A study on factors influencing the hemostatic potential of fresh frozen plasma

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Abstract:

BACKGROUND: Fresh frozen plasma (FFP) is administered to correct deficiencies of various coagulation factors. The level of these factors in FFP varies with donor demographics and ex-vivo processing of plasma. In this study we have compared the quality control parameters of FFP collected from donors of different genders, age groups, ABO blood groups, smoking and alcohol intake habits.

MATERIALS AND METHODS: Four ABO group matched plasma units were pooled, split and further processed by four different freeze-thaw algorithms: frozen by contact shock freezer; thawed at 37°C, frozen by contact shock freezer; thawed at 45°C, frozen by mechanical freezer; thawed at 37°C, frozen by mechanical freezer; thawed at 45°C. The coagulation factor levels in plasma units were compared.

RESULTS: There were no significant differences in the quality parameters with donor age, gender and alcohol intake. Factor VIII levels were significantly lower in O group FFP (P < 0.05). Smokers had significantly higher levels of fibrinogen (P < 0.05). There were no significant differences in PT, fibrinogen and factor VII levels of FFP processed through various algorithms. Plasma frozen rapidly through contact shock freezer had significantly lower aPTT and higher levels of factor V and VIII compared to mechanical freezing. There were no significant differences between PT, aPTT, fibrinogen, factor V, factor VII and factor VIII levels of FFP thawed at 37°C and 45°C. Mean thawing time was 28 minutes at 37°C and 17 minutes at 45°C.

CONCLUSION: Rapid freezing is recommended for optimum preservation of coagulation factors. Thawing may be done at 45°C in cases of emergency, without compromising hemostatic potential.

Keywords: Coagulation factors, fresh frozen plasma, quality control, rapid freezing, thawing

Introduction

Fresh frozen plasma (FFP) is a therapeutic source of several labile and nonlabile coagulation factors. The level of these coagulation factors is varied in the plasma of blood donors due to demographic, genetic, and lifestyle factors. Besides, methods of FFP preparation, storage conditions, and final thawing techniques also determine its quality regarding coagulation factor levels. Epidemiological studies have shown that aging is associated with increased plasma levels of fibrinogen, factor VII, and factor VIII leading to hypercoagulability. Levels of coagulation factors vary in females with menopausal status and hormonal use.[1] The long duration of active smoking is associated with significant changes in the coagulation system, leading to thrombogenic potential.[2] Alcohol consumption is also known to exert a direct effect on hemostasis by modulating coagulation factor levels.[3] Studies to determine genetic predisposition to disease based on ABO blood group type have shown that participants with O
blood group have lower levels of factor VIII and von Willebrand factor (vWF) in their plasma which has a protective effect against thrombotic tendencies.[4]

After the collection and separation, the initial process of freezing is crucial for preserving the activity of labile coagulation factors. For a freezing method to yield a good quality of FFP, the surrounding low temperature should reach the core as early as possible. Similarly, thawing of FFP also requires strict temperature regulations as higher temperatures may denature coagulation proteins. However, the pertaining guidelines are inadequate and ambiguous. According to AABB,[5] plasma may be frozen by placing the bag either in dry ice-ethanol or between layers of dry ice or in a blast freezer or in a mechanical freezer (MF) maintained at −65°C or colder. The thawing should be done at temperatures between 30°C and 37°C in a temperature controlled water bath or in the Food and Drug Administration approved device. According to the BCSH guidelines, plasma should be rapidly frozen to −30°C or below without any further specifications. Thawing should be done at 37°C in either dry oven or microwave oven or water bath.[6]

The standard process of thawing takes >30 min and may delay the delivery of the component during emergencies. It has been proposed that FFP may be thawed at temperatures higher than the current standards, retaining its suitability for therapeutic purposes. This study has been conducted with the aim of determining the effect of various donor variables and freeze-thaw temperatures on the hemostatic parameters of FFP.

Materials and Methods

This prospective study was carried out after taking due approval from the institute’s research committee and ethical committee. The study participants were normal healthy blood donors who visited blood center for blood donations. All participants were given an information sheet, and their consent was taken before inclusion in the study.

To study the effect of donor variables, voluntary blood donors were selected for whole blood donation as per departmental Standard Operating Procedure. ABO blood grouping was done on predonation blood sample, and 25 donors of each ABO blood group were included in the study. Donors were also enquired about the history of smoking and alcohol intake. Donors who gave the history of smoking cigarette of five or more cigarettes in a day for more than a year were considered smokers. Donors who gave a history of consuming alcohol >30 g/day or >2 drinks per day for more than a year were considered alcoholic.

