

Fresh Frozen Plasma for Management of Hemostasis During Minor and Major Surgical Procedures Associated with Coagulopathy

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Introduction

Background: Fresh frozen plasma (FFP) is used to support hemostasis during minor and major surgical procedures in patients (pts) with complex coagulopathy secondary to chronic liver disease. Relatively little information about the effects of FFP transfusion is available with respect to Factor VII levels, hemostatic response, and use of blood components. Due to a short half-life, Factor VII is a key component in FFP for correction of coagulation effects.

Aims: Recently, we completed a randomized, controlled trial to compare the therapeutic efficacy of conventional FFP (C-FFP) and FFP prepared with photochemical treatment for pathogen inactivation (INTERCEPT™, I-FFP). This study was informative regarding the efficacy of FFP to support patients with acquired coagulopathy treated with FFP transfusion.

Figure 1: Mechanism of Action

The Mechanism of Action for plasma consists of amotosalen HCl, a psoralen molecule, and illumination with 3.0 J/cm² ultraviolet A (UVA) light treatment. The amotosalen compound penetrates cellular and nuclear membranes and intercalates into the helical regions of DNA and RNA. Covalent crosslinks to the nucleic acid base pairs form upon exposure to UVA light, blocking DNA and RNA replication. This process inactivates white blood cells and pathogens, rendering them unable to cause disease, while retaining the function of plasma, which does not require nucleic acid replication for therapeutic efficacy.

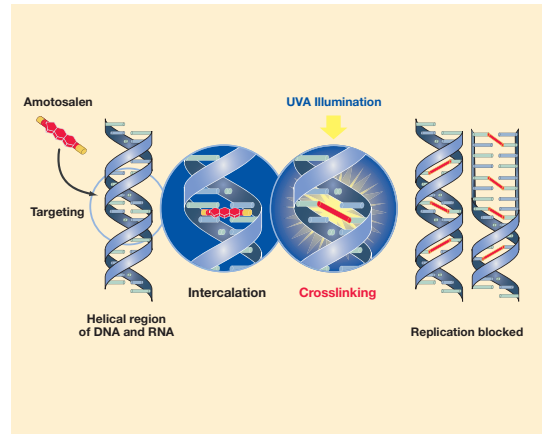
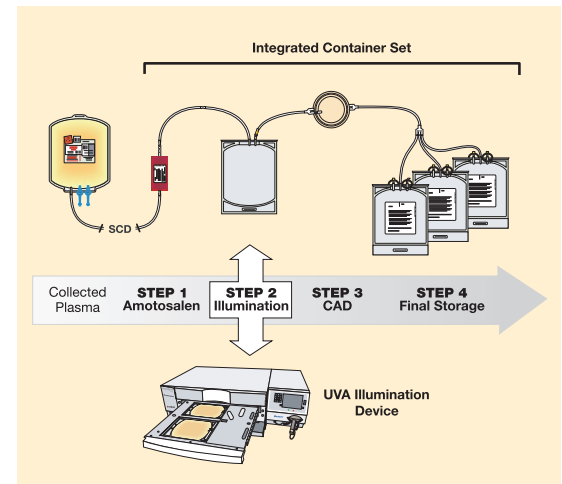


Figure 2: INTERCEPT Blood System for Plasma

The collected plasma is sterile docked to the container set for processing. After addition of amotosalen (1) by gravity flow, and removal of the plasma and amotosalen containers, the plasma is illuminated with UVA light (2). Residual amotosalen and its photoproducts are reduced to low levels using a compound adsorption device (CAD) (3), before transfer to the storage containers (4).

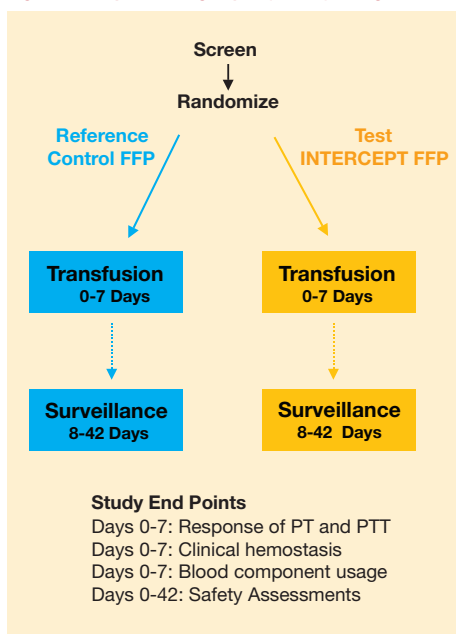


Methods

Pts with coagulopathy of liver disease requiring FFP transfusion for invasive procedures were enrolled to receive FFP for up to 7 days (Figure 3).

C-FFP and I-FFP were prepared as previously described (Transfusion 2005; 45:1362). Following the first transfusion, response of the PT, PTT, and the Factor VII (FVII) increment and incremental recovery (IU/dL)/(IU/kg) were measured. Hemostatic responses after the first transfusion were assessed using a WHO bleeding scale (Blood 2004; 104:1534). Use of FFP, cryoprecipitate, platelets (Plt), and red cell concentrates (RBCC) was tabulated during the 7-day support period.

