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Comparison of Factor 8 (VIII) and fibrinogen Viability in Whole Blood and Fresh Frozen Plasma

Goodnews Nkabari Nwika [1], Ransom Baribefii Jacob[2], Beatrice W. Moore-Igwe[2]

[1] Department of Medical Laboratory Science, Federal University Otuoke, Nigeria. Nigeria.
[2] Department of Medical Laboratory Science, Rivers State University, Port Harcourt, Nigeria.

***Corresponding author's contact:** nwikagbook@gmail.com; +2348064229229

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Abstract

Background: In a special medical condition like coagulopathies, a fresh whole blood or stored FFP are often required, however, questions arise regarding the availability of required blood constituents and their integrity. **Aim:** To evaluate the viability of blood products before transfusion, with a focus on comparing the viability of haemostatic parameters in both whole blood and FFP. **Methodology:** Using an experimental study design, 32 male and female subjects with blood groups A, B, AB, and O in equal proportion were recruited. Following a baseline assessment for the blood under study, blood pints were collected using standard method of phlebotomy. Some pints were fractionated into whole blood and FFP, stored at 4±20C and -600C respectively. Manual Prothrombin time (PT), activated partial thromboplastin time (aPTT) and enzymatic assays for fibrinogen (FIB) and factor VIII (FVIII) were employed, and result obtained statistically analyzed using ANOVA and significance level set at $P < 0.05$. **Results:** The analysis across both storage duration and component types reveals significant temporal and sample-dependent variations in PT, INR, APTT, and FIB ($P<0.05$), whereas FVIII remained consistently non-significant ($P>0.05$). Storage beyond 21 days led to strongly significant increases in PT and INR, alongside a significant decline in FIB and eventual prolongation of APTT. Comparatively, Whole Blood exhibited strongly significant deviations from baseline in PT and INR, while Fresh Frozen Plasma maintained values statistically similar to baseline for both PT and FIB. **Conclusion:** Lower temperatures, especially freezing at -60°C, helped maintain the stability of coagulation factors. Prolonged storage of whole blood led to significant alterations in FVIII and FIB. Fresh frozen plasma (FFP) should therefore be considered as the preferred option for haemostatic transfusion therapy due to its stability in maintaining intrinsic and extrinsic coagulation factors.

Key Words: *Viability, Factor VIII, Fibrinigen*

1.1 Introduction

Whole blood and Fresh frozen plasma (FFP) are vital components in transfusion medicine, and its proper storage and use are essential for managing various clinical conditions. FFP can be prepared from whole blood or plasmapheresis within 8 hours of donation, and when properly stored at -18°C or colder could cause the viability of stable and labile coagulation factors, including fibrinogen and factor VIII, normal plasma proteins, procoagulants, inhibitory components of the coagulation system, acute phase proteins, immunoglobulin, and albumin [1,2]. FFP can be viable for up to 12 months but can be extended to 7 years if stored at -65°C, [3]

Upon request for blood transfusion, FFP is thawed for 30 minutes at 37°C, [4] In the past, it was common practice to store thawed FFP for 24 hours at 1–6°C, after which it was discarded if not transfused, leading to resource wastage. However, the American Association of Blood Banks (AABB) introduced thawed plasma (TP) stored at 1–6°C with an extended expiry date of up to 5 days, helping to reduce wastage [4]. According to Siti and his colleagues [1], a significant reduction in coagulation factor activities over 5 days of storage underlines the importance of proper storage and use to maintain the effectiveness of FFP

Where it is unacceptable to wait for laboratory results, especially in a case of massive blood loss, FFP helps in the replacement of coagulation proteins when specific factor concentrates are unavailable. If this factor VIII and fibrinogen are preserved in the FFP at the ideal storage temperature, it can be used to reverse the effects of warfarin in patients with active bleeding, although specific antidotes like prothrombin complex are preferred when available [5]. It can also be used in treatment of deficiencies in other clotting factors including FII, FV, FVII, FIX, FX, and FXI

