

# Thawed Plasma: Maintaining efficacy while minimizing wastage

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## ABSTRACT

According to regulatory guidelines, Fresh Frozen Plasma expires within 24 hours of thawing. Therefore, if transfusions are delayed or cancelled, FFPs are often wasted. The coagulation factor activity of thawed plasma was extensively researched and it was determined that most of the factor activity maintained its efficacy for four days after thawing making it usable with equivalent clinical results. Although derived from FFP, the composition of this product differs slightly and so, the AABB introduced this product as a separate entity called Thawed Plasma. In the US, many blood banks have been using Thawed Plasma interchangeably with FFPs. This not only increases the inventory of plasma products but also eliminates thawing time, providing faster patient care. There are still some concerns regarding transfusing neonates and liver failure patients, but for the majority of surgical patients or those with elevated INRs, Thawed Plasma is an acceptable alternate to FFP. This manuscript reviews attributes and benefits of thawed plasma and its approval by various recognized authorities.

**KEY WORDS:** *Fresh Frozen Plasma, Warfarin Effect, Extended Life Plasma.*

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## INTRODUCTION

Human blood is an essential element of human life and there are no substitutes. Over ten million blood units are collected every year.<sup>11</sup> Nevertheless many more millions still need to be collected to meet the global demand and ensure sufficient and timely provision of blood.<sup>1</sup> After the introduction of blood banks and better storage techniques blood and its components are more widely used in patients.<sup>1</sup> In Pakistan more than 1.5 million pints of blood are collected each year which are transfused to trauma patients, surgical patients and patients who need lifelong transfusions like Thalassemia.<sup>2</sup>

Once a unit is donated in the form of whole blood it is centrifuged so as to separate the acellular portion of blood that is plasma from packed Red Blood Cells (RBCs) and Platelets. Once platelets, RBCs and plasma are separated they are collected in accessory blood bags using an automated extractor. Next the platelets are stored at 22 – 26°C for five days, RBCs at 1-6°C for an average of 30 days<sup>4,5,6</sup> and plasma is stored at – 18°C for one year and can also be stored for 10 years at – 30°C.

This plasma, also called Fresh Frozen Plasma (FFP) is one of the most frequently ordered blood component as it is used in a multitude of clinical scenarios, including massive bleeding, reversal of warfarin effect and elevated INR.

Regulatory committees worldwide including Pakistan mandate that FFP expires within 24 hours of thawing and cannot be transfused beyond that time period. By strictly following this rule, blood banks end up discarding multiple plasma units, which is not only a waste of resources but also adds to the financial burden of maintaining a sufficient inventory in the blood bank.

Multiple researches were done to see the impact of extending the shelf life of FFPs. When using plasma beyond the expiry time of 24 hours, the results were encouraging and the American Association of Blood Banking (AABB) established this as a new entity called “Thawed Plasma”.

The purpose of reviewing this subject is to weigh the pros and cons of using thawed plasma and

analyze the reasons behind acceptance or rejection of this product by various committees.

## DISCUSSION

### Fresh Frozen Plasma (FFP)

The term FFP is a paradox in itself because things can either be fresh or frozen then why is it called FFP? The answer is that it is frozen while it is fresh that is within 8 hours of collection.<sup>7</sup> FFP is an acellular product derived from blood and mainly composed of coagulation factors, immunoglobulins, fibrinogen, albumin and other plasma proteins.

### Indications for the Use of FFPs

According to the guidelines there are certain indication for the use of FFPs that include dilutional coagulopathy, multiple coagulation factor deficiency, Thrombotic Thrombocytopenic Purpura (TTP), Disseminated Intravascular Coagulation (DIC), reversal of warfarin effect, liver diseases, cardiopulmonary bypass and massive transfusions. All these indications require that FFPs be provided as soon as possible as any delay can be detrimental to the patient's wellbeing<sup>4,8</sup>.

