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Coagulation Factors In Therapeutic Apheresis Plasma Held For 18 Hours At Ambient Temperature Prior To Pathogen Inactivation (INTERCEPT)

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Background

A photochemical treatment (PCT) using amotosalen HCl (S-59) and UVA light inactivates pathogens and leukocytes in therapeutic single donor apheresis fresh frozen plasma (INTERCEPT™, I-FFP) prepared within 8 hr of collection (Figure 1 and Figure 2).

Previous studies demonstrated a broad spectrum of pathogen inactivation (Transfusion 2006;46:1168) and clinical efficacy of I-FFP for support of coagulopathies (Transfusion 2005;45:1362; Blood 2006; 107:3753), and plasma exchange of TTP (Transfusion 2006;46: 1693), (Table 1).

Preparation of therapeutic plasma up to 18 hr after collection would improve production logistics of frozen plasma provided sufficient levels of coagulation factors were retained.

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.

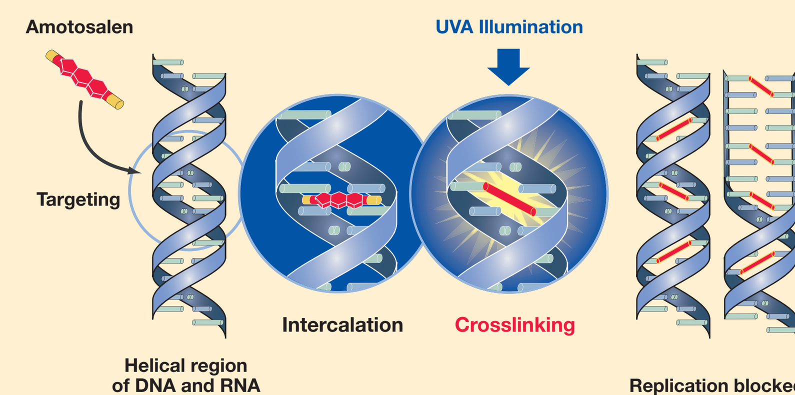


Figure 2: INTERCEPT Blood System for plasma
The collected plasma is sterile docked to the container set for processing. After addition of amotosalen (1) by gravity flow, and removal of the plasma and amotosalen containers, the plasma is illuminated with UVA light (2). Residual amotosalen and its photoproducts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

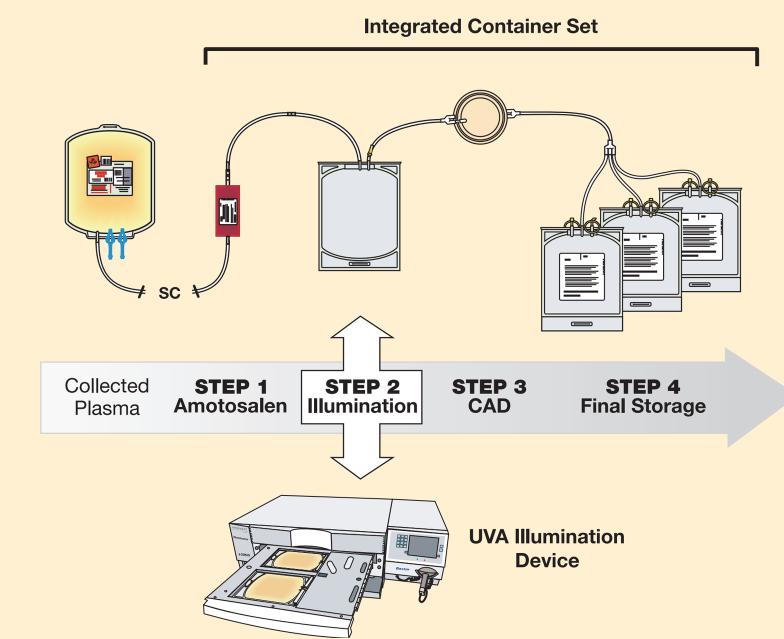


Table 1: Summary of Prior Clinical Trials

Phase	Objective	Patients
I	Safety, S-59 Kinetics	10
II	Factor VII Kinetics	27
II	Protein C Kinetics	17
II	Protein S Kinetics	16
III	Coagulopathy – Pilot	13
IIIA	Congenital Deficiencies	34
IIIB	Aquired Coagulopathy	121
IIIC	TTP	35

Aims

To determine the levels of coagulation factors in apheresis plasma stored for 18 hr at ambient temperature prior to processing with pathogen inactivation, and freezing.

