeneic units of red blood cell concentrates and fresh frozen plasma transfused in the fibrinogen group, was much lower as compared to that in placebo group (85% reduction) [11].

The threshold value of serum fibrinogen concentration that indicates the need for fibrinogen administration, when fibrinogen is measured by the Clauss method, is still a matter of discussion and must obviously differ according to the clinical situation. According to our current knowledge on coagulation pathophysiology, it is crucial to remember that fibrinogen is of critical importance because it warrants effective hemostasis even at low platelet count.

Numerous advantages of fibrinogen over fresh frozen plasma and cryoprecipitate have been proved in several studies. One such advantage is a standardized and well defined fibrinogen content, another is a very low volume of the concentrate required for transfusion as compared to that of blood components [12, 13]. A major disadvantage might be the price though calculations reveal that it is possible to economize on blood components, particularly when fibrinogen administration is based on point of care tests used for prompt and directed diagnosis [14].

Fibrinogen concentrates have been demonstrated as effective as well as safe in a wide variety of clinical settings, also for the newborns. After 22 years of pharmacovigilance the assessed risk of fibrinogen concentrate therapy is considered to be low. Following the experience of the last several years we may say that a dose of 30 mg to 50 mg/kg, dependent on baseline values and clinical situation, is effective and can be repeated.

Prothrombin complex concentrates (PCC)

Originally PCCs were developed as a source of factor IX for Hemophilia B patients and for that reason they all contain the same amount of FIX. Some differences may however be found in the compositions of commercial PCCs. They all contain factors II, VII, IX and X, but may also include proteins C, S, AT and heparin. Their impact on coagulation is different and depends on the content of others factors, especially factor II [4].

The main indications for the use of PCC are the need for rapid reversal of anticoagulation in a bleeding patient or prior to urgent surgery and severe liver disease in patients with prolonged clotting time or with active bleeding [15]. A more recent indication for the use of PCC is bleeding associated with surgery or trauma. These concentrates are also used for the reversal of new oral anticoagulants. This however is still an issue open to discussion.

It should be kept in mind that PCCs might be the cause of thromboembolic events which are dose-dependent (normally administered is a dose of 30 UI/kg). The incidence rate for such thromboembolic events is 2%. It is recommended that each hospital develops algorithms to guide haemostatic therapy.

In Portugal PCCs have been used for many years for reversal of anticoagulation. There is a large retrospective study published in 2012 involving 1152 patients, which deals with PCCs used mainly for reversal of anticoagulation and has proved them to be safe and effective [16]. The use of these concentrates is gradually spreading to other clinical situations, such as uncontrolled bleeding in the perioperative or trauma setting.

Our experience with PCC in the bleeding setting is mostly associated with administration of fibrinogen concentrate following the results of point of care tests. However they are not in routine use in all Portuguese hospitals.

Recombinant factor VII and FEIBA (aPCC)

These activated concentrates called by-pass agents are mostly used for hemophiliac patients with inhibitors. Other indications are congenital deficiencies. FEIBA concentrates usually contain smaller amounts of FII, IX and X and larger amounts of FVII. Recombinant FVIIa is also used in the management of acquired hemophilia and Glanzmann's thrombasthenia. It is occasionally used as an off label indication in cases of uncontrolled bleeding, although data from clinical trials indicate that its efficiency is yet unknown or that it is likely to be beneficial but associated with thrombotic risk. FVIIa is also expensive.

At the moment therefore there seem to be more questions than answers regarding the use of FVIIa in the bleeding perioperative setting [17]. So FVIIa administration should proceed with extreme caution. Prior to use of FVIIa it is essential to correct the patient's parameters such as platelet count, fibrinogen, acidosis, hematocrit, hypothermia and hypocalcaemia. Once the decision for FVIIa administration is made the optimal dose to be applied is 90–120 ug/kg.

Factor XIII

There is some emerging information to suggest the importance of this coagulation factor for bleeding patients, especially in the cardiac setting. One randomized placebo controlled trial in gastrointestinal cancer surgery is also reported. The available data seem to suggest the benefits of factor XIII in terms of post-operative blood loss. [4]. In Portugal factor XIII is used only in major hospitals which follow patients with diagnosis of congenital factor deficiencies. According to reports it can be effectively used in the perioperative bleeding setting. However, the data for our country is still scarce and more studies are required.

