Received: 16 September 2021 | Revised: 7 July 2022 | Accepted: 18 August 2022

DOI: 10.1111/tme.12913

SHORT COMMUNICATION

TRANSFUSION MEDICINE WILEY

Pathogen inactivation treatment of triple-dose apheresis platelets with amotosalen and ultraviolet a light

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Abstract

Background: A triple storage (TS) set allows for pathogen inactivation (PI) treatment of triple-dose apheresis platelet products with amotosalen + UVA. We evaluated the quality and metabolic parameters of platelet concentrates (PCs) pathogen inactivated and stored for 7 days.

Materials and methods: Twelve triple-dose products collected with two different apheresis platforms were treated with amotosalen+UVA. Products were split into three single-dose units. Testing was made pretreatment, after splitting, at days 5 and 7 of storage.

Results: Single-dose PI PCs had a mean platelet content of 2.89 ± 0.35 x 10^{11}. From baseline to day 7, pH remained stable (7.1 ± 0.1 vs. 7.0 ± 0.1), pO_2 increased (11.3 ± 2.4 vs. 18.3 ± 3.5 kPa) as did LDH (201 ± 119 vs. 324 ± 203 U/L) and lactate (3.6 ± 1.7 vs. 12.1 ± 1.5 mmol/L) (all $p < 0.01$); pCO_2 decreased (4.1 ± 0.8 vs. 1.5 ± 0.7 mmHg; $p < 0.01$) and so did bicarbonate (6.6 ± 1.1 vs. 2.5 ± 1.4 mmol/L), glucose (5.6 ± 1.2 vs. 0.4 ± 0.4 mmol/L) and ATP (3.4 ± 0.9 vs. 2.5 ± 1.4 nmol/10^8 platelets) (all $p < 0.05$).

Conclusion: Triple-dose PCs processed with the TS sets fulfilled the quality requirements and displayed metabolic changes of expected extent during 7-day storage.

KEYWORDS
pathogen inactivation, triple-dose apheresis platelet components

1 | INTRODUCTION

The INTERCEPT® blood system for platelets was introduced for pathogen inactivation (PI) treatment of platelet concentrates (PCs) by the Swiss Red Cross transfusion services in November 2011.[1] At the Regional Blood Transfusion Service in Basel, which was involved in the validation process of the method in Switzerland, PI for PCs was implemented by January 2011. The large amount of data collected in more than 8 years of routine use in Basel demonstrates the safety and the clinical efficacy of PI-treated PCs for various clinical indications.[2]

Besides the benefits in safety of PCs, adoption of PI also comes with some cost increase and logistical challenges. To address these issues, possible strategies are the collection of large dose (double- or triple-dose) platelet products by apheresis and the manufacturing of double-dose PC by pooling of whole blood derived buffy coats.[3] The economic advantages of this approach have recently been evaluated.[4]

In our institute, prior to the introduction of PI, approximately 70% of the platelet apheresis products were of double-dose and 20% of triple-dose size with minimum 2.4 x 10^{11} platelets per single unit. PCs were prepared in plasma/platelet additive solution (PAS) and gamma-irradiated. After the implementation of PI, the proportion of double-dose collections

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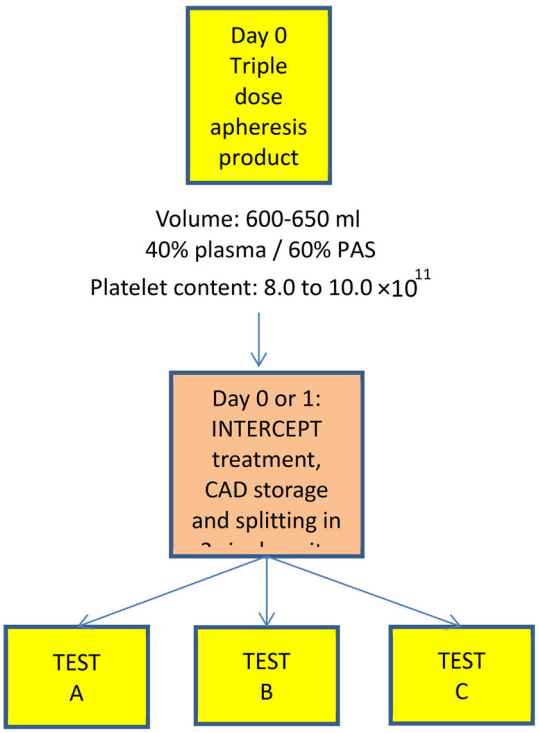