To study the effect of freezing method and thawing technique, additional 200 male voluntary blood donors with body weight of ≥60 kg were selected, and 450 ml whole blood was collected. After collection of whole blood in quadruple blood bags (Terumo Penpol Pvt Ltd., Thiruvananthapuram, India), it was separated into components by buffy coat method using automated component extractor (TACE, Terumo Penpol, Japan) within 2 h of collection.

For studying the effect of donor variables, plasma units under study were frozen instantaneously by contact shock freezer (CSF) (Dometic MBF 21, Luxembourg) and were stored at −40°C in stack position for 2 weeks in deep freezer (M/S Sanyo, Japan). The units were thawed in water bath (Remi laboratories, India) at a temperature of 37°C. Representative samples were tested using semi-automated coagulometer (STart4, Stago Diagnostica, France) for prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and factor VIII.

For studying the effect of freeze-thaw, four ABO group-matched plasma units were selected and pooled using the sterile connecting device (Fresenius Compodock, Homburg) in a dedicated plasma container to make one pool. Twenty-five of such ABO identical pools were made. A representative sample was taken from the pool and tested using semi-automated coagulometer (STart4, Stago Diagnostica, France) for baseline PT, aPTT, fibrinogen, factor V, factor VII, and factor VIII.

The pooled plasma was divided into four aliquots to ensure homogeneity. Two aliquots from each pool were rapidly frozen by CSF (Dometic MBF 21, Luxembourg) which took approximately 40 min to completely freeze the plasma. The other two aliquots were subjected to slow freezing at −40°C in a blood bank MF (M/S Sanyo, Japan).

After complete freezing, one aliquot from each FFP frozen by CSF and MF was thawed in water bath (Remi laboratories, India) at a temperature of 37°C. The remaining two FFPs from the same pool were thawed in the same water bath at 45°C. Thus, FFP units obtained by four different freeze-thaw algorithms [Figure 1] were labeled as CS37 (frozen by CSF and thawed at 37°C), CS45 (frozen by CSF and thawed at 45°C), M37 (frozen by MF and thawed at 37°C), and M45 (frozen by MF and thawed at 45°C).

Representative samples were taken from all the FFP bags after complete thawing. The samples were tested using semi-automated coagulometer (STart4 M/S Stago Diagnostica, France) for PT, aPTT, fibrinogen, factor V, factor VII, and factor VIII.
All statistical analyses were performed with SPSS (IBM Corp. IBM SPSS Version 23.0, New York, United States). The data were tested for normality using the Kolmogorov–Smirnov test. As the data that were found to have non-Gaussian distribution, it was analyzed using Mann–Whitney U-test and Kruskal–Wallis test with pair-wise comparisons for post hoc significance. The results were presented as median along with minimum and maximum values. Significance was assumed with $P < 0.05$.

The data of the difference between baseline and post-freeze-thaw coagulation factor levels ($\Delta$ values) showed a normal distribution. The results were expressed as a mean and standard deviation. One-way ANOVA was used to compare the mean of differences within the groups, with Tukey’s test for post hoc significance. Significance was assumed with $P < 0.05$.

### Results

The results of the comparison of various quality control parameters of FFP in relation to donor variables are shown in Table 1. There were no statistically significant differences in the parameters with gender and age group. On comparing, the parameters of FFP of various ABO blood groups and O group FFP were found to have significantly lower levels of factor VIII ($P < 0.05$) compared to other groups. FFP from smokers had significantly higher levels of fibrinogen ($P < 0.05$) compared to that FFP from nonsmokers. There were no statistically significant differences in parameters of alcoholic and nonalcoholic donors’ FFP.

Mean thawing time was 28 min (range: 25–32 min) at a temperature of 37°C and 17 min (range: 14–20 min) at 45°C. Comparison of PT, aPTT, fibrinogen, factor V, factor VII, and factor VIII levels of FFP frozen and thawed by different algorithms is shown in Table 2. There were no statistically significant differences in the PT of different groups. The aPTT was significantly prolonged in M37 and M45 group ($P < 0.05$) in comparison to baseline, CS37, and CS45. There were no statistically significant differences in the levels of fibrinogen in different groups. Factor V levels were significantly lower in MF FFP (M37 and M45) compared to CSF FFP (CS37 and CS45). There were no statistically significant differences in the levels of factor VII in different groups. Factor VIII levels were also significantly lower in MF FFP (M37 and M45) compared to CSF FFP (CS37 and CS45).