According to a study conducted in South Africa in 2012 the major cause of FFP use was DIC and bypass procedures.<sup>9</sup> In Pakistan liver disease is one of the common indications for the use of FFPs.<sup>10</sup>

Another study was conducted in Pakistan in 2009 which showed different trends of FFP usage and the data showed that 37% FFP requests were by the paediatric medicine unit, followed by the medicine units and then others.<sup>11</sup>

### Conflicting Opinions Regarding Expiry of FFPs

Whenever an FFP is indicated a unit is taken out from the freezer and melted or thawed for about 30 to 45 minutes in a water bath before they are transfused into the patient.<sup>4</sup> The guidelines set by American Association of Blood Banking (AABB) state that FFP should be used within a short time after thawing that is 6 hours if stored at room temperature and 24 hours if stored at 1 to 6°C.<sup>4,12</sup>

The current international guidelines for the storage of fresh-frozen plasma are established by AABB<sup>5</sup>, United Kingdom (UK)<sup>13</sup> and European Union (EU).<sup>14</sup> There are slight differences in the international guidelines for temperature and timing but both AABB and UK agree to store plasma for 24 hours at 1 to 6°C after thawing whereas the EU uses plasma immediately after its production.<sup>15</sup>

## Establishment of a New Entity... Thawed Plasma

After a request of FFP, a unit is taken out from the freezer and thawed but is not always transfused immediately either due to cancellation of a surgery or delay of a procedure or for any other reason it is kept for a period of time. These FFP units often have to be discarded if 24 hours pass by.<sup>12,16</sup>

Furthermore, while FFPs remain the first choice for the treatment of large volume of blood loss and prevention of DIC and coagulopathies, its immediate availability is delayed by the thawing procedure which takes about 30 to 45 minutes and pre-thawing for possible use within the expiry time would result in large quantities of FFP being discarded.<sup>17</sup>

Since regulatory committees worldwide mandate that FFP expires within 24 hours of thawing and cannot be transfused beyond that time period, hence blood banks end up discarding multiple plasma units, which is not only a waste of valuable resources but also leads monetary loss.

In the US, this was recognized as an ongoing problem and research was conducted to study the decline of coagulation factor activity within FFP after expiration. In a 2001 study by Downes et al<sup>18</sup>, it was determined that Factor VII activity dropped by 20% between Day 1 and Day 4, Factor V dropped by 16% in that time period, whereas Factor II and Factor X had a 1% and 6% change respectively. There was no change in fibrinogen levels during this time period. All results had a p value of <0.05.

These results were considered clinically not significant although there was a decline in the factor activity level by the fifth day after thawing, but were still good enough to maintain haemostasis and could be transfused to the patients with equal efficacy as FFP with a slight difference in the indications.

On the other hand, Factor VIII activity was seen to drop by approximately 40% due to its short half life. This was not considered to have a significant impact on the clinical efficacy of Thawed Plasma as Factor VIII levels are usually normal in bleeding surgical patients and Factor VIII plays no role in warfarin reversal. Patients with a solitary deficiency of Factor VIII should be treated with factor concentrates (purified and recombinant) and if unavailable, the next line of treatment should be cryoprecipitate, not plasma.

Multiple studies followed which showed similar results<sup>12,19,29</sup> and subsequently, FFP began to be used beyond the 24 hr expiration period. The clinical outcomes were equivalent to FFP and this product began to gain popularity with transfusion medicine specialists and clinicians alike.