FIGURE 1 Design of the study. Day 1–7: testing for volume and platelet content (units A, B, C). Testing for storage parameters (unit A on day 1, unit B on day 5, unit C on day 7).

rose to 90%, because triple-dose apheresis were no longer performed. This was because the available sets for PI only allowed the treatment of products up to a maximum volume of 420 ml with a maximum platelet content of up to 7.0 x 10^{11} (large volume set) and 8.0 x 10^{11} (dual storage set). Thus, PI of triple-dose products was not possible in a closed system.

The INTERCEPT platelet processing set with triple storage containers (TS set) was designed to treat buffy coat and apheresis derived platelet products with a platelet content of 5–12 x 10^{11} in a volume of 420–650 ml in 32%–47% plasma and PAS. As additional improvement, the TS sets are manufactured with a plastic composition of containers which improves gas transfer properties.[5] The di(2-ethylhexyl) phthalate (DEHP) plasticiser is present in isolated components of the kit that have limited exposure to the product during processing. The TS set received the CE mark in January 2018.

We conducted a study to evaluate platelet standard quality parameters and metabolism in PCs obtained from triple-dose apheresis collections, pathogen inactivated and stored in TS sets during 7 days. Hereby we present the results of this analysis.

2 | MATERIALS AND METHODS

2.1 | Study design and platelet collection

Twelve triple-dose apheresis products were collected to obtain a total of 36 single-dose PCs. Experienced blood donors who had donated triple-dose platelets by apheresis in the past were asked to take part in the study. Donors had to comply with the eligibility criteria for blood donation and were tested for infectious disease markers according to the national regulations. Blood donors provided written informed consent before their participation in the study. The trial protocol was approved by the local Scientific Ethic Committee (trial number 2017–00516).

Figure 1 illustrates the general design of the study. Platelets were collected on the Amicus (AM, Fresenius Kabi, Frankfurt, Germany; $n = 6$) and Trima (TR, Terumo BCT, Lakewood, Colorado, USA; $n = 6$) apheresis devices and suspended in 40% plasma/60% PAS (SSP+; Macopharma, Tourcoing, France). Targeting a minimal amount of 2.4 x 10^{11} platelets per single-dose unit, and anticipating a loss of about 10% of platelets due to processing and PI treatment, the goal was to collect a dose of 8.0–10.0 x 10^{11} in a volume of 600–650 ml with each procedure. Specifically, the target yield was set at 9 x 10^{11} platelets for both AM and TR. After collection and before PI treatment, apheresis products were stored on a flatbed platelet agitator (~60 cpm) in an incubator at 22 ± 2°C for at least 2 h.

2.2 | Processing and PI treatment

The TS set consists of the following sequentially integrated components: 6 mM amotosalen solution in a 15 ml container, a 1L illumination container, a 1.3L container with dual compound adsorption device (CAD) wafers, an in-line filter, and three 1.3L storage containers (Figure 2). For processing, the PC unit was passed from the collection bag through the amotosalen container into the illumination container and was then exposed to UVA light (3.0 J/cm^2) in an INT100 Illuminator (Cerus Europe B.V., Amersfoort, The Netherlands). Following illumination, platelets mixed with amotosalen were transferred into the CAD container, which was then placed in an incubator at 22 ± 2°C on a flatbed platelet agitator for the removal of amotosalen and photoproducts. Six apheresis products (AM $n = 4$; TR $n = 2$) were treated on day 0 (day of collection) and stored in the CAD for a period of about 16 h (maximum CAD time); six products (AM $n = 2$; TR $n = 4$) were treated on day 1 (day after collection) and kept in the CAD for about 4 h (minimum CAD time). After CAD incubation, platelets were transferred evenly into the three final storage containers. The units were labelled (test unit A, test unit B, and test unit C, respectively) and stored at 22 ± 2°C on a flatbed platelet agitator for 7 days post-donation. PCs were used for study purposes only.

