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Pathogen Inactivation of Double Dose Platelets with the INTERCEPT Dual Storage Container Set

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Objectives

This study was designed to evaluate the *in vitro* function of platelets stored in two 1.3 L containers following INTERCEPT™ pathogen inactivation treatment. The INTERCEPT Blood System™ inactivates pathogens and leukocytes in platelets by the covalent modification of nucleic acids using photo-activation of 150 µM amotosalen HCl by 3 J/cm² ultra violet A (UVA) light (Figure 1). Cerus is currently developing an extension to the INTERCEPT product line by modifying the INTERCEPT Large Volume Set to include an additional storage container. This INTERCEPT Dual Storage Container set will allow blood centers to create two platelet doses from a single INTERCEPT Blood System treatment process in a closed system (Figure 2).

Aims

- Evaluate the function of platelets stored in two 1.3 L storage containers following INTERCEPT pathogen inactivation treatment.
- Evaluate platelets stored in the INTERCEPT Dual Storage Container Set in volumes between 135 mL and 185 mL.

Design and Methods

Three independent experiments were performed for this study. Each experiment utilized two double dose apheresis platelet units containing approximately 7×10^{11} platelets. In experiments 1 and 2, each apheresis platelet unit was individually suspended in 35% plasma and 65% InterSol™ and individually treated with the INTERCEPT Blood System for Platelets (150 µM amotosalen and 3 J/cm² UVA treatment). Following 16 hours on CAD the units were pooled and split into three storage containers, generating one low volume split Test unit containing 2.2 to 2.5 $\times 10^{11}$ platelets in 135 mL (Test Low Split Volume), one high volume split Test unit containing 3.0 to 3.5 $\times 10^{11}$ platelets in 185 mL (Test High Split Volume) and one Control unit containing 4.8 to 5.5 $\times 10^{11}$ platelets in 270 mL (Control). Excess platelet concentrate was discarded. In the third experiment, the two double dose apheresis platelet units were pooled and processed into two units prior to treatment: a Control unit containing approximately 5.4×10^{11} platelets in approximately 285 mL of 35% plasma/65% InterSol and a Test unit containing approximately 5.6×10^{11} platelets in 313 mL of plasma/InterSol. Both units were treated with INTERCEPT (150 µM amotosalen and 3 J/cm² UVA treatment). Following 15 hours on CAD, the Test unit was split into two storage containers, each containing 2.2-2.4 $\times 10^{11}$ platelets in 150 mL. 35% plasma/65% InterSol was added to one of the storage containers to increase the volume to approximately 185 mL. All units were stored at 22°C with gentle agitation and evaluated for *in vitro* function on day 7.

The Test conditions used in this study were designed to approximate the limits of platelet dose and unit volume anticipated during use of the dual container set and the Control conditions approximate the nominal condition of the current treatment process.

Figure 1: INTERCEPT Mechanism of Action

The INTERCEPT Blood System uses a combination of amotosalen HCl and long wavelength ultraviolet A (UVA) light. 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 leukocytes and pathogens, rendering them unable to cause disease, while retaining the function of plasma/platelets, which do not require nucleic acid replication for therapeutic efficacy.

