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Coagulation factors and inhibitors in thawed plasma stored at 1–6 °C for 5 days in China

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ABSTRACT

Introduction: Many transfusion services are keeping thawed plasma (TP) ready for trauma patients. According to Chinese guidelines, once thawed, fresh frozen plasma (FFP) should be used within 24 h. This may increase plasma wastage and delay plasma administration to critical patients. However, it can be avoided by being relabeled as TP. In this study we evaluated coagulation-related proteins in thawed apheresis FFP during 5 days of storage at 1–6 °C.

Materials and methods: Thirty apheresis fresh plasma units were aliquot and stored at −70 °C. Aliquots were thawed at 37 °C and stored at 1–6 °C for 0, 1, 2, 3, 4 and 5 days, respectively. Prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen (Fbg), factor (F) II, FV, FVII, FVIII, FIX, FX, FXI, FXII, protein C (PC), protein S (PS), antithrombin III (ATIII) and ADAMTS13 levels were assessed at Days 0–5, respectively.

Results: For 5 days of refrigerated storage, no significant differences were observed in Fbg, PC, PS, ATIII and ADAMTS13. FII, FV, FVII, FVIII, FIX, FX, FXI and FXII declined significantly over time. The storage presented major decrease for FVIII, with a drop of 40%. However, at least 60% levels of all measured proteins were remained on Day 5, when compared to Day 0.

Conclusion: All measured proteins in TP for 5 days of refrigerated storage were adequate. These could provide evidence that thawed FFP could be relabeled as TP, which is a potential to ensure rapid plasma availability in emergency situations in China.

1. Introduction

Currently, plasma is frequently transfused for coagulation disorders (hereditary and acquired), for thrombotic thrombocytopenic purpura (TTP), for warfarin reversal, and for replenishment of specific coagulation factors without an available factor concentrate (e.g. factor [F] V, FX and FXI). Although the guidelines are limitedly supported by evidence from randomized clinical trials [1–3], the recommended indications for FFP are almost similar in different countries (e.g. US [4], UK [5] and China [6]).

Nowadays, six plasma products are available in the US, four of which are frozen and the other two are liquid [7,8]. The four frozen plasma products are fresh frozen plasma (FFP), plasma frozen within 24 h after phlebotomy (FP24), cryoprecipitate-reduced plasma and solvent/detergent-treated (S/D) plasma. And the two liquid state products are liquid plasma (LP) and thawed plasma (TP). The recommended indications for FFP administration are rare coagulation factor deficiencies, TTP, severe liver disease, massive transfusion and reversal of warfarin therapy. In

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comparison to FFP, FP24 has slightly decreased FV (less than 10% decrease) and moderately decreased FVIII (20–50% decrease) levels and has almost identical indications, excepting the replacement of labile coagulation factors, such as FV and FVIII. According to American Association of Blood Banks (AABB), after 24-h post-thaw period of refrigerated storage, plasma can no longer be labeled as FFP or FP24 but most can be relabeled as TP, which could be stored at 1–6 °C for up to 5 days prior to transfusion. Though TP has not been licensed by the Food and Drug Administration (FDA) until now, the indications recommended by AABB are massive transfusion, rapid reversal of the effects of warfarin and TTP. This seems contradictory, while it actually means that blood centers cannot license the product with FDA, but can use it in their own transfusion services. The indication for LP is only massive transfusion in patients with life-threatening hemorrhages. In addition, indications of S/D plasma recently approved by FDA are replacement of multiple coagulation factors in patients with liver disease, liver transplant and cardiac surgery and plasma exchange for TTP [8]. In Canada and Europe, there are even more plasma products, such as quarantine plasma, methylene blue, amotosalen or riboflavin-treated plasma and lyophilized plasma [9–12]. However, in China, only frozen state plasma (FFP, methylene blue-treated FFP and cryoprecipitate-reduced plasma) are available.

