10 Years of Experience with the First Thawed Plasma Bank in Germany

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Keywords

Thawed plasma bank · Liquid plasma · Clotting factor stability

Abstract

Background: Plasma is stored at -30°C , which requires thawing before transfusion, causing a time delay between ordering and issuing of at least 30 min. In case of bleeding emergencies, guidelines strongly recommend a 2:1 transfusion ratio of RBCs and plasma. In addition, each minute delay in issuing of blood products in bleeding emergencies increases the mortality risk. To provide plasma in time in bleeding emergencies, a thawed plasma bank was introduced in 2011.

Summary: The thawed plasma bank of University Medicine Greifswald has provided 18,924 thawed stored plasma units between 2011 and 2020. The workflow in the laboratory as well as in the emergency room, the operating room, and the intensive care unit have been optimized by thawed stored plasma. In case of emergencies, the stress factor for the transfusion medicine laboratory staff has been reduced substantially. The thawed plasma bank allows to transfuse patients with massive transfusion demand at a 2:1 ratio of RBCs and plasma according to guidelines. To reduce storage time, we issue all plasma requests from the thawed plasma bank except for pediatric patients. This results in a median storage time in the thawed plasma bank of 24 h. The “just in time” availability of plasma within the entire hospital based on the thawed plasma bank has reduced precautionary ordering of plasma, and hereby the unnecessary use of plasma. After introduction of the thawed plasma bank, plasma usage decreased substantially by 24% within the first year and by 60%

compared to 2019/2020. However, as the overall approach to using blood products has changed over the last 10 years due to the patient blood management initiative, quantification of the effects of the thawed plasma bank in reduction of plasma transfusion is difficult. **Key Messages:** (1) A thawed plasma bank for the routine supply of blood products in a large hospital is feasible in Germany. (2) The thawed plasma bank allows to supply RBCs and plasma in a 2:1 ratio in bleeding emergencies. (3) The beneficial logistical effects of the thawed plasma bank are optimal if all plasma requests are supplied from the thawed plasma bank. This results in a median storage time of 24 h for thawed plasma.

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Introduction

Major blood loss is one of the few indications to transfuse plasma [1]. Further indications are deficiency in clotting factors for which no factor concentrates are available like for factor V, improvement of hemostasis in coagulopathy, e.g., in case of liver impairment, increased general clotting factor consumption, plasma exchange for thrombotic thrombocytopenic purpura, and other rare indications [1].

In case of massive blood loss, it becomes increasingly clear that early plasma transfusion and maintenance of a red cells to plasma and single donor buffy coat platelets transfusion ratio of at least 2:1:1 improve patient outcome [2–7]. In this situation, plasma transfusion should be started as early as possible. In a prospective trial, each minute from activation of a massive transfusion protocol

Table 1. Therapeutic plasma formulations [22]

Plasma formulation	Abbreviation	Processing	Preparation time (ready to use), min	Storage temperature, °C	Shelf life	Approval by German regulatory body
Fresh frozen plasma	FFP	frozen within 8 h	30–45	<–30	2–3 years	yes
Thawed FFP	tFFP	thawed FFP	0	2–6	up to 7 days	no
Liquid plasma	LP	not frozen	0	2–6	26 days	no
Plasma, frozen within 24 h	FP24	frozen within 8–24 h	45	–20	365 days	no
Dried plasma	Lyoplas (German Red Cross)	freeze-drying	few minutes	2–25	15 months	yes
	FLYP (France)	freeze-drying	6	room temperature	2 years	no
	Bioplasma FDP (South Africa)	freeze-drying	<10	<25		no
Under development	spray-dried plasma (on-demand plasma), Entegriion Inc. (Research Triangle Park, NC, USA) partnered with Kedrion S.p.A (Barga, Lucca, Italy)	spray-drying	5	?	?	

to arrival of the cooling container at the patient's bedside increased the odds of mortality by 5% [3].