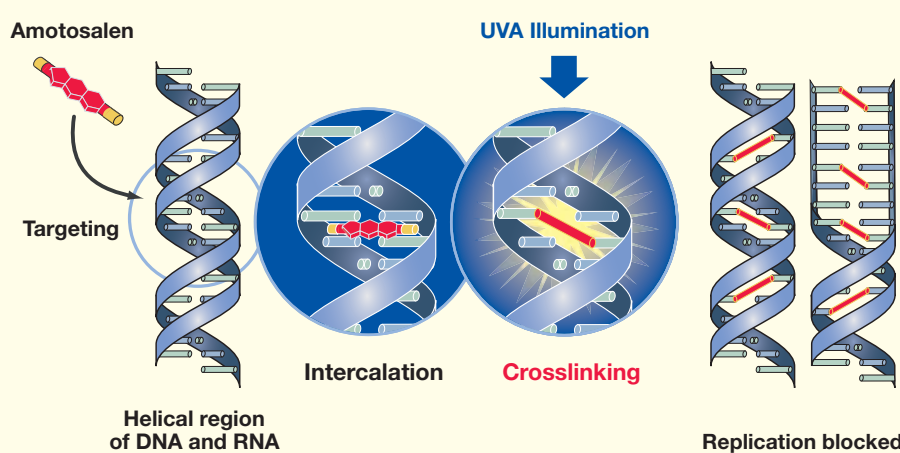
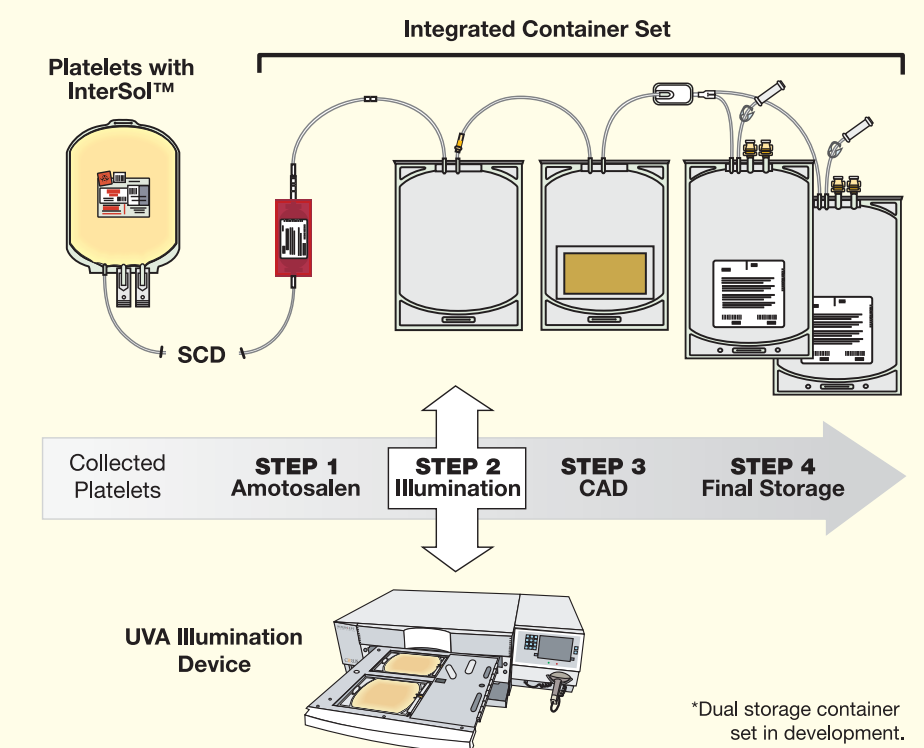


Figure 2: The INTERCEPT Blood System for Platelets

Using a sterile connecting device (SCD), the platelet container is sterilely connected to the INTERCEPT kit. Amotosalen (1) is added by gravity flow and the platelet mixture is illuminated with UVA light (2). Residual amotosalen and its photoproducts in the platelet mixture are reduced to low levels using a compound adsorption device (CAD) (3) before the platelets are transferred to the storage containers (4).*



Results

After 7 days of storage all platelet units met Council of Europe standards for platelet dose above 2.0×10^{11} and pH greater than 6.4 (22°C), see Table. In addition, neither low nor high volume Test units were statistically significantly different from Control units in pH, hypotonic shock response (HSR), extent of shape change (ESC), glucose or lactate. High volume Test

units differed statistically from Control units only in pCO₂ and pO₂ levels, while low volume Test units differed statistically from Control in these parameters and also in ATP levels. These differences are expected given differences in platelet number and in surface-to-volume ratios between the Test and Control units, which are exaggerated in the low volume Test units.

Table 1: Platelet Function Post INTERCEPT Treatment of Double Dose Platelets Followed by 7 Day Storage in Two Containers as Compared to Treated Control Platelets (N=3)

In Vitro Platelet Function Parameters	Test Units		Control Units (without splitting)
	Low Split Volume Mean ±SD	High Split Volume Mean ±SD	
Volume (mL)	135 - 150	185	270 - 285
Platelet dose ($\times 10^{11}$)	2.3 ± 0.2	3.0 ± 0.6	4.8 ± 0.6
pH (at 22°C)	7.04 ± 0.07	7.02 ± 0.07	6.98 ± 0.10
pCO ₂ (mm Hg)	8.1 ± 0.9*	12.0 ± 2.0*	20.7 ± 2.7
pO ₂ (mm Hg)	137.0 ± 7.0*	113.3 ± 18.1*	68.4 ± 23.9
HSR (%)	29.1 ± 5.5	28.1 ± 5.2	39.7 ± 10.0
ESC (%)	9.1 ± 0.9	10.5 ± 0.9	11.9 ± 2.4
Total ATP (nmol/10 ⁸ platelets)	3.3 ± 1.0*	3.4 ± 1.1	3.8 ± 0.9
Glucose (mM)	0.5 ± 0.3	0.3 ± 0.3	0.3 ± 0.2
Lactate (mM)	14.3 ± 2.3	14.4 ± 1.9	14.3 ± 2.0

*p<0.05 compared to Control, two-sided, paired student t-test

Conclusions

These preliminary results indicate that platelets produced using a dual storage container processing set, split and stored utilizing two 1.3 L final storage containers in platelet doses between 2.2 and 3.5×10^{11} and volumes between 135 mL and 185 mL maintain platelet function comparable to that

of platelets stored in a single 1.3 L container for up to 7 days following treatment with the INTERCEPT Blood System. INTERCEPT platelets produced utilizing the dual storage disposable set can be stored in either one or both of the final 1.3 L PL2410 storage containers until transfusion.