Although the viability and function of stored whole blood have been a subject of ongoing research and concern in the field of transfusion medicine, there is indeed considerable variation in the viability and function of FVII and FIB in fresh whole blood and in FFP. In such regards, Proper storage solutions are also critical to ensure the conservation of both the viability and functions of these factors during storage [6]. The effects of storage on blood viability are significant, and it has been suggested that blood transfusion may increase mortality in certain patient categories due to improper storage. Such mortality could be due to the presence of white blood cells, residual plasma, or nonviable red blood cells in the stored whole blood. As a result, the specific use of FFP when factor VIII is needed are considered mandatory for critically ill patients in that regard [6]

Current studies have established that early fibrinogen administration will also be of high benefits to women that experience massive post-partum haemorrhage [7]. Early administration of adequate amounts of fresh frozen plasma to women under such condition should therefore be recommended and in the right ratio [8]. This serves as an effective transfusion strategy in massive post-partum haemorrhage [8]. In this regard, it is also on record that, Factor VII and fibrinogen in stored whole blood is a pointer to the haemostatic viability in case of emergency. The same study has also shown that 2–4 g of fibrinogen concentrate is effective in achieving hemostasis in patients with massive post-partum

haemorrhage whose plasma fibrinogen levels are <150 mg/dL [8]

Although the Prothromnin Time (PT) test and Activated Partial thromboplastin Time (APTT) test could be a useful tool in the assay of these clotting factors, direct enzymatic assay of the FVIII and FIB has showed a better picture of their viability over a long storage period. A study on the coagulation levels of thawed quarantine fresh frozen plasma has reported that, during storage at room temperature for up to 6 hours, the aPTT is prolonged by 6% . During storage at 4 °C for 2 weeks, the aPTT and PT are prolonged by 17 and 15%, respectively and fibrinogen was decreased by 8%. The study therefore, drew a conclusion that fresh frozen plasma (FFP) stored at room temperature for 6 h or at 4 °C for 2 weeks can provide sufficient support for adequate haemostasis. [9]

A study has it that, deterioration of factor V lll is possible if blood is stored under an ideal blood bank conditions [10]. Genny in 2020 stressed that stored blood use in transfusion seems to be the only source of all coagulation factors including factor VIII [11]. Under this assumption, the levels of coagulation factors in the patient should exponentially approach the levels being transfused [11]. This study focused on evaluating the viability of blood products before transfusion, with a focus on comparing the viability of factor VIII and fibrinogen in both whole blood and FFP.

2.0 MATERIALS AND METHODS

2.1 Study Area

This research was carried out at Rivers State University Teaching Hospital (RSUTH) in Port Harcourt**,** located at Global Positioning System (GPS) Coordinates of 4.77978 N, 7.01579 E and has a population of 1,382,592 out of the total population of 5,198,716 people in Rivers State.

2.2 Study Design

An experimental study design was employed in this research, involving freshly donated blood at stored blood at normal banking temperature of 4±2^{0}C and fresh frozen plasma stored at -60^{0}C, examined at day 1 (24 hours), days 7, 14, 21, 28 and 35, as well as day 180 at -60^{0}C extended temperature. A simple random sampling technique based on multi-stage probability sampling, as described by Bhandari [18] was used to assess the 32 voluntary blood donors used for this study. Recruitment selection based on the inclusion and exclusion criteria specified by the World Health Organisation, resulted in a gender and blood group-stratified donor sample, with an equal proportion of ABO blood groups (A, B, AB and O) for males and females.

Samples from the assessed study population was divided into two parts, one used as whole blood and the other group used for components preparation of the fresh frozen plasma (FFP) and analysed for haemostatic parameters (prothrombin time-PT, activated partial thromboplastin time –aPTT, fibrinogen-FIB and antihaemophilic factor-FVIII) and analysed at day 1 (24 hours), days 7, 14, 21, 28 and 35, as well as day 180 at -60^{0}C extended temperature.

The prothrombin time and activated partial thromboplastin time, were measured using the manual method described by Akbar [10] while the Fibrinogen and anti-haemophilic factor (FVIII) were assessed using enzymatic method described by Ben [14]

2.3 Study Population

A total of 32 male and female donors in the age bracket of 18 to 59 years was calculated using

F tests - ANOVA: Repeated measures, between factors with G-power statistical package version 3.1.9.2 (2014).