Plasma is stored at <–30°C and has to be thawed before transfusion usually at 37–40°C. Thawing of plasma usually requires approximately 30 min using a conventional water-based plasma thawing device, e.g., plasmatherm (Barkey, Leopoldshöhe, Germany). The use of specially designed microwave ovens for thawing introduced in the late 1980s or thawing at higher temperatures can reduce thawing time [8–12]. Thawing at temperatures of 45°C is safe if the plasma is removed before thawing is completed. Otherwise the hemostatic capacity of the plasma is reduced [13].

Options to provide plasma for transfusion are summarized in Table 1: Primarily used is fresh frozen plasma (FFP) after quarantine storage and thawing at the time of transfusion request. Storage of plasma directly after blood donation without freezing is approved by the Food and Drug Administration (FDA) in the USA, called liquid plasma, with a shelf life up to 26 days [14]. Liquid plasma is not an option in Germany because of the risk of pathogen transmission. As an alternative it is accepted by the FDA to store FFP at 1–6°C for up to 24 h after thawing and to relabel it as thawed FFP (tFFP) for further storage for up to 4 days at 1–6°C [14] based on data by Downes et al. [15] and others [16–20]. Freeze-dried (lyophilized) plasma can be used after reconstitution directly before transfusion [21]. With Lyoplas® (German Red Cross NSTOB, Germany), such a product is available in Germany, but reconstitution takes time and the development of foam during reconstitution seems to be sometimes a problem for the transfusing physician. Spray-dried plas-

ma, also called on-demand plasma, is under investigation but not yet available [22].

The German hemotherapy guidelines accept for FFP a factor VIII activity after thawing of at least 70% of the value before freezing [23]. There are no definitions for minimal clotting factor activities in the product for plasma therapy, and no data from clinical studies are available assessing the efficacy of FFP or liquid plasma transfused after variable days of storage after thawing. Based on the experiences in treatment of severely injured military casualties [24], the recommendation for development and use of a massive transfusion protocol rose [25]. All massive transfusion protocols require the immediate availability of plasma for transfusion.

Under conditions of quarantine storage of plasma to reduce pathogen transmission, thawing of plasma and storage of thawed plasma for up to 7 days has been established by University Medicine Greifswald in 2011. Here we report our experience of working with this thawed plasma bank.

Organization of the Thawed Plasma Bank

Plasma is produced and stored by the manufacturer according to specifications approved by the regulatory body Paul Ehrlich Institute. Hemotherapy-qualified physicians (transfusion committee of the hospital with its head “Transfusionsverantwortlicher”) establish and supervise the organizational structure of hemotherapy in the hospital, including management of the blood bank according to the German hemotherapy guidelines [23].

Fig. 1. Representative results of the endogenous thrombin generation potential (ETP) of one thawed plasma (three measurements of the same plasma at each time point) immediately after thawing (day 0), on days 3, 5 and 7 and storage at 2–6°C. Although the thrombin peak is slightly reduced, the time to peak and overall thrombin generation (area under the curve) do not differ between day 0 and day 7 as both pro- and anticoagulatory factors decrease [17].

The hemotherapy guidelines recommend storage of plasma after validation of specified conditions and immediate transfusion after release of thawed plasma from the blood bank to the recipient [23]. This allows storage of thawed plasma as part of the quality management system of hemotherapy. Specific conditions require individualized regulations for each hospital, including validation and standard operation for plasma processing and transfusion. Accordingly, we performed extensive validation of clotting factor activities using 50 thawed apheresis plasmas to evaluate the hemostatic quality of thawed FFP over 7 days [16, 17]. Plasma units were divided into three biologically identical subunits and either stored for 7 days at 4°C, at room temperature, or at 4°C after methylene blue/light treatment. Single clotting factor activities (II, V, VII, VIII, IX, X, XI, XII, XIII, fibrinogen, antithrombin, von Willebrand factor antigen, protein C and S) and functional hemostasis assays (aPTT, PT/INR, endogenous thrombin generation, and ProteinC® Global) were assessed after thawing and on days 3, 5, and 7. Thawed FFP stored at 4°C for 7 days revealed major changes (activities outside the reference range) only for factor VIII (median 56%, range 33–114%) and protein S (median 51%, range 20–88%). The most pronounced decrease in factor VIII and protein S activity occurred within the first 3 days after thawing (about 50% and 15%, respectively). Thereafter, a further decrease in activity occurred within a 10% range compared to day 3. The storage for 7 days at room temperature affected activities of all clotting factors and inhibitors except for protein C [16].