Comparison of the differences in factor levels from baseline levels ($\Delta$) resulting from various algorithms denoting the recovery of factors is shown in Figure 2. There were no statistically significant differences in $\Delta$ fibrinogen levels and factor VII levels of all groups. For
Table 1: Quality control parameters of fresh frozen plasma according to the donor variable

| Factor                  | PT (s) Control: 13.2 s | aPTT (s) Control: 32.8 s | Fibrinogen (g/dL) | F VIII (IU/mL) |
|-------------------------|------------------------|--------------------------|-------------------|----------------|
| Gender                  |                        |                          |                   |                |
| Male (n=78)             | 14.10 (12.60-16.20)    | 27.20 (25.30-31.30)      | 3.90 (3.10-5.23)  | 1.31 (0.89-1.61) |
| Female (n=22)           | 13.80 (12.60-14.30)    | 27.0 (23.40-32.60)       | 3.81 (3.21-4.32)  | 1.32 (1.03-1.56) |
| Age group (years)       |                        |                          |                   |                |
| 18-30 (n=42)            | 13.90 (12.60-16.20)    | 26.80 (25.30-32.60)      | 3.91 (3.12-4.82)  | 1.25 (0.89-1.56) |
| 31-45 (n=43)            | 14.10 (12.70-16.20)    | 27.8 (24.90-32.60)       | 3.62 (3.10-5.23)  | 1.35 (1.05-1.61) |
| 46-60 (n=15)            | 13.90 (12.60-15.30)    | 26.60 (23.40-31.10)      | 3.80 (3.18-4.80)  | 1.35 (1.10-1.60) |
| Blood group             |                        |                          |                   |                |
| A (n=25)                | 14.10 (13.10-16.20)    | 26.80 (24.90-28.60)      | 3.92 (3.22-5.23)  | 1.32 (1.14-1.52) |
| B (n=25)                | 13.80 (12.80-15.40)    | 27.20 (25.40-30.10)      | 4.12 (3.10-4.62)  | 1.32 (1.18-1.61) |
| AB (n=25)               | 13.90 (12.60-16.20)    | 26.20 (23.40-28.20)      | 4.09 (3.22-4.25)  | 1.45 (1.18-1.56) |
| O (n=25)                | 14.20 (12.90-16.20)    | 30.20 (28.90-32.60)      | 3.54 (3.14-4.32)  | 1.08 (0.89-1.40)*|
| Smoking                 |                        |                          |                   |                |
| Yes (n=14)              | 14.40 (13.60-15.90)    | 27.20 (25.40-30.60)      | 4.20 (3.22-5.23)* | 1.38 (1.05-1.60)*|
| No (n=86)               | 13.90 (12.60-16.20)    | 27.70 (24.30-32.60)      | 3.82 (3.10-4.62)  | 1.32 (0.89-1.61) |
| Alcohol                 |                        |                          |                   |                |
| Yes (n=11)              | 13.80 (12.60-16.20)    | 26.80 (25.60-31.20)      | 3.80 (3.14-5.23)  | 1.20 (0.92-1.61) |
| No (n=89)               | 13.90 (12.60-16.20)    | 27.20 (24.30-32.60)      | 3.89 (3.10-4.82)  | 1.34 (0.89-1.54) |

*P<0.05 in comparison to a baseline. CS37 = Activated partial thromboplastin time, PT=Prothrombin time

Table 2: Quality control parameters of fresh frozen plasma frozen and thawed by different algorithms

