PATHOGEN INACTIVATION OF PLASMA WITH THE INTERCEPT BLOOD SYSTEM – EXPERIENCES FROM ROUTINE PRODUCTION –

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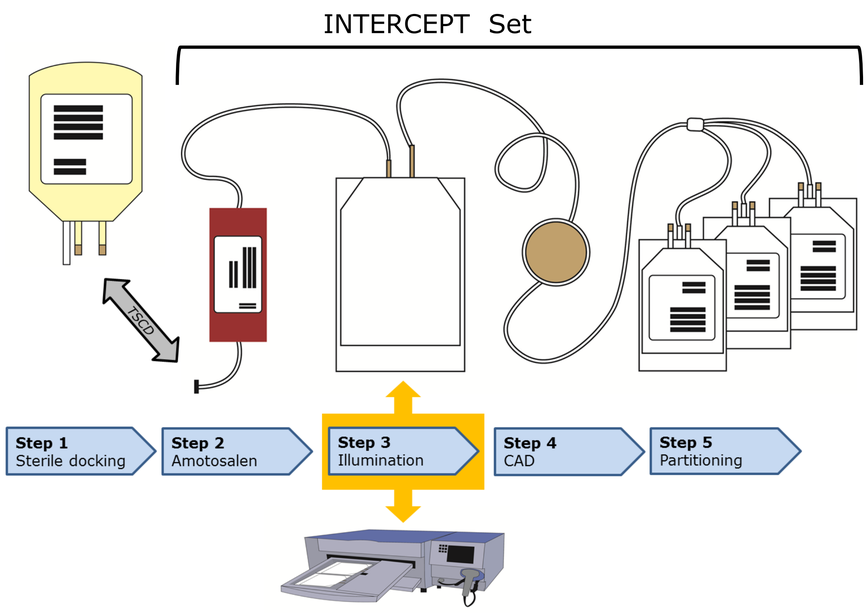
Introduction

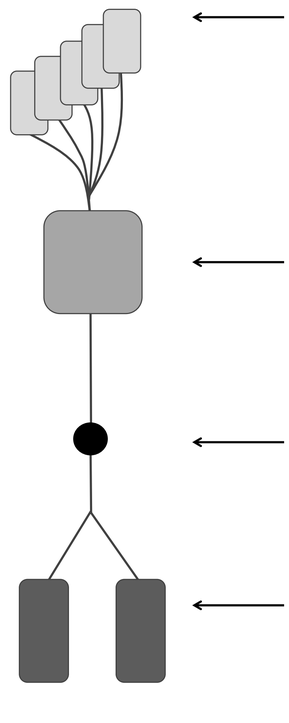
Blood Transfusion Service Zurich is the first Swiss centre that established the INTERCEPT® Blood System to manufacture pathogen inactivated plasma (Pi-FFP). We introduced Pi-FFP in 2014 because of its safety profile and the possibility to cease quarantine storage. This work investigates how well the 2 main challenges in routine production were handled: freezing in time and minimizing plasma loss. To fulfil Swiss regulations, Pi-FFP must be frozen within 20h after donation. This de facto means, Pi-FFP should be ready for freezing within 18.5h since loading the freezer takes up to 0.5h and freezing another 1h. Concerning plasma loss, the challenge is that plasma for INTERCEPT treatment should meet the narrow range of 630-650mL. At least 630mL are necessary to use full production capacity of the INTERCEPT set (i.e. 3 Pi-FFPs). Hence, recovered plasma has to be pooled. On the other hand, 650mL are the set's upper limit. Excess plasma is discarded (Fig. 1). Therefore, proper pooling of recovered plasma is important (Fig. 2). In case of source plasma, units with optimal volumes can be generated by plasmapheresis.