The endogenous thrombin generation potential remained stable after storage at 4°C ($1,287 \pm 283$ nmol vs. $1,260 \pm 278$ nmol; $p =$ not significant; a representative example is shown in Fig. 1) [17]. The change in procoagulatory factors is compensated by the concomitant decline of the anticoagulatory factors resulting in a new balance. INR and aPTT showed only modest alterations.

Although reports about clotting factor activities after storage of thawed plasma at 1–6°C for several days are sometimes controversial [15, 18, 26–33], a general finding of these studies is that storage is feasible without relevant impairment of hemostatic activity of plasma. Published data have been generated with thawed apheresis as well as with whole-blood (recovered) plasma. Recovered plasma is often later shock-frozen than apheresis plasma, and clotting factor activities might therefore be lower. Whether this has any impact on clinical efficacy is unresolved. No clinical studies or prospective trials evaluating the clinical efficacy of tFFP (apheresis or recovered) in relation to storage time are available.

Patient Populations to Whom Thawed Plasma Is Issued

Situations of massive transfusion are relatively rare. Maintaining a thawed plasma bank for massive transfusion only would result in a major wastage rate. In this case, we expected that the majority of plasmas would be stored up to the end of the storage period (7 days). We therefore provide thawed plasma to all patients for whom plasma is requested, with the exception of pediatric pa-

Table 2. Trauma management policy of University Medicine Greifswald includes consecutively issued trauma boxes by the blood bank, which contain a defined number of blood products for massively bleeding patients

<i>Blood type of the patient is unknown (admission of a severely bleeding patient with unknown blood type to the emergency room)</i>	
First medical care supported by a sub-depot of blood products in the emergency room	4 RBCs blood type O (Rh-positive) 4 g fibrinogen concentrate 2,400 U prothrombin complex concentrate
Trauma box 1 (issued by the blood bank)	4 RBCs blood type O (Rh-positive) 2 tFFP blood type AB (from the thawed plasma bank) 1 platelet concentrate 4 g fibrinogen concentrate
<i>Blood type of the patient is determined (a blood sample was received and serological testing of the ABD red cell antigens was performed; FFP is freshly thawed)</i>	
Trauma box 2	4 RBCs compatible with the patient's ABO blood type, Rh-positive 4 FFP compatible with the patient's blood type or tFFP blood type A from the thawed plasma bank 1 platelet concentrate 2 g fibrinogen concentrate
Trauma box 3, 4, ... (until bleeding is stopped or the anesthetist orders special products)	4 RBCs compatible with the patient's ABO blood type, Rh-positive 4 FFP compatible with the patient's blood type 1 platelet concentrate 2 g fibrinogen concentrate
FFP, fresh frozen plasma; tFFP, thawed stored plasma.	

tients and patients with known single clotting factor deficiencies for whom clotting factor concentrates are available. All other patients, including patients with liver disease, receive thawed plasma. Importantly, patients do not receive more than 4 units of thawed stored plasma because not more than 4 units are thawed in advance. All additional plasma demand is supplied by freshly thawed FFP.