2.4 Eligibility Criteria

The study subjects were carefully selected based on WHO eligibility criteria,

2.5 Ethical Clearance/Informed Consent

Ethical approval for this research was obtained from Rivers state Research and Ethics Committee. Also, a written consent was obtained from the individuals whose samples were used for this study.

2.6 Sample Collection Procedure

With the vacutainers sample collection system, using the venipuncture method in line with the WHO recommendations bottles, 2 ml of fresh blood was collected directly from the donors for serological screening. With strict adherence to pre-donation requirements and donors management, **a** 450ml unit of blood was collected from qualified donors using the venipuncture method as described by the World Health Organization [15]

3.7 Blood Components Preparation

The sedimentation method using the Cold Centrifuge as described by Lotens in 2015 [15] was used.

The donor was bled into 450 bag attached with multiple satellite bag. **150 mls of the whole blood** was expressed into a satellite bag, cut and stored as whole blood. The remaining 300mls of the whole blood with that attached satellite bags were balanced and centrifuged at a light spin of 2500 rpm 8^0C (that is, 1500G at 22^0 C) for 5 minutes. The separated platelet rich plasma (PRP) was expressed off the packed red cells (PRP) into a satellite bag (haven broken the internal barrier). The red cells bag was clamped (sealed) then cut off. The platelet rich plasma satellite bag was then centrifuged with a heavy spin of 3200 rpm at 4^0c (that is, 5000G at 22^0C) for 15 minutes. The platelet poor plasma (PPP) was then expressed off the platelet concentrates (PLC) into the second satellite bag and was rapidly stored at -60^0C as fresh frozen plasma (FFP) [15]

3.8 Statistical Analysis

The excel spreadsheet was used to organize the raw data of the results of the samples obtained from the study subjects of this research. Data obtained were inputted into the SPSS version 27 and statistically analyzed using, independent t-tests, descriptive analysis and univariate analysis. Value obtained were considered significance at alpha level <0.05 and 95% confidence interval.

3.0 RESULTS

Table 1. Haemostatic Parameters at different storage duration

Parameters	PT (s)	INR	APTT (s)	FIB (mg/dl)	FVIII (%)
Duration	MEAN±SD	MEAN±SD	MEAN±SD	MEAN±SD	MEAN±SD
Baseline	14.50±1.07	1.15 ±0.12	39.51±3.26	342.00±18.94	0.94±0.06
1HR	14.49±1.10	1.16±0.10	40.16±2.89	340.75±18.69	0.95±0.06
24HR	14.69± 0.76	1.17±0.09	40.40±2.75	340.79±18.27	0.91±0.05
Day 7	15.99±0.88	1.29±0.08	40.73±3.16	328.54±26.69	0.77±0.19
Day 14	17.01±1.28	1.37±0.09	41.25±3.23	281.25±46.41	0.76±0.17
Day 21	24.31±6.67[a]	4.25±7.95[a]	46.63±6.28	227.96±84.13[b]	0.62±0.22
Day 28	25.25±7.17[a]	4.34±7.92[a]	49.42±8.54[a]	221.04±88.55[a]	0.53±0.28
Day 35	25.25±7.17[a]	4.34±7.92[a]	49.71±8.59[a]	113.63±164.49[a]	0.48±0.29
Day 180	0.00	0.00	0.00	338.63±35.51	0.86±0.05
F-value	22.03	1.85	11.47	19.99	0.81
P-value	0.00[s]	0.01[s]	0.00[s]	0.00[s]	0.58[ns]

[s]= Significant at P < 0.05, compared with the baselines at 0Hr;
[ns]= Not significant at P < 0.05, compared with the baselines at 0Hr
[a]= strongly significant at P < 0.05 (Post hoc) at specific storage duration.
[b]= moderately significant at P < 0.05 (Post hoc) at specific storage duration.