2.3 | Quality parameters and in vitro analysis of platelet metabolism

The acceptability criteria for PI treated PCs were those of the Council of Europe Recommendation No. R(95) 15[6] and those of the Swiss Regulations (Vorschriften BSD SRK Kap. 18B) that require a dose of ≥2.4 x 10^{11} platelets/unit in at least 90% of units tested.

On day 0 or day 1, before INTERCEPT treatment, volume, platelet concentration, residual red blood cells, and residual leukocytes were

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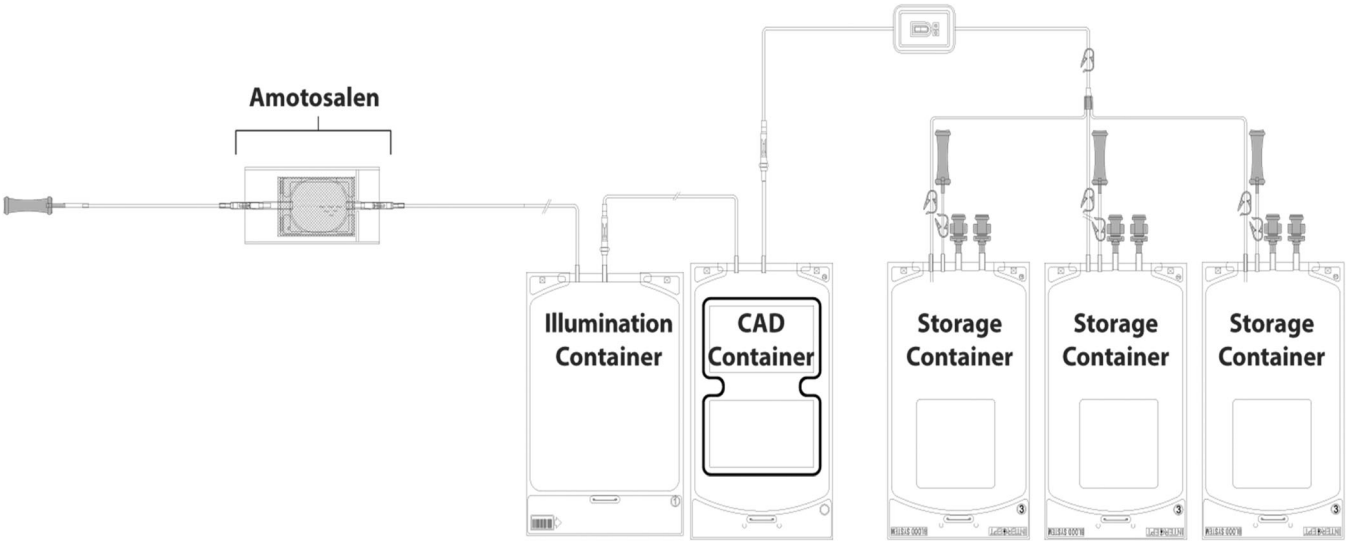

FIGURE 2 Schematic view of the INTERCEPT platelet processing set with triple storage containers. The required ranges of platelet content and volume in apheresis products in plasma/PAS (32%–47% plasma content) are 5–12 x 10^{11} and 420–650 ml, respectively.

measured in each triple-dose apheresis product. Visual inspection for swirling (present or absent) and platelet aggregates were also performed. Volume was calculated based on the weight before and after sampling (volume in ml = weight in g/1.01), Platelet concentrations were measured on a blood cell counter (Sysmex K-4500, Sysmex Digitana AG, Horgen, Switzerland) for the calculation of the platelet yield per unit. Residual leukocytes were measured with a flow cytometer (Attune™ NxT, Thermo Fisher, Life Technologies, Carlsbad, CA, USA) and the red blood cell contamination by microscopy with a Neubauer counting chamber.

On day 1 after PI treatment, volume and platelet content of Test units A, B, and C were measured in order to calculate the percentage of recovery after processing.

Samples (10 ml) for in vitro quality assessment with single measurements were collected on day 1 (immediately following transfer from the CAD), day 5, and day 7 from test units A, B, and C, respectively.