Impact on Blood Bank Management

The use of the thawed plasma bank has reduced workload and stress factors for the technologists of the blood bank. In case of emergencies, plasma can be issued immediately, and also regular requests from the operation theater, the intensive care unit, or any ward can be handled without time delay. This allows the staff to focus on organizational issues associated with the management of bleeding emergencies. In addition, storage of thawed plasma allowed to introduce a trauma management policy at our hospital, including early plasma transfusion and achievement of an RBC:plasma transfusion ratio of at least 2:1 immediately after hospital admission of the patient. With activation of this massive transfusion protocol a "trauma box" is issued to the emergency room containing a defined number of blood products shown in Table 2. Special in-hospital transport staff is activated by phone call (the number is unique for this emergency situation), who then transports the trauma boxes and blood samples of the patient between the blood bank and the emergency room.

The thawed plasma bank has also improved the workflow in the operating room. Plasma can now be ordered when transfusion is definitely indicated. Before the availability of thawed plasma, the anesthetist had to plan always 30–60 min in advance and to order plasma prospectively in case plasma transfusion might be needed; if not needed, the thawed plasma was wasted or transfused based on a weak indication. Furthermore, for surgery with high risk of acute major blood loss (risk of arterial bleeding), we now provide RBCs and thawed plasma in a stand-by cooling container in the operating room. If the RBCs and plasma are not needed, they can be returned to the blood bank and further stored for the next transfusion request. For reintegration of the blood products, the cooling chain must not have been interrupted (monitored by a minimum-maximum thermometer). The annual plasma consumption has declined from a mean of 4,386 units between 2010 and 2016 to 1,779 units in 2020 (Fig. 2). However, due to the parallel establishment of patient blood management with stricter consideration of plasma transfusion indication and use of blood products, it is difficult to differentiate the effects of the patient blood management program and of the thawed plasma bank. Nevertheless, plasma wastage rate has to be evaluated and weighed against the advantages of a thawed plasma bank.

Storage time of the thawed plasma is often a matter of concern. To keep storage times short, we issue all plasma requests from the thawed plasma bank. When plasma is issued from the blood bank, FFP is immediately thawed and the plasma bank is restocked. This results in short

Fig. 2. Overall consumption of plasma from the thawed plasma bank between 2011 and 2020 demonstrating the transfusion and wastage rate. The overall reduction in plasma transfusion in the hospital is also reflected by the reduction in tFFP in the thawed plasma bank. At the end of 2015, type B plasma was omitted from the thawed plasma bank. However, if type B plasma had been issued as FFP and not transfused, the returned plasma bags were integrated into the thawed plasma bank. Total plasma includes freshly thawed and issued FFP and thawed plasma from the plasma bank. FFP, fresh frozen plasma; tFFP, thawed stored plasma.

Fig. 3. Issuing of plasma from the thawed plasma bank. More than half of the thawed units were issued within the first 2 storage days and 81% were issued within 3 days storage time. tFFP, thawed stored plasma.

storage times of the thawed plasma units. During the 10-year period most units (81%) were issued within the first 3 days after thawing (shown in Fig. 3). The median storage time for thawed plasma was 1 day, the mean was 1.81 ± 1.88 days. The overall wastage rate was 6.26% (Fig. 2). This is higher compared to the plasma wastage rate of about 3% (2010: 3.13%; 2018: 3.17%; 2019: 2.92%) reported to the Paul Ehrlich Institute by blood product users in Germany [34], but considering the decline in plasma consumption (by 24.5% within the first year and by 66.7% in 2020 compared to 2011), the introduction of the thawed plasma bank reduced the overall usage of plasma due to the advantages of “just in time” availability. Mostly plas-

ma of blood type B (17.06%) and blood type AB (8.13%) expired in the thawed plasma bank. The lowest wastage rate and close to the overall wastage rate in German hospitals was plasma of blood type A (3.49%). Blood type B patients are rare, and in case of transfusion requests for type B patients, type AB plasma can be used. Therefore, we stopped using type B plasma for the thawed plasma bank in 2015. The ideal product for the thawed plasma bank would be “universal plasma” without isoagglutinins, which can be transfused independently of the patient’s blood group. We are currently developing such a product independently of blood type AB donors [35].