Thus it was established by the AABB (Association of American Blood Banks) Circular of Information for the Use of Human Blood and Blood Components<sup>2</sup> that FFPs could be used after thawing if maintained at 1 to 6°C for another 5 days as most of the clotting factors do decline in their activity level but still retain their clinical efficacy and could still be used with equivalent clinical results.<sup>12,17,19 – 27</sup>

Although derived from FFPs the composition of this product differs slightly and so the AABB introduced this product as separate entity called Thawed Plasma or Extended Life Plasma.<sup>4,5</sup>

**Table 1. Comparison of mean values for the coagulation variables from four different studies**

| Factor Assay | References   | Day 1 | Day 5 | Mean Difference (%) |
|--------------|--------------|-------|-------|---------------------|
| Factor VIII  | Reference 12 | 79.4  | 59.7  | 25                  |
|              | Reference 18 | 70    | 41    | 41                  |
|              | Reference 19 | 83    | 64    | 23                  |
|              | Reference 29 | 72    | 62    | 14                  |
| Factor V     | Reference 12 | 75.8  | 60.4  | 20                  |
|              | Reference 18 | 79    | 66    | 16                  |
|              | Reference 19 | 91    | 81    | 11                  |
|              | Reference 29 | 130   | 87    | 30                  |
| Factor X     | Reference 12 | 98.3  | 87.1  | 11                  |
|              | Reference 18 | 85    | 80    | 6                   |
|              | Reference 19 | 96    | 91    | 6                   |
|              | Reference 29 | ---   | ---   | ---                 |

Values of Reference 18 (Factor VIII) is for blood group O.

Reference 29 did not perform the assay on factor X

**Figure 1. Changes depicted observed in clotting factor levels in thawed plasma on Day 1 and Day 5, Downes et al.**



#### The AAB Approved Indications for Thawed Plasma

- Preoperative or bleeding patients requiring replacement of multiple coagulation factors except for patients with a consumptive coagulopathy
- Initial treatment of massive transfusion in patients with clinically significant coagulopathies
- Patients taking warfarin who are bleeding or require an immediate invasive procedure or who need only transient reversal of warfarin effect

FFP is often requested prophylactically by clinicians for patients undergoing cardiac surgery or those with slightly elevated INRs. Although this is commonly seen in clinical practice, it is an unapproved indication. In a study performed in 2006, Holland et al established that only 50% of non-bleeding patients with an INR of 1.7 show a significant change in INR with FFP transfusion.<sup>3</sup> Studies conducted in different parts of the world, have confirmed that indications for transfusing FFP are not clearly understood by ordering physicians and the product is often used inappropriately. Data from Singapore, in 2003, showed that approximately 70% of FFP requests are inappropriate<sup>4</sup>, whereas in Canada 45% of FFP transfusions are not clinically indicated.<sup>5</sup> A

2007 study conducted in Pakistan by Shariff et al indicated that approximately 34% of FFP was inappropriately used due to lack of awareness of guidelines and ignorance of risks.<sup>6</sup>

Research was undertaken to determine the efficacy of thawed plasma in all, approved or unapproved situations in which FFP is used, including hypovolemic shock. Pati S et al studied the beneficial effects of Thawed Plasma on endothelial permeability, vascular stability, and resuscitation in rats after hemorrhagic shock. Just like with FFP, Thawed Plasma showed no benefit in hypovolemia, making it a suboptimal resuscitation medium.<sup>7</sup>

In another study, Lambou et al studied the activity of ADAMTS13 in FFP stored at room temperature for 6 hours and FFP stored at 4°C for two weeks. The study showed that Thawed Plasma can provide sufficient support for adequate haemostasis and can be used for plasmapheresis in patients with thrombotic thrombocytopenic purpura (TTP).<sup>8</sup>

The proposal to extend the expiration date of plasma was welcomed by blood banks nationwide. One study claimed that their plasma wastage declined from 79.7% to 64.9% with cost savings of \$15,654.79<sup>9</sup> whereas another study concluded that an annual saving of \$17,800 could be achieved by storing thawed FFP for 3 days.<sup>1</sup>

Another study was done which claimed that thawed plasma made sense and saved cents.<sup>28</sup> Furthermore, Sidhu et al alleviated fears of contamination by proving that thawed apheresis FFP stored at 1-6 °C for 5 days showed no aerobic and anaerobic growth at 7 days.<sup>10</sup>

There is still some concern about the use of Thawed Plasma in patient groups with severe coagulation factor deficiencies. Some hospitals which have a predominant population of pregnant women and neonates still prefer FFP as they want to provide the highest amount of coagulation factors possible. The same rule applies for liver failure patients or patients with DIC as these groups require large quantities of coagulation factors to prevent or treat life threatening bleeding episodes.