Figure 1: The INTERCEPT Process for Plasma



Step 1: Sterile connection between plasma and INTERCEPT set. Process entry criteria for plasma are red blood cells < $4x10^6$mL and volume 385 – 650mL. At least 630mL are necessary to use full production capacity of the set, i.e. generating 3 units of Pi-FFP. Step 2: Plasma flows through a small bag containing the reactive compound amotosalen. Step 3: Plasma containing amotosalen gets illuminated with UVA light (DNA/RNA crosslinks irreversibly). Step 4: Removal of excessive amotosalen by filtration. Step 5: Partitioning Pi-plasma prior to freezing (final volume per unit approx. 200mL)

Figure 2: Principle of Plasma Pooling prior to INTERCEPT



5 units of recovered plasma are sterile connected to a pooling and filtration system.

Alternative options:

- 6 units may be linked if 5 units are not enough to reach the minimal volume necessary to fill both split bags.
- If pooling of 5 or 6 units is not feasible, only 3 units may be linked. As a consequence, only 1 split bag can be filled properly.

Pool of recovered plasma

Filter for leukodepletion

2 split bags each containing 630 – 650mL leukodepleted plasma. Each bag will be connected to an INTERCEPT^T set and will give rise to 3 Pi-FFPs with a volume of 200 mL +/- 10% per unit.

(Only possible if 5 or 6 units of recovered plasma are pooled. In cases where only 3 units are pooled, only 1 split bag can be filled)

In general, five plasma units are filtered after pooling to remove leucocytes and then evenly distributed on two bags. Each bag must contain 630 – 650mL plasma to use full capacity of the set and contain less than $4x10^6$ RBC/mL to fulfil process entry requirement for INTERCEPT. In addition, white blood cell content must be < $1x10^6$ per final Pi-FFP and platelet concentration must be < $50x10^9$/L to meet Swiss specifications.

Methods

Data from December 2016 to May 2017 were analysed. Pi-FFPs were produced from recovered plasma or from source plasma (Blood groups AB and B only). Leukodepleted source plasma was directly sterile connected to the INTERCEPT processing set. In case of recovered plasma, 5 or 6 unfiltered units were manually pooled, filtered and split with a dedicated set (Fig. 2). Each split was then connected to an INTERCEPT set. If only 3 units were available, they were pooled and filtered but not split. Usually, whole blood was either separated on the day of collection (day 0) and plasma was stored overnight (o/n) for pooling and pathogen inactivation on day 1 or WB was stored o/n and separation, pooling and inactivation were done on day 1 (Tab. 1). Following parameters were assessed: Time until ready for freezing, plasma loss because of exceeding the 18.5h limit or missing the 630–650mL range, and Factor VIII content based on routine QC data.

Table 1: Standard Organization of Pi-FFP Production

Infectious markers are available as of 2 pm

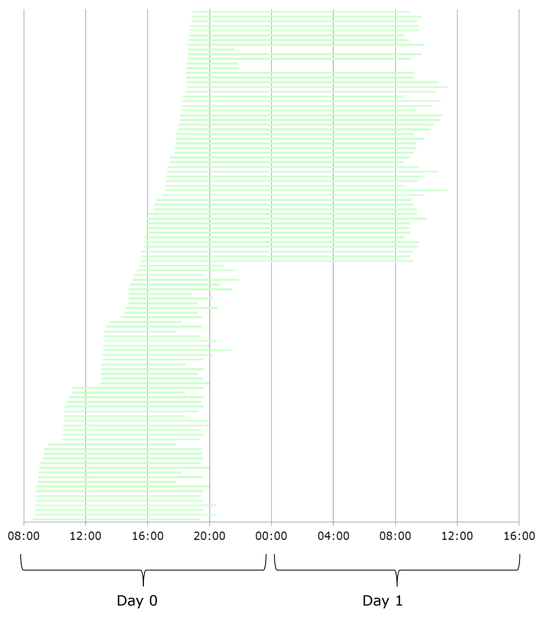
	Day 0											Day 1											
	12:00 - 13:00	//	15:00 - 16:00	16:00 - 17:00	17:00 - 18:00	18:00 - 19:00	19:00 - 20:00	20:00 - 21:00	21:00 - 22:00	22:00 - 23:00	23:00 - 00:00	//	06:00 - 07:00	07:00 - 08:00	08:00 - 09:00	09:00 - 10:00	10:00 - 11:00	11:00 - 12:00	12:00 - 13:00	13:00 - 14:00	14:00 - 15:00	15:00 - 16:00	16:00 - 17:00
Pi-FFP from WB (1st run)		//			WB arriving							//											
		//					Processing WB					//											
		//						Storing Plasma				//											
		//										//	Pooling										
		//										//		Illumination									
		//										//			Freezing								
		//										//									Release		
Pi-FFP from WB (2nd run)		//						WB arriving				//											
		//										//	Processing WB										
		//										//				Pooling							
		//										//					Illumination						
		//										//						Freezing					
		//										//									Release		
Pi-FFP from Aph.	Plasma arriving											//											
		//	Illumination									//											
		//			Freezing							//											
		//		Plasma arriving								//											
		//		Storing Plasma								//											
		//										//	Illumination										
		//										//			Freezing								
		//										//									Release		

