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The Appropriate Use of Liquid Plasma

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Background

For over a decade medical research, performed primarily by the U.S. military, has increasingly demonstrated the value of transfusing massively bleeding trauma patients with a balanced mix of red blood cells (RBCs), plasma, and platelets that recapitulates "fresh" whole blood. The rationale for this practice – known as damage control resuscitation (DCR) – is that the early transfusion of these patients with plasma and platelets (along with RBCs) ameliorates: (1) the acute coagulopathies of trauma (i.e., disseminated intravascular coagulation and hyperfibrinolysis); (2) the dilutional coagulopathies associated with the infusion of non-plasma-based resuscitation fluids; and (3) the traumatic endotheliopathies that lead to coagulation factor dysregulation and inflammation.[1] The PROPPR trial demonstrated similarly improved, DCR-related patient outcomes in the setting of civilian trauma.[2] Accordingly, the American College of Surgeons recommends that liquid-state plasma be "on hand and available for immediate release" in support of massively bleeding trauma patients.[3]

This "do-not-wait-to-give-the-yellow-stuff" approach is supported further by results from the recently published PAMPer multicenter randomized clinical trial (RCT), which revealed that the prehospital administration of Thawed Plasma (TP)* results in a substantially lower 30-day mortality rate than standard-care resuscitation with crystalloids.[4] While the similarly-designed COMBAT study, a single-center RCT, yielded negative results (likely at least in part due to the impressively short accident-to-hospital transport times seen in the Denver, Colorado community),[5] additional work investigating the pre-hospital use of plasma in trauma patients is in progress. Nevertheless, the demand for plasma that is available for immediate (i.e. without the delay inherent in thawing) use has surged.

Maintaining a TP inventory (with only a 5-day shelf life) and/or thawing frozen plasma (e.g., Fresh Frozen Plasma [FFP] or Plasma Frozen Within 24 Hours After Phlebotomy [PF24]) rapidly on-demand is challenging – especially for smaller rural hospitals and in the pre-hospital setting. The former too often leads to product wastage, i.e., when products expire unused, while the latter can lead to unacceptable delays in transfusions, given that thawing frozen plasma generally takes 20-to-30 minutes. Mehr et al. reviewed how massively bleeding trauma patients in their institution received an average of eight units of RBCs before plasma was made available for transfusion (at a median of 26 minutes into resuscitation).[6] Maintaining a refrigerated plasma inventory for immediate use is therefore considered essential at some facilities. For these reasons, demand for Liquid Plasma (LP), which typically has an outdate of 26 days, has increased substantially in the United States during the past several years.

Key Points about Liquid Plasma (LP)

- LP is:
  - Manufactured from whole blood collections;
  - Stored in a liquid, refrigerated (1-6° C) state;
  - Never frozen; and
  - Immediately available for transfusion.
- LP has a 26-day shelf life when manufactured in CPD/CP2D anticoagulant-preservative solutions.
- While LP contains stable levels of most clotting factors, variably reduced levels of Factors V and VIII, von Willebrand Factor, and Protein S (e.g., to 50-60% activity) are seen after 14 days and further gradual declines are seen thereafter.
- LP serves as a "bridge product" to meet the plasma transfusion needs of massively bleeding trauma patients.
- Its use should be coordinated via an approved protocol agreed upon jointly by the transfusion service, the emergency department/trauma team, the operating room, and other affected departments/services.

A number of studies have compared the hemostatic properties of LP to those of TP and Thawed FFP. Coagulation factor levels are generally maintained equally up to 7 days; and hemostatic levels in LP (though lower than for TP and Thawed FFP) appear sufficient for at least 14 days. Platelet-derived microparticles, moreover, are in abundance and can boost thrombin generation potential as well as correct endotheliopathy *in vitro* for 28 days.[7-9] Some centers conservatively apply a shelf-life of <14 days to avoid significant coagulation protein loss. Given the lack of *in vivo* studies, LP is generally used as a "bridge product," i.e., to be transfused only until other plasma components – e.g., TP or thawed FFP – can be issued.

Liquid Plasma's Indication

LP is indicated for "the initial treatment of patients who are undergoing massive transfusions because of life-threatening trauma/hemorrhage and who have clinically significant coagulation deficiencies."[10]

Liquid Plasma's Contraindications

These include:[10]

- The prolonged transfusion management of massively bleeding patients (for whom LP is indicated only for "initial treatment") – i.e., these patients, after having received

**TP is previously frozen plasma that is thawed ahead of anticipated use, has an outdate of 5-days from thawing and is distinguished from LP by virtue of the latter never having been frozen.*

approximately 2 units of LP, should thereafter receive traditional, frozen-then-thawed plasma products.

- The treatment of single or isolated coagulation factor deficiencies where other (e.g. fractionated plasma derivatives or recombinant) products are available with higher factor concentrations.
- Contraindications that also apply broadly to the use of traditional plasma products – i.e., LP should not be used as a:
  - Volume expander when blood volume can be safely and adequately replaced with other volume expanders;
  - Substitute for a readily available coagulation factor-enriched product (e.g., cryoprecipitate, single factor concentrates, and prothrombin complex concentrates) or other, more suitable treatment modalities (e.g., vitamin K); and
  - Reversal agent for heparin (where protamine sulfate is the suitable antidote).

Liquid Plasma – Other Considerations

- The dosage, administration, and potential risks of LP are identical to those of traditional plasma products.[10]
- For TRALI (transfusion-related acute lung injury) mitigation purposes, LP is manufactured from whole blood donated by male, never-pregnant female, and/or HLA-antibody-screened parous female donors.
- Because LP contains viable leukocytes, some customers request this product be irradiated to prevent transfusion-associated graft-versus-host disease. Such adverse events, however, are vanishingly rare in the literature and there is no consensus on the use of irradiation in this setting.
- LP sometimes has a pink-red hue associated with the settling of trace quantities of intact red blood cells. This coloration usually is not seen in thawed FFP because these cells are lysed, and their contents distributed uniformly throughout the product, as a result of the freeze/thaw process.
  - It is unknown whether these intact red cells are more or less immunogenic than the lysed red cells found in frozen-and-then-thawed plasma.
  - It therefore also is unknown whether or not the potential benefits of administering Rh immune globulin following the transfusion of Rh(D)-negative women of childbearing age with Rh(D)-positive LP outweigh the risks and costs.
- Given that the use of Group A plasma has become standard-of-care during the initial transfusion support of adult trauma patients,[11] the exclusive/near-exclusive use of Group A LP (as opposed to Group AB LP, that is in short supply) is strongly recommended.
  - Note: A meaningful safety advantage has not been observed in association with the use of "low titer"-anti-B/-A,B (i.e., as opposed to "un-titered") Group A plasma.
  - Most U.S. programs therefore have accepted the use of un-titered Group A plasma when transfusing their massively bleeding patients.
- With increased morbidity/mortality observed after excessive crystalloid use in the prehospital setting, some are beginning to explore the substitution of >14 day-old LP which, in addition to volume expansion, provides an isotonic solution with variable levels of coagulation factors. Studies are needed to better characterize potential benefits in this setting.[12]

Summary: The expanded prehospital and early resuscitative use of plasma and consequent need for immediately-available plasma for massive hemorrhage have led to a steady increase in LP requests. The practical impact of this has been reduced time-to-transfusion and decreased expiration rates for frozen-then-thawed plasma products, thereby leading to greater efficiencies and hospital satisfaction. LP's equivalency has not yet been extensively studied; thus its primary use to date has been as a bridging product.

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