The statistical analysis shows significant changes over time for PT, INR, APTT, and FIB (P<0.05), while Factor VIII remained non-significant (P=0.58). Specifically, PT and INR exhibited a strongly significant increase starting at Day 21, and APTT reached a similar level of significance by Day 28. Fibrinogen levels showed a significant decline beginning with a moderate change at Day 21 and a strong reduction by Day 28 and Day 35. By Day 180, PT, INR, and APTT values were recorded at 0.00, whereas Fibrinogen and Factor VIII levels remained detectable and comparable to earlier levels.

Table 2. Variation in Haemostatic Parameters in Whole blood and FFP

Parameters	PT (s)	INR	APTT (s)	FIB (mg/dl)	FVIII (%)
Component Types	MEAN±SD	MEAN±SD	MEAN±SD	MEAN±SD	MEAN±SD
Baselines	14.50±1.07	1.15±0.12	39.51±3.26	342.00±18.94	0.94±0.06
Whole Blood	16.49±6.74[a]	3.37±6.95[a]	43.12±4.77	246.38±116.42	1.88±9.28
Fresh Frozen Plasma	15.33±0.76[ns]	1.24±0.08	39.95±2.88	341.15±18.14[ns]	0.89±0.05
f-value	23.71	2.33	37.48	25.82	0.88
P-value	0.00[s]	0.00[s]	0.00[s]	0.00[s]	0.42[ns]

[s]= Significant at P < 0.05, across the sample types compared with the baselines;
[a]= strongly significant at P < 0.05 (Post hoc) in specific sample type
[ns]= Not Significant at P < 0.05, across the sample types compared with the baselines
[ns]= Not significant at P < 0.05 (Post hoc) in specific sample type

The result shows significant variations in PT, INR, APTT, and FIB across the different sample types (P<0.05), while FVIII levels remained statistically comparable to the baseline (P=0.42). Specifically, Whole Blood exhibited a strongly significant increase in PT and INR values compared to the baseline (P<0.05). Conversely, Fresh Frozen Plasma showed no significant difference from baseline for PT and FIB levels. Overall, while the global comparison indicates significant differences in most coagulation parameters based on the component type, Factor VIII levels did not show a significant change across the groups.

4.0 DISCUSSION

A holistic consideration of this result revealed loss of intrinsic and extrinsic factors of coagulation under the different storage conditions, this finding align with a study conducted by Nwika [16], which observed a prolonged aPTT in eight units of CPD-stored blood. A similar study in the Netherlands reported that during storage at room temperature up to 6 hours, and at 4±2°C for 2 weeks, aPTT and PT were prolonged by 17% and 15% respectively, with a decreased fibrinogen. This occurred due to time-dependent changes in the stored blood leading to changes like degradation of clotting factors under different storage conditions. Over time, these clotting factors could degrade or become less active, leading to prolonged aPTT and PT. Also, extreme temperatures or inadequate anticoagulation, can affect the integrity of clotting factors and lead to prolonged aPTT and PT results. Factors like inadequate mixing, contact with foreign surfaces, or other pre-analytical variables could also cause the observed elongation [16]

Despite the slight reduction in fibrinogen, the non-significant decrease observed in factor VIII

contradicts the findings of Akbar et al. [10], who concluded that platelet viability and the activities of certain coagulation factors, primarily factor V and factor VIII, are significantly reduced during storage. These differences may be attributed to previous researchers' comprehensive examination of these changes exclusively in whole blood at temperatures between 2°C and 6°C [17]. Nevertheless, the current study critically investigated haemostatic changes in both whole blood and various blood components at both frozen and standard storage temperatures, which may be the reason for such observed differences. In the FFP at -60°C, cellular activities are halted, leading to less degeneration compared to the active cellular metabolism in units stored at 4±2°C and room temperature. This active metabolism results in the production of substances that affect their viability.

4.2 Conclusion

Strict adherence to appropriate storage temperatures for blood and its components**,** with a preference for freezing at -60°C to preserve FVIII and fibrinogen**.** Lower temperatures, especially freezing at -60°C, helped maintain the stability of coagulation factors. Prolonged storage of whole blood led to significant alterations in FVIII and FIB**.** Fresh frozen plasma (FFP) should therefore be considered as the preferred option for haemostatic transfusion therapy due to its stability in maintaining intrinsic and extrinsic coagulation factors.

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