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Review

Use of fresh frozen plasma: from the 2012 French guidelines to recent advances

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ABSTRACT

Fresh frozen plasma (FFP) is widely used by anesthetists and/or intensivists managing bleeding patients. In this context, two clinical situations with different benefit/risk ratio for FFP transfusion should be distinguished: moderate or controlled hemorrhage on one side, and massive hemorrhage on the other. In the former situation, administration of FFP is most often ineffective, associated with potential side effects (pulmonary complications, product shortage) and should therefore be restricted. In case of massive hemorrhage, transfusion of FFP, red blood cells and platelets using a ratio close to 1:1:1 is recommended based on a large number of studies. A goal-directed strategy, based on the utilization of point-of-care hemostatic devices, might be used as an alternative or in combination with this ratio-driven strategy.

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Transfusion of fresh frozen plasma (FFP) in anesthesia and intensive care medicine is mainly indicated in situations of hemorrhage. For the purpose of this review, one should separate two main situations that the physician may be facing. Slowly occurring or moderate bleeding leads to complications such as ischemia and late coagulopathy, while massive hemorrhage with rapid and intense bleeding may lead to exsanguination or hemorrhagic shock and acute coagulopathy. For each of these two situations, diagnosis and treatment widely differ. Recently updated guidelines have been published which describe the use of blood transfusion as a whole in some acute conditions [1,2]. As well, major studies designed to set up the optimal threshold for red blood cell transfusion have been performed [3,4]. However, recent guidelines centered on the use of FFP are not numerous [5]. In this short review, we will use the French Guidelines published in 2012 as a leading guide [6] and will describe questions or changes which have appeared since their publication. Guidelines describing the use of FFP in apheresis will not be detailed here [7].

1. Which types of FFP are available?

In France, up to 31 January 2015, four types of therapeutic FFPs were available for clinical use [8] and were delivered through a monopolistic system by the French Blood Agency (Etablissement Français du Sang [EFS]). The Quarantine FFP is a single donor FFP. It does not undergo any biological or pharmaceutical treatment. Its safety is ensured by quarantine of at least 60 days and it cannot be released unless the donor has returned to verify the absence of any new event during the above defined time frame. The volume of bags is between 200 and 650 mL but for 80% of bags, the volume ranges between 200 and 3450 mL.

Other FFPs are obtained through a pathogen reduction technology (Table 1). FFP may be treated with solvent-detergent to disrupt enveloped viruses, or with photoactive agents methylene blue plus light, or amotosalen (AM) or riboflavin (RF) plus ultraviolet (UV)

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Table 1
Efficacy of the different pathogen inactivation techniques against the various types of microorganisms which may be found in the blood [14].

Microorganisms	Solvent detergent	Amotosalen	Methylene blue	Riboflavin
Viruses with envelope				
(HCV, HBV, HIV, CMV, HTLV, WNV)	+	+	+	+
Emergent	?	+	?	+
Chikungunya		+		
Dengue				
Non enveloped viruses				
HVA	–	–	–	(+)
HVE	–	–	(+)	–
Parvovirus	–	+	+	+
Bacteria	+ (filtration)	+	–	+
Spores (Bacteria)	?	–	?	?
Parasites (Chagas, plasmodium)	+ (filtration)	+	+ (*Trypanosoma cruzi*)	+

+: concentration of the pathogen reduced by 3–7 log.
(+): concentration of the pathogen reduced by 1–3 log (mainly if large viral load).

light, to disrupt pathogen nucleic acids. Pathogen inactivated FFPs have average clotting factor activities of 75–85% of untreated FFP.

Starting in 2008 in France, pathogen inactivation was mainly obtained by methylene blue reduction. However, due to a significantly increased number of severe allergic reactions with this product [9], the French drug and Blood Agency decided to withdraw this FFP in 2011 [10]. This withdrawal led to the increased use of amotosalen-treated FFP which represented 31% of FFPs distributed in France in 2013 [11] as compared to less than 5% in 2010.