Pi-FFP from WB is either separated on day 0 or on day 1 (depending on time of donation) and freezing is scheduled in both cases for day 1; Plasma from apheresis (source plasma) is frozen on day 0 or on day 1, depending on the time of donation; Release of Pi-FFP is possible after infectious marker results are available, i.e. after 2 pm on day 1; WB=Whole Blood; Aph=Apheresis

Results

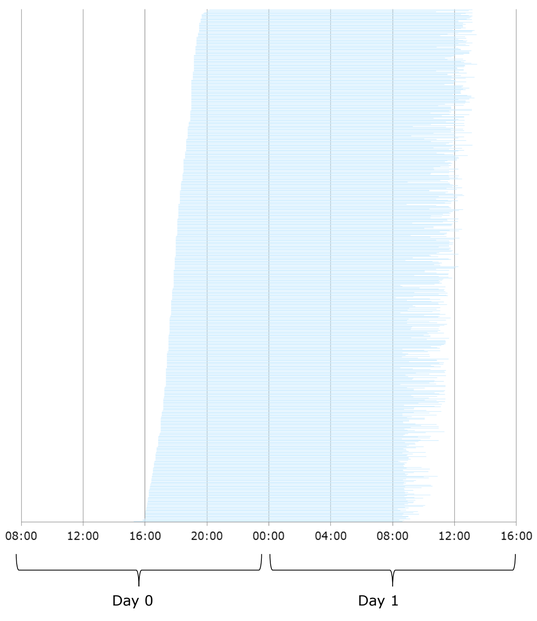
3,300 Pi-FFPs were successfully made from recovered plasma (86% pools of 5) and 327 from source plasma. 5 failed meeting the 18.5h limit. Range of time to freezing was 3.1-11.7 h for source plasma frozen on day 0 (54% of source plasma) and 13.9-18.3 h if frozen on day 1 (Fig. 3). Range of time for recovered plasma frozen on day 0 (1%) was 7.4-13.1 h and 14.4-18.5 h if frozen on day 1 (99%, Fig. 4)). No plasma was lost because of coming under 630mL. Loss due to exceeding 650mL was 1.6% of total plasma pooled (pools of 3: 12.8% loss; pools of 5: 0.5%; pools of 6: 11.3%; filtration loss not included). Factor VIII specification (≥ 0.5 IU/mL) was met at 100%.

Figure 3: Data Source Plasma



Time from donation to freezing of source plasma (n=109 donations): Usually, plasma from donations given after 15:30 h were frozen on the following day (day 1). Earlier donations were frozen on day 0.

Figure 4: Data Recovered Plasma



Time from donation to freezing of the oldest plasma in the pool (n=577 pools): Only plasma from donations given after approx. 16:00 h was used to manufacture Pi-FFP. Plasma was almost exclusively frozen on day 1 (99%).

Conclusions

Meeting the limit of 20h from donation until end of freezing is not a problem in routine. Hence, INTERCEPT allows reducing manufacturing time of FFP from ≥4 months to <1 day compared to quarantine storage. This tremendously increases the possibility to react on fluctuations in demand. Plasma loss can be minimized by generating as many pools of 5 as possible since their splits are closest to 650mL.

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