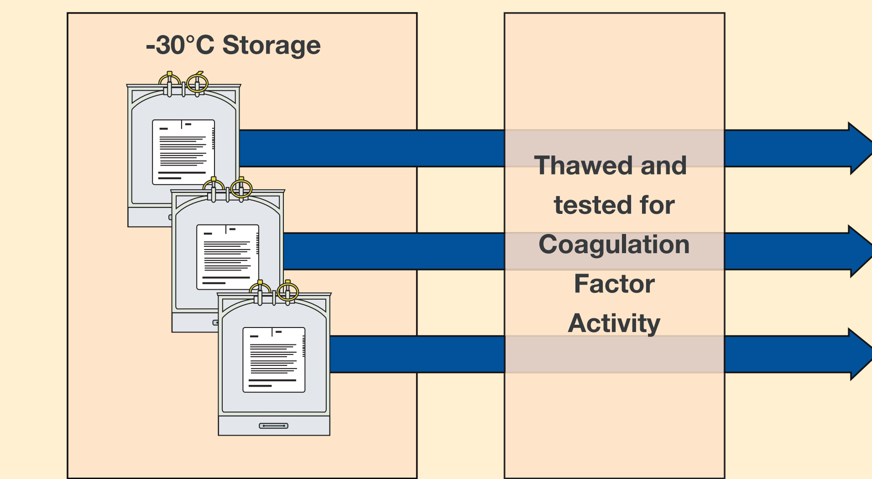
Methods

Fifteen jumbo plasma units (650 mL), were collected by apheresis with AB16 anticoagulant from group A, B, AB and O donors (MCS+. Haemonetics, Braintree, MA). Plasma collections were held at ambient blood bank temperature (20–24°C) prior to further processing. After 18 hr, baseline samples for assay of coagulation factors were withdrawn before PCT. Plasma (635 mL plasma) was mixed with 15 mL of 6 mM amotosalen (150 μM: final concentration) and illuminated with a 3 J/cm² UVA treatment. Following illumination (~8 min) and passage through a flow compound adsorption device (~20 min) to reduce levels of residual S-59, treated plasma units (650 mL) were divided into 3 equal storage units of 200 mL.

Before freezing, post-treatment samples were withdrawn for factor assays. Treated plasma units were flash frozen at -80°C, and transferred to -30°C for 12-month storage (Figure 3).

Plasma units were withdrawn to measure total protein, albumin, IgG, IgM, IgA, fibrinogen, factors II, V, VII, VIII, IX, X, XI, XII, VIII-vWF, Proteins C and S, AT III, plasminogen, alpha-2 antiplasmin, D-dimers, PT, and APTT.

Figure 3: Study Design
Treated FFP units were withdrawn from storage after 2 weeks to measure pH, total protein, albumin, IgG, IgM, IgA, fibrinogen, factors II, V, VII, VIII, IX, X, XI, XII, vWF, Proteins C and S, AT III, plasminogen, α-2 antiplasmin, D-dimers, PT and PTT.



Results

Baseline coagulation factor levels (Mean±SD) were in therapeutic ranges after 18 hr storage at ambient temperature. After PCT, all units had residual platelets < 1x10⁹/L, WBC < 1x10⁴/L, and RBC < 1 x 10⁹/L. After PCT, total protein (59 ± 4 g/L), albumin (38 ± 2 g/L) g/L), IgG (9.0 ± 1.7g/L), IgA (1.6 ±0.8 g/L) and IgM (0.9 ± 0.5 g/L) were unchanged from baseline. Mean values for fibrinogen (g/L), coagulation factors (IU/dL), coagulation inhibitors (IU/dL) were variably reduced from baseline, but within the ranges defined for therapeutic plasma (Table 2).

Treated plasma showed no evidence of activation.

Table 2: Coagulation and Anti-Thrombotic Activities Before and After Treatment

Factor	Baseline	Post PCT
PT (s)	13.6 ± 0.7	14.8 ± 0.9
APTT (s)	33.4 ± 1.9	37.0 ± 2.1
Fibrinogen (g/L)	2.8 ± 0.4	2.3 ± 0.4
II (IU)	95 ± 8	84 ± 8
V (IU)	94 ± 22	87 ± 22
VII (IU)	94 ± 23	75 ± 20
X (IU)	96 ± 17	87 ± 16
IX (IU)	106 ± 28	84 ± 21
VIII:c (IU)	112 ± 27	72 ± 19
VIII:vWF (IU)	107 ± 31	102 ± 29
XI (IU)	93 ± 21	61 ± 13
XII (IU)	102 ± 20	87 ± 17
AT III (IU)	95 ± 12	90 ± 11
Protein C (IU)	108 ± 16	97 ± 15
Protein S (IU)	86 ± 15	81 ± 14
Plasminogen (IU)	101 ± 16	93 ± 15
α-2-PI (IU)	108 ± 14	89 ± 10
D-DImer (ng/mL)	248 ± 77	247 ± 59

Summary

Apheresis plasma held for 18 hr before processing with the INTERCEPT system for pathogen inactivation retained coagulation factor activity levels in conformance with French national standards for therapeutic frozen plasma (FP). Approximately 36 units (200 mL) could be prepared per hr with this system. A single UVA platform is compatible with the operational requirements of a regional blood center producing 12,000 doses (200 mL) of therapeutic FP and 12,000 doses of platelets per year.

Conclusions

- **Delayed processing of plasma improves blood center logistics for the production of therapeutic plasma**
- **After PCT (INTERCEPT), plasma Ig and fibrinogen levels were maintained with-in suitable ranges**
- **After PCT (INTERCEPT), pro-coagulant factor levels were maintained within suitable ranges**
- **After PCT (INTERCEPT), anti-thrombotic factor levels were maintained within suitable ranges**
- **There was no evidence of thrombin activation after PCT**

Disclosures

Laurence Corash, Marc Slaedts, Linda Pinkoski, and Yasmin Singh are employees of, and own stock and stock options in, Cerus Corporation. Jean Pierre Cazenave received funding to support this study and serves on the Cerus European Advisory Board.

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