FFP inactivated by amotosalen (PFC-IA) is made from single donor blood and treated by apheresis, although a mixture of blood from 5 to 6 donors and extracted from whole blood will probably soon be released in France. Blood is treated by pathogen inactivation using psoralen (amotosalen-HCl) combined with illumination with A-UV light. Volumes of bags range between 200 and 240 mL.

Lyophilized FFP (PLYO) is up to now only available to and used by French military service during international missions [12]. It is made from a mixture of blood from 10 donors and also treated with amotosalen pathogen inactivation.

The solvent/detergent (SD) technique is another well-known virus inactivation technology used for almost 30 years. SD-FFP is made of blood from 500 to 1000 donors. The owner of this pathogen inactivation technique is Octapharma® which was used by the EFS in France up to 31 January 2015. This pharmaceutical group had previously launched a litigation procedure near the European Justice court against the French authorities stating that the SD technique was an industrial technique and that FFP obtained through this technology should not be considered anymore as a labile product in French regulation. This request was validated by the European Court, SD-FFP being now considered a drug and no more a blood product. This change led to the fact that FFP prepared with SD technology cannot be produced anymore by the French Blood Agency (EFS) [13] as this institution is labelled to prepare only labile blood products. As the same time, marketing authorization was obtained by Octapharma in France. A major practical change derived from this European regulatory decision lies in the fact that in French hospitals, FFP can now be ordered from both the blood bank and the Pharmacy. Local practice patterns and protocols should be modified which will also require marketing decisions by hospitals. Modified regulatory rules will lead to competition between manufacturers and might have an impact on purchasing prices. Because of its industrial production, SD-FFP has a standardized content of clotting factors, is free of antibodies that might lead to transfusion-related acute lung injury, and is very effective against transfusion-transmissible infectious agents (Table 1).

French Guidelines concluded that all types of FFP are equivalent in terms of biological activity and tolerance. Biological content (especially clotting factors) and in vitro hemostatic activity are extremely similar between the various preparations although minor differences have been detected [15]. SD-FFP might be associated with a reduced risk of allergic reactions [11]. There are few randomized trials which have compared the various available FFP products but overall no clinically significant difference could be detected. Conclusions similar to those of the French Guidelines have been published by other expert groups [16,17].

2. Clinical applications and recommendations

One should well separate two clinically different situations. As shown by Murad et al. [18], very-low-quality evidence suggests that plasma infusion in the setting of massive blood transfusion (MT) for trauma patients may be associated with a reduction in the risk of death and multiorgan failure. A survival benefit was not demonstrated in most other transfusion populations and in patients undergoing surgery without MT, plasma infusion was associated with a trend toward increased mortality [18]. Differently stated, FFP should not be administered in settings other than MT.

2.1. Minor alterations of coagulation or controlled hemorrhage

In minor or moderately severe alterations of blood coagulation and at-risk situations, prophylactic use of FFP is not indicated in patients with normal or moderately decreased coagulation factor concentrations [19]. Muller et al. [20] showed using a randomized design that transfusions of 12 mL/Kg of FFP did not modify the bleeding complication rate in critically ill patients undergoing invasive procedures such central venous catheter, percutaneous tracheostomy, chest tube, or abscess drainage. Prothrombin time (PT) is a global test with a poor predictability capacity of the risk of hemorrhage. Change in PT after FFP transfusion is extremely limited or at best modest. FFP transfusion cannot be recommended to correct a moderately altered PT, even before an invasive procedure is performed. In the well known study by Abdel Wahab et al. [21], patients who had a PT between 13.1 and 17 s (international normalized ratio [INR], 1.1–1.85) were transfused with FFP according to their physician's decision. PT and INR activity measured within 8 h after transfusion showed almost no improvement whatever the number of FFP units that had been administered. PT became normal after FFP transfusion in only 0.8% of cases. In the study by Muller et al. [20], performed in ICU patients, 12 mL/kg of FFP transfusion resulted in a reduction of INR to less than 1.5 in only 54% of transfused patients. To simply remember this limited efficacy, it could be said that one FFP unit leads to increase the PT expressed in per-