Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

Note:
CPD /CP2D Whole Blood oudate = 21 days
CPD/CP2D Liquid Plasma outdate = 26 days

CPDA-1 Whole Blood Outdate = 35 days
CPDA-1 Liquid Plasma Outdate = 40 days

LIQUID PLASMA (LIQUID PLASMA) is separated and infused no later than 5 days after the expiration date of the Whole Blood and is stored at 1 to 6 C. The profile of plasma proteins in Liquid Plasma is poorly characterized. Levels and activation state of coagulation proteins in Liquid Plasma are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage. This product contains viable lymphocytes that may cause graft versus host reactions in susceptible patients.

Action

This component serves as a source of plasma proteins. Levels and activation state of coagulation proteins are variable and change over time.

Indications

Liquid Plasma is indicated for the initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhages and who have clinically significant coagulation deficiencies.

Contraindications

See Fresh Frozen Plasma. Do not use Liquid Plasma as the treatment for coagulation factor deficiencies where other products are available with higher factor concentrations.

Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

Cryoprecipitated Components

Overview

Description

Cryoprecipitated Antihemophilic Factor (AHF) is prepared by thawing whole blood-derived FFP between 1 and 6 C and

CME/SAM

A paired comparison of thawed and liquid plasma

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BACKGROUND: To make plasma readily available to treat major hemorrhage, some centers are internationally using either thawed plasma (TP) or "never-frozen" liquid plasma (LP). Despite the routine use of both, there are limited data comparing the two. The hemostatic properties of LP were evaluated and compared to TP in a paired study.

STUDY DESIGN AND METHODS: Two ABO-matched plasma units were pooled and split to produce 1 unit for LP and 1 unit for TP. Samples of TP and LP, stored at 2 to 6°C, were tested for a range of coagulation factors, thrombin generation, and rotational thromboelastometry. An additional 119 units of LP were collected and analyzed for markers of contact activation (S-2302 cleavage) and cellular content.

RESULTS: LP and TP were compared, up to 7 days of storage, with results showing no difference in the rate of change over time for any variable measured. When compared to Day 5, LP on Day 7 showed no difference for any factors measured; however, on Day 11 Factor (F)II, FV, FVII, and protein S (activity) were lower. Analysis of 119 LP units showed that 26 of 119 (22%) exhibited cold-induced contact activation by Day 28.

CONCLUSION: LP and TP were comparable in terms of hemostatic variables up to 7 days of storage. Decreasing coagulation factor activity along with an increased activation risk during storage of LP needs to be balanced against availability to supply and clinical need when considering using LP with more than 7 days of storage.

The past two decades have seen great changes in the care of the patient with major hemorrhage, especially traumatic hemorrhage. Early resuscitation of trauma patients with blood components is becoming increasingly widespread in both civilian and military practice. A randomized controlled study recently showed that in patients with severe trauma major bleeding, the early administration of plasma, platelets (PLTs), and red blood cells (RBCs) in a 1:1:1 ratio reduces death due to exsanguination at 24 hours, compared with a 1:1:2 ratio, albeit with no significant differences in mortality at 24 hours and 28 days.[1] The results of this study led to the British Committee for Standard in Hematology guideline recommending that fresh-frozen plasma (FFP) be given in the initial resuscitation process

ABBREVIATIONS: APTT = activated partial thromboplastin time; C1INH = C1 inhibitor; CT = time to initial clot formation; DEHP = (diethylhexyl)phthalate; ETP = endogenous thrombin potential; LP = liquid plasma; MCF = maximum clot firmness; MEHP = mono(2-ethylhexyl)phthalate; PS = protein S; PT = prothrombin time; ROTEM = rotational thromboelastometry; TG = thrombin generation; TP = thawed plasma; ttPeak = time to peak.

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analyzer in all 119 units tested and therefore met current FFP specification in terms of residual cellular content. Units also met specification for total protein and volume.

DISCUSSION

Many studies have evaluated the effect of storing thawed FFP at 2 to 6°C for an extended time, with results showing a decrease in coagulation proteins over time, particularly FVIII, in which most of the activity is lost within the first 24 hours after thawing.[11] Since some countries use LP as an alternative to TP we therefore compared the hemostatic properties of LP directly with those of TP stored for up to 7 days. Our study shows that never freezing plasma does not significantly improve the coagulation factor content of the plasma over 7 days of storage and in fact levels of FVII, FXI, fibrinogen, and protein C were higher in TP, albeit by less than 5%. This is consistent with a previous study from our laboratory, where freeze-thawing of plasma before pathogen inactivation had minimal effect on coagulation factor content.[19]

Results of global clotting tests (up to 7 days) suggest that the initiation and propagation phases (lag time for TG and clotting time for ROTEM) of clot formation are shorter in LP than TP, even though individual clotting factors in TP were higher overall than LP. If these differences are not attributable to the levels of clotting factors in the two products, then what is it in LP that influences the initiation of clot formation, and is this important clinically? One possible explanation for the results of TG and ROTEM (up to 7 days) could be the difference in levels of microparticles or intact cells between TP and LP (although this was not measured in our study). Several studies have demonstrated that microparticles derived from PLTs and RBCs influence the TG potential of plasma.[20-22] Matijevic and colleagues[22] compared LP and TP in an unpaired study design and concluded that LP had a better capacity to form a clot and generate thrombin compared to TP. This result is likely to be due to higher PLT count seen in the LP in their study (81×10^9/L) compared to TP (7.5×10^9/L). Further, they went on to demonstrated that when LP was frozen and thawed the thrombelastogram trace became very similar to that of TP, presumably due to the lysis of PLTs.