By extending the expiration date of thawed plasma not only does it help the blood banks optimize resources and prevent wastage, but as plasma plays an important role in major blood

loss situations, it provides better services to clinicians and improves patient care as a whole.

Thawed plasma is now being used at multiple facilities across the United States. Most blood banks use FFP and Thawed Plasma

interchangeably for all their patients, whereas other places still prefer FFP over thawed plasma in certain vulnerable sets of population. The decision is left to the Transfusion Medicine Committee in individual hospitals keeping in mind their clinical set up and patient population.

### REFERENCES

- <sup>1</sup> Whitaker BI. The 2011 National Blood Collection and Utilization Survey Report. US Department of Health and Human Services. Report Number: 0990-0313, 2011.
- <sup>2</sup> Malik MR, Majid S, Laghari MS. Determinants of Blood Donation Behaviour of General Public in Pakistan. *Pak J Med Health Sci* Apr-Jun 2010;4(2):137-42.
- <sup>3</sup> WHO. Global Database on Blood Safety Summary Report. Geneva, WHO Press, World Health Organization, 2011. Available at: [http://www.who.int/bloodsafety/global\\_database/GDBS\\_Summary\\_Report\\_2011.pdf](http://www.who.int/bloodsafety/global_database/GDBS_Summary_Report_2011.pdf). Accessed July 25, 2013.
- <sup>4</sup> American Association of Blood Banks (AABB), America's Blood Centers (ABC), the American Red Cross (ARC) and the Armed Services Blood Program (ASBP). An Acceptable Circular of Information for the Use of Human Blood and Blood Components. Bethesda, MD: Food and Drug Administration; 2009. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187348.pdf>. Accessed July 25, 2013.
- <sup>5</sup> Standards Committee of the American Association of Blood Banks. Standards for Blood Banks and Transfusion Services. 28th ed. USA: American Association of Blood Banks; Jul 20, 2012 Available at: <http://www.aabb.org/sa/standards/Documents/sigchngst28.pdf>. Accessed July 25, 2013.
- <sup>6</sup> New York State Council on Human Blood and Transfusion Services. Guidelines for the Administration of Plasma. 2nd ed. Albany, New York: New York State Department of Health; 2004. Available at: [http://www.wadsworth.org/labcert/blood\\_tissue/FFPadminfinal1204.pdf](http://www.wadsworth.org/labcert/blood_tissue/FFPadminfinal1204.pdf). Accessed July 25, 2013.
- <sup>7</sup> Brecher ME. Technical Manual. 16th ed. Bethesda, MD: AABB, 2008.
- <sup>8</sup> Luc C, Eckert KM, Barr RM, Chin-Yee IH. Prospective audit of the use of fresh-frozen plasma, based on Canadian Medical Association transfusion guidelines. *CMAJ* 2002;166(12).
- <sup>9</sup> Visser A, Geldenhuys A, Preez S, Vyver A. Fresh-frozen plasma use in a South African tertiary hospital. *S Afr Med J* 2012;102(6):366-367.
- <sup>10</sup> Moiz B, Arif FM, Hashmi KZ. Appropriate and inappropriate use of Fresh Frozen Plasma. *J Pak Med Assoc* August 2006;56(8).
- <sup>11</sup> Pervaiz A, Naseem L. The Trends of Use of Fresh Frozen Plasma at a Tertiary Care Hospital. *IJP* 2009;7(2): 88-93.
- <sup>12</sup> Naghadeh HT, Maghsudloo M, Tabatabaei MR. Coagulation factors V, VIII, and X, prothrombin time and activated partial thromboplastin time test results in thawed plasma stored at 1-6 °C for 5 days. *Blood Transfus* 2011 Jan;9(1):95-98.
