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Efficacy of solvent/detergent plasma after storage at 2–8 °C for 5 days in comparison to other plasma products to improve factor V levels in factor V deficient plasma

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ABSTRACT

Objectives: Factor V (FV) plays an important role in coagulation. As no purified concentrate is available to restore critical FV levels, the main blood product used to replace FV is plasma. The aim of the present in vitro study was to compare the efficacy of the different available plasma products on the reversal of moderate and severe FV deficiency as assessed by ROTEM® and FV levels.

Methods: Five different plasma products (6 batches of each) were compared to determine their effectiveness in replacing FV in plasma moderately or severely deficient in FV. Effectiveness was measured using the ROTEM® EXTEM clotting time (CT) and a factor V assay.

Results: FFP, plasma frozen within 24 hours (FP24), Octaplas (solvent/detergent treated pooled plasma), as well as Octaplas and FP24 thawed and stored for 5 days (Octaplas TP and TP), were all used for in vitro replacement of FV. TP was significantly less effective at reversing a prolonged EXTEM CT and FV levels in FV deficient plasma than other tested products. There were no significant differences in EXTEM CT between Octaplas and Octaplas TP, while factor V activity was significantly lower in the Octaplas TP. There was no significant difference between Octaplas and FFP for EXTEM CT or FV activity.

Conclusions: Octaplas and Octaplas TP appear to have an equivalent ability to improve the EXTEM CT and could be considered as a treatment alternative to FFP in patients with FV deficiency.

1. Introduction

Blood coagulation factor V (FV) plays an important role in the coagulation pathway [1,2]. Hereditary FV deficiency is a rare autosomal recessive bleeding disorder with a reported prevalence of 1 per million and a variable clinical phenotype [3]. In addition to the reported occurrence of acquired FV deficiency due to development of inhibitors [1,4], low FV levels have also been observed in early trauma-associated coagulopathy [5].

As no purified concentrate is available to restore critical FV levels, the main blood product used to replace FV is plasma. However, the clinical problem is that thawing and preparation of plasma is a time-consuming process that requires additional blood bank resources, and thereby limits immediate plasma availability in true emergencies. This may be overcome by preemptive preparation of thawed plasma products for emergency use, which in turn may lead to increased wastage of thawed unused plasma products. Notably, there is reported evidence that prolonged storage of thawed plasma, including solvent/detergent (S/D) treated plasma stored at 2 to 6 °C for up to 6 days may preserve sufficient

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coagulation factor activities as required for quality assurance [6–8]. However, the impact of using thawed and stored S/D plasma as compared to other plasma products to improve low FV levels has not yet been investigated.

The aim of the present in vitro study is to compare the efficacy of the different available plasma products on the reversal of moderate and severe FV deficiency. In our study, we chose to use a combination of standard coagulation factor analysis plus viscoelastic point-of-care testing. Viscoelastic testing (ROTEM®/TEG®) is advantageous in the fast and reliable detection of acquired coagulopathies [9]. The ROTEM® device (TEM International, Munich, Germany) has been successfully used to assess moderate to severe FV deficiency reflected by a prolonged EXTEM clotting time (CT) [10,11]. To cover the spectrum of FV deficiency, we chose to investigate moderate FV deficiency (<30%) as observed in trauma or dilutional coagulopathies, as well as the severe FV deficiency observed in hereditary FV deficiencies (<1%).

2. Materials and methods

2.1. Preparation of plasma

Five different plasma products (6 batches of each product) were prepared for this study (Table 1). Fresh frozen plasma (FFP), plasma frozen within 24 hours after phlebotomy (FP24), and commercially available solvent/detergent (S/D) pathogen reduced plasma (Octaplas®, Octapharma USA Inc., Hoboken, NJ, USA; marketed as Octaplas® LG in Europe and other markets) were thawed over 20 minutes using a plasma thawer (Helmer Quick Thaw, Helmer Scientific, Noblesville, IN) and utilized for the in vitro dilution immediately thereafter. Another six batches of both FP24 and Octaplas® were thawed as previously described 5 days before the investigation and stored at 2–8 °C. After 5 days of storage, FP24 plasma was referred to as thawed plasma (TP), while thawed Octaplas® was referred to as Octaplas®TP. Immediately before starting the investigation, the stored plasma batches were rewarmed as described to ensure comparable temperature of 22 °C between all plasma products used.