| Factor                  | Baseline | CS37 | CS45 | M37 | M45 |
|-------------------------|----------|------|------|-----|-----|
| PT Control: 13.2 s      | 13.40 (12.80-14.70) | 13.70 (12.80-14.80) | 13.80 (13.0-15.40) | 14.10 (12.90-15.50) | 14.30 (13.50-15.80) |
| aPTT Control: 32.8 s    | 29.20 (27.10-31.60) | 30.60 (28.20-32.80) | 31.0 (28.40-33.60) | 33.50 (30.20-35.60) | 33.80 (30.6-36.20) |
| Fibrinogen (g/dL)       | 3.98 (2.88-5.26)    | 3.92 (2.81-5.12)    | 3.90 (2.78-5.06)   | 3.86 (2.81-5.07)    | 3.84 (2.80-5.04) |
| F V (IU/mL)             | 1.34 (0.84-1.54)    | 1.24 (0.80-1.45)    | 1.18 (0.75-1.37)   | 1.06 (0.71-1.24)    | 1.04 (0.70-1.20) |
| F VII (IU/mL)           | 1.23 (0.98-1.57)    | 1.06 (0.82-1.35)    | 1.06 (0.84-1.44)   | 1.02 (0.80-1.44)    | 1.04 (0.82-1.30) |
| F VIII (IU/mL)          | 1.43 (0.96-1.69)    | 1.35 (0.87-1.65)    | 1.32 (0.87-1.62)   | 1.12 (0.80-1.35)    | 1.10 (0.77-1.29) |

P<0.05 in comparison to * baseline CS37 CS45. aPTT=Activated partial thromboplastin time, PT=Prothrombin time

Discussion

Therapeutic efficacy of FFP is determined by the levels of various coagulation factors contained in the unit. Factors which influence the concentration of coagulation factors in FFP may be donor-specific or related to the process of preparation, storage, and thawing. In this study, we have evaluated the influence of donor variations and ex vivo factors on the quality parameters of FFP with the aim of optimizing its hemostatic potential for clinical use.

On assessing the donor-related factors, we could not discern any significant differences due to gender and age group of the donor, which is in line with several previous studies. In a study to examine the quality of plasma in relation to a donor’s age and gender, Madla et al. found that females exhibited noticeably lower aPTT levels than male donors which could be due to lower dilution affected by citrate phosphate dextrose anticoagulant as compared to male plasma rather than gender-based differences. They also found elevated INR, factor VIII, and fibrinogen with increasing age of the donors. The authors, however, could not identify any major shifts between procoagulating, anticoagulating, or fibrinolytic activities with increased age, thus concluded that these alterations are of no consequence in influencing the product quality.

The relationship between coagulation factor levels and ABO blood group has been well reported by several studies wherein lowest factor VIII levels are present in O blood group population. Factor VIII with a lower threshold value of 0.70 IU/ml is considered as a representative of all the other proteins of the coagulation system as per the international guidelines, thus an important parameter for checking the quality and stability of FFP. In this study, we have found significantly lower levels of factor VIII (P < 0.05) compared to FFP of all other ABO blood groups, but still, the levels are well above the threshold for exerting optimum hemostatic effect. Thus, O group FFP qualifies the quality control criteria, and the therapeutic efficacy is uncompromised.

The quality control parameters were not significantly different among FFP of other ABO blood groups. The authors, however, could not identify any major shifts between procoagulating, anticoagulating, or fibrinolytic activities with increased age, thus concluded that these alterations are of no consequence in influencing the product quality.
Cigarette smoking is known to exert diverse effects on human physiology. Numerous epidemiological studies have reported an elevated coagulation factor levels and hence reduced PT and aPTT among the smokers. In this study, we have found significantly increased ($P < 0.05$) fibrinogen levels in the FFP of chronic smokers. There were, however, no significant differences in the levels of other coagulation factors. It has also been reported that ethanol intake affects hemostasis by decreasing fibrinogen, factor VIII, and vWF levels.[3,15] In the present study, we could not find any significant differences in coagulation factor levels compared to nonalcoholics. The plausible reason may be that we have taken normal healthy donor population who have visited the blood center with the intention of donating blood. These donors are less likely to be heavy drinkers, and hence, their hemostasis was not deranged significantly compared to control population.

Freezing of plasma is an important process to ascertain the optimum quality of FFP. In case of slow freezing when the freezing time is >1 h, ice formation occurs at periphery and solutes are concentrated in the center. Inactivation of factor VIII occurs due to exposure to high concentration of salts for a prolonged period. During rapid freezing, the ice formation overtakes the solute displacement and small clusters of solidified solute are homogeneously trapped in the ice, and there is no prolonged contact between highly concentrated salts and factor VIII.[14] Thus, by bringing core temperature to −30°C or below within 1 h, factor VIII activity is preserved.