- <sup>13</sup> National Blood Service. Guidelines for the Blood Transfusion Services in the United Kingdom. 8th ed. London: TSO (The Stationery Office); 2013
- <sup>14</sup> European Directorate for the Quality of Medicines & HealthCare (EDQM). Guide to the Preparation, Use and Quality Assurance of Blood Components. 16th ed. Strasbourg, France: Council of Europe; 2010
- <sup>15</sup> Standing Advisory Committee on Blood components. Shelf-life of Frozen Plasma components following thawing. UKBTS General Information: 09, January 2013.
- <sup>16</sup> Lamboo M, Poland DCW, Eikenboom JCJ, et al. Coagulation parameters of thawed fresh-frozen plasma during storage at different temperatures. *Transfus Med* 2007;17(3):182-186.
- <sup>17</sup> von Heymann C, Keller MK, Spies C, et al. Activity of clotting factors in fresh-frozen plasma during storage at 4 degrees C over 6 days. *Transfusion* 2009 May;49(5): 913-920.
- <sup>18</sup> Downes KA, Wilson E, Yomtovian R, et al. Serial measurement of clotting factors in thawed plasma stored for 5 days. *Transfusion* Apr 2001;41(4):570.
- <sup>19</sup> Yazer M H, Cortese-Hassett A, Triulzi D J. Coagulation factor levels in plasma frozen within 24 hours of phlebotomy over 5 days of storage at 1 to 6 degrees C. *Transfusion* Dec 2008;48(12):2525-2530.
- <sup>20</sup> Keller MK, Pruss A, Sander M, et al. Thawed solvent/detergent-treated plasma: too precious to be wasted after 6 hours? *Blood Transfus* Jul 2012;10(3): 360-367
- <sup>21</sup> Sidhu RS, Le T, Brimhall B, et al. Study of coagulation factor activities in apheresed thawed fresh frozen plasma at 1-6 degrees C for five days. *J Clin Apher* Dec 2006;21(4): 224-226.
- <sup>22</sup> Scott EA, Puca KE, Pietz BC, et al. Comparison and stability of ADAMTS13 activity in therapeutic plasma products. *Transfusion* 2007;47: 120-125.
- <sup>23</sup> Kakaiya RM, Morse EE, Panek S. Labile coagulation factors in thawed fresh frozen plasma prepared by two methods. *Vox Sang* 1984;46: 44-46.
- <sup>24</sup> O'Neill EM, Rowley J, Hansson-Wicher M, et al. Effect of 24-hour whole-blood storage on plasma clotting factors. *Transfusion* 1999;39: 488-491.

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<sup>25</sup> Smith JF, Ness PM, Moroff G, et al. Retention of coagulation factors in plasma frozen after extended holding at 1-6 degrees C. *Vox Sang* 2000;78: 28-30.

<sup>26</sup> Cardigan R, Lawrie AS, Mackie IJ, et al. The quality of fresh-frozen plasma produced from whole blood stored at 4 degrees C overnight. *Transfusion* 2005;45: 1342-1348.

<sup>27</sup> Tholpady A, Monson J, Radovancevic R, et al. Analysis of prolonged storage on coagulation Factor (F)V, FVII, and FVIII in thawed plasma: is it time to extend the expiration date beyond 5 days? *Transfusion* 2013 Mar;53(3): 645-650.

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<sup>28</sup> Wehrli G, Taylor N E, Haines A L, et al. Instituting a thawed plasma procedure: it just makes sense and saves cents. *Transfusion* 2009 Dec: 49(12): 2625-2630.

<sup>29</sup> Hiihppala S. Replacement of massive blood loss. *Vox Sang* 1998; 74 (Suppl 2): 399-407.