To investigate two distinct phenotypes of FV deficiency, plasma with severe FV deficiency (FV activity <1%) and moderate FV deficiency (FV activity of approximately 30%) were prepared for this study. Commercially available factor V deficient plasma (<1% FV) (Code 0020011500; Instrumentation Laboratory, Bedford, MA, USA) was used as severely FV deficient plasma, while the 30% formulation was prepared by mixing FV deficient plasma with pooled normal human plasma (91% FV activity, George King Biomedical, Overland Park, KS, USA) in a ratio of 3:1 to generate plasma with approximately 30% FV activity.

FV activity levels of the FV deficient plasma formulations were checked at baseline and at the end of the study with a modified PT assay on an ACL TOP 700 (Instrumentation Laboratory, Bedford, MA, USA) using FV deficient plasma (Precision Biologics, Dallas, TX, USA). ROTEM® EXTEM Clotting Time (CT) was also measured at baseline and at the end of the study. Only an EXTEM CT was performed since this is the ROTEM variable most affected by FV level, and represents the ability of the extrinsic and common pathway coagulation factors to generate thrombin. A normal ROTEM® tracing with labeled parameters is provided in Fig. 1.

Table 1
Investigated plasma products.

Plasma product	Description
Fresh frozen plasma (FFP)	Single donor plasma
Plasma frozen within 24 hours after phlebotomy (FP24)	Single donor plasma
FP24 thawed and stored at 2–8 °C for 5 days (TP)	Single donor plasma
Octaplas® (Octapharma, Hoboken, NJ, USA)	S/D pooled plasma, prion reduced
Octaplas® thawed and stored at 2–8 °C for 5 days (Octaplas TP)	S/D pooled plasma, prion reduced

2.2. In vitro supplementation of FV

The study was conducted at the New York-Presbyterian Hospital/Weill Cornell blood bank laboratory. All plasma products and the FV deficient plasma were kept at room temperature during the entire in vitro supplementation of FV and ROTEM® measurements. Samples of FV deficient plasma (both 30% and <1% FV plasma) were aliquoted into 1 mL tubes, and supplemented with 333 µL of each of the plasma products. This was based on the assumption that an already fluid-resuscitated trauma patient with a 75 kg bodyweight and a blood volume of 70 mL kg^{-1} (5250 mL) with a mild anemia (hematocrit 35%) would have a theoretical plasma volume of 3412 mL. Transfusion of 15 ml kg^{-1} of a plasma product would require a transfusion volume 1125 mL; thus, the ratio between calculated plasma volume and transfused plasma volume is approximately 3.0. An assumption was made that the infusion would not be accompanied by a compensatory change in blood volume during the time it took to infuse the treatment fluid. Based on those calculations, supplementation of 333 µL of each plasma product with 1 mL of FV deficient plasma corresponds to an in vivo transfusion of 15 ml kg^{-1}. ROTEM® EXTEM CT was assessed immediately after supplementation with each of the plasma products and ROTEM® measurements were stopped after CT time was displayed. The remainder of each specimen was immediately frozen at –80 °C until FV analysis the following week. Each substitution step was performed using six different bags of each type of plasma leading to an overall sample size of 60 supplemented plasma samples.

2.3. Statistical analysis

After non-normal distribution of the data was confirmed, descriptive analyses and an overall Friedman test were performed. When an overall significant difference between coagulation measurements was detected, a pairwise comparison using the Wilcoxon test was performed to test for significant differences between each of the different plasma products. Results are given as median and 25% to 75% quartiles (IQR), if not otherwise indicated. All statistical calculations were carried out using SPSS, IBM® SPSS® Statistics, Version 22, Armonk, NY, USA).