With the consideration of the stability of coagulation factors, the post-thaw shelf life of FFP is only 24 h stored at 1–6 °C in China, like in the USA, Canada and European countries. Differently, thawed FFP can not be re-labelled as TP and must be abandoned beyond 24 h of refrigerated storage in China. In the past, multiple studies were carried out to investigate the stability of coagulation factors and inhibitors in TP at various temperatures over different days of storage [13–15]. According to these studies, different results were obtained, which might be due to the various thawing temperatures, storage time or temperatures, the source of plasma and the measured coagulation factors and inhibitors. Therefore, these published results may be not directly applicable for China.

In this study, we investigate the long-term stability of coagulation factors and inhibitors in thawed apheresis FFP stored for up to 5 days at 1–6 °C. Based on the observed results, additional data could be provided for transfusion services to alternate the interchangeable use of FFP and TP, to boost the maintenance of a TP inventory for rapid plasma availability and to reduce plasma wastage in China.

2. Materials and methods

2.1. Sample processing

Thirty apheresis fresh plasma units (9 blood group A, 9 blood groups B, 3 blood group AB and 9 blood group O) from 30 single qualified blood donors were randomly offered by Guanghan Plasmapheresis Center (Deyang, China). Each of the plasma was divided into aliquots and then they were frozen and stored at −70 °C until used for parallel testing. After thawing in a circulating water bath at 37 °C, aliquots were prepared for factor assays at days of 0, 1, 2, 3, 4 and 5 of refrigerated storage.

2.2. Laboratory analysis

Prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen (Fbg), FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, ADAMTS13, protein C (PC), protein S (PS) and antithrombin III (ATIII) were determined in this study.

Unless otherwise stated, all assays were performed according to manufacturer's instructions on a CA-1500 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan). PT, aPTT and TT (Chengdu Union Biotechnology Co., Ltd., Chengdu, China) results were determined to screen the overall integrity of the coagulation system. Fbg, FII, FV, FVII, FVIII, FIX and FXI reagents were purchased from Chengdu Union Biotechnology Co., Ltd. FX and FXII deficient plasma regents were from Thermo Scientific (Mieldletown, USA). All the coagulation factors were assayed by clot-based endpoint method. PS (Dade Behring, Marburg, Germany) was determined by clotting method. For PC and ATIII (Dade Behring) were measured with chromogenic substrate assays. ADAMTS13 antigen was performed using an enzyme-linked immunosobent assay (Sekisui Diagnostics, LLC, Stamford, USA) and measured at 450 nm using SpectraMax M2[e] (Molecular Devices, Sunnyvale, CA, USA).

2.3. Statistical analysis

Kolmogorov–Smirnow test was used for the normality of the distribution. Mean ± standard deviation (SD) of the results were calculated for the tests at all time points. Results of Days 1, 2, 3, 4 and 5 were compared to that of Day 0 by means of a two-tailed, paired Student's *t*-test. For the factors varied due to different ABO blood groups, one-way ANOVA was performed. Confidence interval was defined as 95% (2.5–97.5%). A *p*-value of less than 0.05 was considered statistically significant. In addition, Statistical analyses were conducted using SPSS statistics software, version 17.0 (SPSS Inc., Chicago, USA).

3. Results

3.1. Measurements of basic coagulation tests

Table 1 and Fig. 1A display results for basic coagulation tests (i.e. PT, international normalized ratio [INR], aPTT and TT). When compared with Day 0 values (11.8 s), PT showed significant differences from Day 1 onward, with a maximum mean value of 13.8 s and about 17% ($p < 0.001$) increase on Day 5. INR demonstrated the similar results with a maximum increase of 25% ($p < 0.001$), since INR values were derived from PT. APTT increased significantly on Day 1 onward, with an accumulative increase of 25% ($p < 0.001$) over time. TT significantly increased from 17.6 s on Day 3 to 19.1 s on Day 5 (approximately 10% increase, $p = 0.007$).