In our study, we have compared the efficacy of contact shock and MFs. The CSF had an operating temperature of −50°C, and the plasma attained a core temperature of −30°C in 40 min. We have found that rapid freezing through CSF leads to significantly better preservation of factors V and VIII. Several previous studies have also demonstrated better FFP quality through rapid freezing. The results of one study have shown that slow freezing rate results in heavier cryoprecipitate formation which has lower specific factor VIII activity. The authors have recommended complete freezing of plasma within 30 min.[16] Results from another study have shown that short freezing time of within 60 min is advantageous in avoiding unnecessary loss of factor VIII activity and freezing times of 4 h or more cause a significantly more pronounced fall of factor VIII in plasma.[17] In a study conducted to compare the quality
of source plasma produced by slow freezing versus rapid freezing, Hellstern et al.[18] examined plasma units which had been deep frozen either slowly at −30°C in walk-in freezers or rapidly within 1 h to a core temperature below −30°C. They found substantially lower yields of factors V and VIII in slow frozen plasma. Akerblom et al.[19] found higher residual coagulation factor levels with rapid freezing. They reported that factor VIII levels were reduced to 90% by rapid freezing and 80% by slow freezing, whereas factor V levels were unaffected by rapid freezing and decreased to 92% of prefreezing levels by slow freezing.

We have found no significant variation in the PT, fibrinogen level, and factor VII levels with any of the freeze-thaw algorithms. The aPTT was higher on mechanical freezing compared to baseline. A study on fresh plasma samples from healthy blood donors, frozen by rapid and slow techniques at −20°C and −70°C, Alesci et al. found that freezing temperatures have little effect on fibrinogen levels. The effect on PT and aPTT was inconstant and unpredictable.[20] Another study to evaluate the effects of the thawing process on various coagulation factors of FFP showed a decline in factor VII levels which were independent of the thawing procedure.[21] A recent study by Runkel et al. showed that while slow freezing at −18°C reduced factor VIII levels by 17%–25% as compared to rapid freezing at −30°C, the losses in factor VII levels very small.[22]

Thawing techniques for FFP are varied and imprecise across the world as temperature control of the equipment is not stringently monitored. This may lead to variation in quality of FFP and hence a deviation in therapeutic efficacy. We have thawed FFP at two distinct temperatures in our study. Thawing at 37°C took nearly double the time but as compared to thawing at 45°C. There was no significant decline in factor levels by thawing at a higher temperature. The residual levels of factor levels were well above the minimum prescribed levels of >70% in all FFP units.

A study done by the South African Blood Transfusion Services to evaluate the effects of various thawing temperatures on coagulation parameters also showed that fibrinogen levels remain stable between 22°C and 45°C and decreased significantly at 60°C.[23] Another study by Plotz and Ciotola showed no significant differences in PT, aPTT, fibrinogen concentration, and factor VIII activity while thawing the FFP at 45°C compared to 37°C presumably due to the shorter duration of heat exposure which balances the higher intensity.[24] In this study, FFP thawed at 45°C was removed when a slight “slushy” consistency remained, well before complete thawing. Their thawing time at 37°C ranged from 14 to 20 min and at 45°C from 7 to 12 min. In our study, units were removed only after complete thawing yet we did not find any significant decrease in coagulation factor levels.

A study by von Heymann et al.[25] to evaluate the effect of three thawing procedure, namely, water bath at 37°C, microwave blood warmer, and running water at 42°C showed that thawing procedures under study exhibited no significant influence on activity and stability of the markers of coagulation. Thawing temperature of 42°C did not significantly reduce the activity of clotting factor and allowed a faster thawing process and allocation of FFP in cases of massive transfusion. Westphal et al.[25] also found that thawing FFP units at 56°C are much rapid than at 37°C. The activities of factor V and factor VIII declined at 56°C, but there were no demonstrable alterations in fibrinogen, PT, aPTT, factors II, VII, IX, and XI between the two thawing temperatures. The authors have proposed rapid thawing of FFP at higher temperatures in case of emergency emphasizing on the removal of units just before complete thawing and immediate transfusion to prevent heat denaturation of coagulation proteins.

It is important to optimize all steps in the collection, separation, freezing, storage, and thawing of FFP for obtaining good hemostatic outcome and to avoid unnecessary losses. Donor demographic factors have little influence on the quality of FFP if donor selection has been done stringently based on the standard guidelines. Based on findings, it is recommended that plasma component should be frozen rapidly within 1 h and thawed at controlled temperatures as per the validated procedure. Furthermore, rapid thawing of FFP at 45°C may be considered to circumvent delays in emergency cases where FFP is required urgently, without compromising on therapeutic hemostatic potential.

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Conflicts of interest
There are no conflicts of interest.

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