Figure 3: Acquired Coagulopathy—Study Design



Results

121 pts were enrolled: 61 received C-FFP and 60 received I-FFP (Figure 4). 51 pts had orthotopic liver transplant (OLT) and 70 had minor surgical procedures (non-OLT) with FFP support. Among the 70 pts with minor surgical procedures, the types of procedures were distributed (%) between I-FFP and C-FFP as follows: paracentesis: 24/28; endoscopy: 10/22; catheter placement: 8/12; shunt placement: 10/12; liver biopsy: 8/9; and bleeding: 40/16. The PT (s) and FVII levels of pts undergoing non-OLT procedures tended to be more prolonged and lower than pts undergoing OLT. The PT and PTT decreased comparably for I-FFP and C-FFP (Figure 5). OLT pts received larger FFP doses and larger doses of F VII than

non-OLT pts reflecting the nature of the procedures supported (Table 1, Table 2). FVII increments ($p=0.001$), and PT responses ($p=0.04$) were correlated with FVII dose. FVII levels rose to a greater extent in OLT pts reflecting larger FFP doses. Incremental FVII recovery was greater in non-OLT pts, perhaps due to less intra-operative bleeding with less plasma loss. Among OLT pts, bleeding increased post op after FFP support, largely due to blood loss from drains. In non-OLT pts, the proportion without bleeding (Grade 0) increased substantially after FFP. Only a few pts developed Grade ¼ bleeding after FFP. FFP, RBC, Plt, and Cryoprecipitate usage over 7 days was greater for OLT than non-OLT pts (Table 3, Table 4).

Figure 4: Acquired Coagulopathy—Patient Disposition

Phase 3, double blinded, controlled, intent-to-treat design

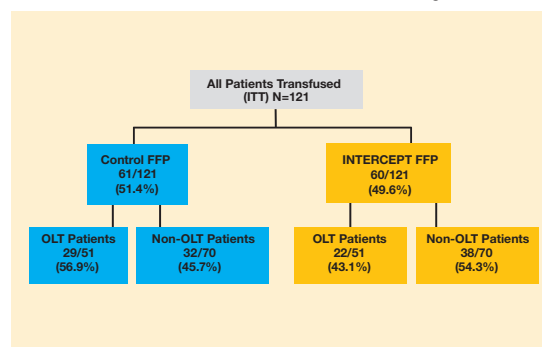


Figure 5: Acquired Coagulopathy—PT and PTT Responses (All Patients)

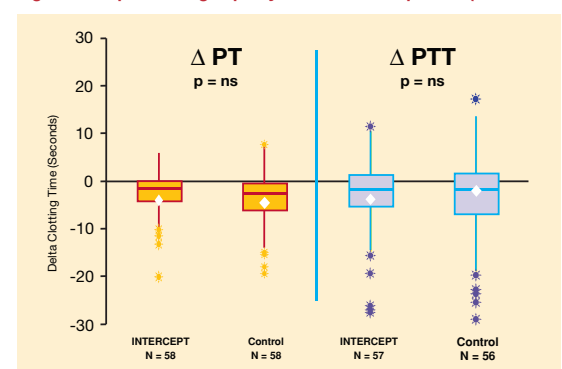


Table 1: VII Recovery One Hour After the First Transfusion (All Patients)

| | INTERCEPT | Control | p-Value ^a |
|---|-----------|-------------|----------------------|
| Number of patients | 60 | 61 | N/A |
| Factor VII activity (IU/dL) | | | |
| Pre transfusion | 33.2±24.0 | 36.0 ± 26.5 | 0.547 |
| Post transfusion | 45.4±29.1 | 51.0 ± 32.9 | 0.333 |
| Change | 12.3±26.3 | 15.0 ± 31.4 | 0.608 |
| Factor VII recovery (IU/dL)/ (IU/kg) | 0.69±1.80 | 0.48 ± 0.76 | 0.422 |

a. p-Value for mean treatment difference using t test

Table 3: Acquired Coagulopathy: Blood component use (Liver Transplant)

| | INTERCEPT | Control |
|------------|-----------|-----------|
| FFP* | 21.3±16.1 | 22.7±15.8 |
| RBC* | 11.8±6.1 | 13.4±10.2 |
| Platelets* | 13.4±11.3 | 16.5±17.3 |
| Cryo ppt* | 15.8±8.4 | 13.8±5.2 |

*units transfused
p>0.05 for all components

Conclusions

- Transfusion of FFP improved the PT and PTT for patients with acquired coagulopathy
- Factor VII levels increased significantly with FFP transfusion
- Transfusion of FFP improved clinical hemostasis scores and prevented grade 4 bleeding
- There were not statistically significant differences between I-FFP and C-FFP

Table 2: VII Recovery One Hour After the First Transfusion (Liver Transplant)

| | INTERCEPT | Control | p-Value ^a |
|---|-----------|-----------|----------------------|
| OLT Population | | | |
| Number of patients | 22 | 29 | N/A |
| Total vol. of FFP transfused (L) | 3.7±1.9 | 4.0±3.3 | 0.763 |
| Factor VII activity (IU/dL) | | | |
| Pre transfusion | 36.0±30.1 | 42.6±31.2 | 0.470 |
| Post transfusion | 62.0±37.9 | 67.9±37.4 | 0.599 |
| Change | 26.0±40.2 | 25.8±43.3 | 0.987 |
| Factor VII recovery (IU/dL)/ (IU/kg) | 0.48±0.74 | 0.31±0.75 | 0.444 |

a. p-Value for mean treatment difference using t test

Table 4: Acquired Coagulopathy: Blood Component Use (Non-Liver Transplant)

| | INTERCEPT | Control |
|------------|-----------|----------|
| FFP* | 7.2±7.9 | 9.6±12.9 |
| RBC* | 3.8±2.2 | 4.9±4.9 |
| Platelets* | 7.6±17.0 | 6.1±7.2 |

*units transfused
p>0.05 for all components