Other clotting factors and hemostatic agents

When a patient is bleeding it is recommended to consider other clinical aspects and one of them is the development of acquired coagulation factor deficiencies such as von Willebrand disease. The situation is rare but might occur in patients with no history of bleeding.

It may happen that congenital deficiencies are not diagnosed in the preoperative period. Therefore it is never too much to emphasize the importance of collecting clinical history and performing laboratory tests to diagnose coagulation factors deficiency in the case of patients scheduled for elective surgery.

There is a natural balance within the hemostatic system. On the one hand the system protects the organism against bleeding. But there is also a number of mechanisms that work simultaneously to control hemostasis: the fibrinolytic system, natural anticoagulants and tissue factor pathway inhibitors. It is extremely important to have control over the mechanisms referred to above; otherwise a premature dissolution of the clot may result in prolonged bleeding.

Tranexamic acid (TXA) may be of special interest in this context. In several trials it has been shown to prevent severe bleeding in situations prone to premature hyperfibrinolysis. TXA is routinely used in trauma and cardiovascular surgery but has also been found effective in other contexts such as obstetric complications and urologic surgery.

Conclusion

To summarize, it may be said that during the last decades the understanding of healthcare professionals regarding the haemostatic system has undergone major revision. As consequence, the therapeutic choices in the field of acquired bleeding disorders are shifting from classic non-specific therapies to specific plasma factor concentrates.

References

1. Manucci P.M., Levi M. Prevention and treatment of major blood loss. New England Journal of Medicine 2007; 22: 2301–2310.
2. Schochl H., Maegele M., Solomon C., Goerlinger K., Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. Trauma, Resuscitation and Emergency Medicine 2012; 20: 1–15.
3. Smith S.A. The cell-based model of coagulation. Journal of V.E. and Critical Care 2009; 19: 3–10.
4. Haas T. Seminar on Severe Bleeding Management: Lecture. Salzburg, January–February 2013.
5. Kozek-Langenecker S. Management of massive operative blood loss. M. Anestesiologica 2007; 73: 401–415.
6. Sorensen B., Fries D. Emerging treatment strategies for trauma-induced coagulopathy. British Journal of Surgery 2012; 99 (suppl. 1): 40–50.
7. Reinhofer M., Brauer M., Franke U., Barz D., Marx G., Lösche W. The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. Blood Coagulation and Fibrinolisys 2008; 19: 212–219.
8. Sorensen B., Larsen O., Rea C.J., Tang M., Foley J.H., Fenger-Eriksen C. Fibrinogen as a hemostatic agent. Seminars on Thrombosis and Hemostasis 2012; 38: 268–273.
9. Fenger-Eriksen C., Lindberg-Larsen M., Christensen A.Q., Ingerslev J., Sorensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. British Journal of Anesthesia 2008; 101: 769–773.
10. Fenger-Erikson C. Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J. Thromb. Haemost. 2009; 7: 795–802.
11. Rahe-Mayer N., Solomon C., Hanke A. et al. Effects of fibrinogen concentrates first-line therapy during major aortic replacement surgery. Anesthesiology 2013; 118: 40–50.
12. Levy J.H., Szlam F., Tanaka K.A., Sniecienski R.M. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. Anesthesia-Analgesia 2012; 114: 261–274.
13. Kozek-Langenecker S., Sørensen B., Hess J.R., Spahn D.R. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. Critical Care 2011; 15: R239.
14. Goerlinger K., Dirkmann D., Hanke A.A. et al. First line therapy with coagulation factor concentrates combined with point of care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery. Anesthesiology 2011; 115: 1179–1191.
15. Pabinger I., Brenner B., Kalina U. et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. JTH 2008; 6: 622–631.
16. Carvalho M.C., Rodrigues A.G., Conceição L.M., Galvão M.L., Ribeiro L.C. Prothrombin complex concentrate (Octaplex): a Portuguese experience in 1152 patients. Blood Coagulation and Fibrinolysis 2012; 23: 1–7.
17. Editorial. Recombinant FVIIa for intractable hemorrhage. More questions than answers. Transfusion 2003; 43: 1649–1650.