From Day 11 onward, there was a further decrease in FII, FV, FVII, and PS activity in LP. However, apart from PS activity all other factors remained more than 0.5 IU/mL. Similarly the thrombin potential (i.e., ETP and peak thrombin) and MCF also reduced, and these results are consistent with those of others.[5]

Regarding the results of contact activation markers, 26 of 119 (22%) units showed signs of activation by Day 28 and this was more prominent from Day 15 onward (i.e., 24 of 26 units activated from Day 15 onward). In vitro studies from Sweden have also shown that contact activation markers increase during storage of LP[6,23] and that this activation is more pronounced in women than men,[8] resulting in the shelf life of LP being 7 to 14 days in Sweden. Considering that in our study all units were from male donors, a 22% incidence of contact activation at Day 28 cannot be ignored. Therefore, from our data it follows that a shelf life of LP beyond 14 days could be clinically unacceptable insofar as contact activation markers are concerned. We do not fully understand the consequences of contact activation in plasma for transfusion. However, in other clinical settings, activation of FXI in certain batches of IVIG is thought to have been related to increased thrombotic events following infusion[24] and activation could also trigger proinflammatory products such as bradykinin.[25]

With respect to hemostatic properties, the main question remains: could the shelf life of LP be extended beyond 7 days (but <15 days) for it to be practically more advantageous than TP, whose current shelf life in many countries is 5 days? One of the main limitations when addressing this question is that currently we do not know what the minimum individual clotting factor (or inhibitors) levels should be for FFP to maintain its efficacy and safety. However, from our data it seems fair to say that while free PS and FII reduced significantly between Days 7 and 14, they still remained more than 0.8 IU/mL and thus might not be of major concern clinically. However, the changes in FV, FVII, and PS activity were more prominent and thus deserve more careful consideration. FVII and FV are key factors in the initiation and amplification of clot formation, respectively,[26] and from clinical experience on the use of recombinant FVIIa in acquired and inherited bleeding disorders, we know that FVII is effective in stopping bleeding, so effective, in fact, that in acquired bleeding disorders it can lead to an increase in arterial thrombosis.[27] Furthermore, considering that FVII and FV have the shortest half-lives (5 and 10 hr, respectively) compared with other clotting factors ($\geq$15 hr), it could be argued that their low levels, coupled with short half-lives, could result in LP being less effective and thus requiring greater quantities thereof for transfusion in bleeding patients, compared with standard FFP.

Studies on TP have shown highly variable results with respect to loss of PS in storage,[28] which we considered may be attributable to not only how plasma was produced, but the type of assays used to quantify PS. We observed that the loss in PS activity was disproportionately higher compared with the loss of free PS. This could be due to the PS activity assay used in our study being dependent on endogenous FV present in the LP, and it is possible that concomitant loss of FV during storage of LP contributed to the apparent loss of PS activity. However, if we examine past experience of a type of solvent/detergent (S/D) plasma produced in the United States, which led to an increased risk of thrombosis, the S/D plasma from the United States also contained nearly normal

concentrations of free PS antigen, but almost completely absent PS activity.

We also assessed 119 units of LP for residual RBCs, WBCs, and PLTs and showed levels to be well below the current specification for FFP[10] as well as the lower limit of detection for each analyzer. In the United Kingdom, we do not match FFP transfusion for RhD, on the basis that it contains very few RBCs and that those that pass the filter lose their immunogenicity after the freeze-thawing process.[29] Published studies suggest that 0.03 mL of RBCs may cause primary immunization to RhD.[30] This equates to approximately 0.8×10^9/L RBCs in 1 unit of FFP. Since patients receive on average 4 units of FFP, then RBC contamination would need to be below 0.2×10^9/L to prevent immunization. In our study levels of RBCs in LP were below this level, but this will clearly be dependent on how plasma is processed and the type of LD filter used.

The other consideration with LP, that is not relevant to TP, is the need to consider risks associated with transfusion of viable WBCs such as transfusion-associated graft-versus-host disease and transmission of cytomegalovirus or human T-lymphotropic virus. With leukoreduced LP it could be argued that these risks are not of concern, but this will require robust data sets on residual WBC levels in routine use and risk assessment.

Potential concerns as well as possible benefits regarding the use of DEHP have been evaluated previously[31] and debated for many years. It has also been suggested that transfusion communities should move toward DEHP-free disposable plastics.[32] A study on TP showed that DEHP levels increased from 22 ppm post-thaw to 66 ppm on Day 5,[33] which is comparable to our data (LP) that showed an increase from 27.7 to 68.6 ppm on Day 7. Although LP stored for 7 days shows a 2.5-fold increase compared to the baseline, it is unknown what the implications of this are, and the data should be viewed in the context of the benefit outweighing the risk in terms of providing rapid availability of plasma in emergency situations. We also measured MEHP, a toxic breakdown product of DEHP, to ensure that low levels of DEHP are not due to high levels of MEHP.

Our study has compared TP and LP with results suggesting there is no benefit of not freeze-thawing plasma in terms of coagulation factor content. In LP we observed deterioration in some clotting factors between Day 7 and Day 14 and cold-induced contact activation from Day 14 in most units; as such, we do not recommend a shelf life of greater than 14 days for this component. Blood services should balance the aforementioned factors against availability to supply and clinical need when determining a suitable shelf life.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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