Additional Advantages of the Liquid Plasma Bank

A spinoff of our thawed plasma bank is the blood product supply for the helicopter emergency medical service (HEMS). Only with the background of a thawed plasma bank, the plasma supply for the helicopter allows an acceptable wastage rate of plasma because of the rare pre-hospital transfusion frequency. We provide type A thawed plasma for the HEMS to reduce AB plasma shortage. Since we introduced blood supply for the HEMS, the challenge for the management of the thawed plasma bank was to integrate the returned HEMS plasma without expanding the number of thawed plasmas and increasing their wastage rate.

Possible Risks of the Thawed Plasma Bank

There is the theoretical risk of bacterial growth in plasma during storage at 2–6°C. This risk is not expected to be different from that of red cell concentrates for which 15–20 products are checked monthly after >7 days of storage (49 ± 3 days) [23]. Within 10 years we have not received a single report about a septic transfusion reaction after transfusion of tFFP. However, we have established an additional safety step. After quarantine storage, the frozen plasma bags are labeled and put into a vacuum-sealed plastic bag. The thawed plasma is maintained in this plastic bag to reduce any risk of contamination from the outside in case of microlesions in the plastic bag, which may occur during handling of frozen plasma bags. This overpacking also allows easy discovery of minor leakage.

There could be a risk of providing insufficient clotting factors to a bleeding patient. However, the patient receives a maximum of four plasmas from the thawed plasma bank. Thereafter, freshly thawed FFP is issued. Thus, in any situation where more than four plasmas are transfused, there is no risk of clotting factor activity reduction. In situations where a maximum of four plasmas are transfused, the reduction in factor VIII of the 4 plasma units is barely relevant. This is especially true in patients with liver impairment who typically have elevated factor VIII levels. As the situation is different in newborns and children, we issue thawed plasma only for adult patients.

An additional potential risk of the thawed plasma bank is an increase in plasticizers dissolved from the blood bag into the lipids of the plasma [36]. Higher levels of diethylhexyl phthalate are present in plasma after 5 days of storage than in RBC units after 30 days of storage [36]. But again, the maximal number of tFFP transfused is limited to 4 units. With the introduction of new diethylhexyl phthalate-free whole-blood bag systems, e.g., 1,2-cyclohexane dicarboxylic acid diisononyl ester-containing blood bags, the risk of transmission of plasticizers can be reduced.

Conclusion

The thawed plasma bank of the University Medicine Greifswald has provided 18,924 thawed stored plasma units between 2011 and 2020. The workflow in the laboratory as well as in the emergency room, the operating room, and the intensive care unit have been optimized by thawed stored plasma. In case of emergencies, the stress factor for the transfusion medicine laboratory staff has been reduced substantially. The thawed plasma bank allows to transfuse patients with massive transfusion demand at the 2:1 ratio of RBCs and plasma according to guidelines. The “just in time” availability of plasma within the entire hospital has reduced precautionary ordering of plasma and hereby unnecessary use of plasma or wastage. As the overall approach to using blood products has changed over the last 10 years due to the patient blood management initiative, quantification of the effects of the thawed plasma bank in reduction of plasma units by a before-after comparison is problematic.

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Conflict of Interest Statement

K. Selleng received research funding from Immucor, traveling support from SOBI, and consultant fees from Aspen outside the submitted work. A. Greinacher reports grants and nonfinancial support from Aspen, Boehringer Ingelheim, MSD, Bristol Myers Squibb, Bayer Healthcare, Instrumentation Laboratory; personal fees from Aspen, MSD, Macopharma, Bristol Myers Squibb, Chromatec, Instrumentation Laboratory; and nonfinancial support from Portola, Ergomed, and Biokit outside the submitted work.

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Author Contributions

K. Selleng and A. Greinacher analyzed the data and wrote the manuscript.

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