Parameters of extracellular metabolic environment (pO_2, pCO_2, bicarbonate, glucose, and lactate) were measured on a blood gas analyser (ABL 800 Flex, Radiometer GmbH, Copenhagen, Denmark) immediately after sampling, and pH at 22°C with a pH metre (Seven Compact S210-Basic, Mettler-Toledo, Albstadt, Switzerland). Lactate dehydrogenase (LDH) activity was measured with a UV-based spectrophotometric test (Cobas 8000 c702 Roche, Roche Diagnostics Gmbh Rotkreuz Schweiz). ATP was extracted from platelet samples with the addition of strong trichloracetic acid followed by pH neutralisation of the supernatant, then stored below −25°C until the ATP content was analysed using a firefly luciferase bioluminescence assay with ENLITEN® ATP Assay System (Promega, Fitchburg, WI, USA).

The concentration of residual amotosalen was measured in post-CAD samples with a reverse-phase high-performance liquid chromatographic method using a Zorbax SB-CN column (Agilent, Santa Clara, CA, USA).

2.4 | Statistical analysis

Data generated from this study was analysed by basic statistical methods. Mean and standard deviation of amotosalen concentrations and in vitro data at each sampling interval were calculated. When applicable, the *p*-value from a paired *t*-test was calculated to evaluate whether the mean change from baseline to each testing period was different from zero as indicated by a *p* value of <0.05. Results between the two apheresis platforms (AM vs. TR) were also compared and *p*-values from 2-sample *t*-test were calculated. Statistical analyses were performed using SAS® software (Version 9.4).

3 | RESULTS

The 12 triple-dose apheresis collections were performed without technical problems or donor adverse events.

3.1 | Platelet preparation parameters

Table 1 summarises the platelet preparation data of products before and after PI treatment. Before PI processing, all apheresis products exhibited swirling upon visual inspection and met the PI process guard bands (volume 420–650 ml, platelet content 5–12 x 10^{11}, plasma content 32%–47%, red blood cell count <4 x 10^6/ml).

The average volume of products before PI treatment was 617 ± 24 ml. After PI treatment and separation into the three storage containers, the mean volume of the final single-dose units was 188 ± 9 ml. The volume loss after processing and PI treatment, including 15 ml amotosalen, was 52 ± 5 ml on average, corresponding to 8% ± 1% and to a volume recovery of about 92%.

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TABLE 1 Data of platelet products preparation and quality before and after PI treatment

	AM ($n = 6$)	TR ($n = 6$)	Combined ($n = 12$)
Volume before PI (ml)[a]	600 ± 25	634 ± 5	617 ± 24
Volume after PI (ml)[a]	183 ± 8	194 ± 7	188 ± 9
Volume Loss (ml)	52 ± 6	53 ± 5	52 ± 5
Volume recovery (%)	91 ± 1	92 ± 1	92 ± 1
PLT content before PI (10^{11}/unit)[a]	8.58 ± 2.30	9.87 ± 0.76	9.23 ± 1.77
PLT content after PI (10^{11}/unit)[b]	2.83 ± 0.41	2.96 ± 0.26	2.89 ± 0.35
PLT recovery (%)[c]	92 ± 5	90 ± 2	91 ± 3
CAD incubation (h)	11.8 ± 5.9	7.9 ± 5.9	9.8 ± 6.0
Residual Amotosalen (μM)	0.17 ± 0.07	0.39 ± 0.26	0.28 ± 0.21

Note: Results are expressed as mean ± SD.
[a]Values refer to the final single-dose platelet units ($n = 18$ for AM and TR; combined $n = 36$).
[b]Two values above 100% for Amicus (AM) were not taken into account.
[c]Values refer to the triple-dose apheresis products ($n = 12$).

The mean platelet yield of triple-dose products after collection was 9.23 ± 1.77 x 10^{11}. After PI treatment and splitting, the mean final platelet concentration was 2.89 ± 0.35 x10^{11}/unit. Overall, the platelet recovery post-PI processing was 91%.

Both the mean red blood cell and white cell count before PI treatment were below 4 x 10^6/ml and 1 x 10^6/unit, respectively.

After CAD incubation residual amotosalen was 0.28 ± 0.21 μM on average, complying with the value below 2.0 μM required in the current Swiss regulations.

3.2 | Parameters of platelet metabolism during storage

Storage parameters of platelet products are presented in Table 2. Since no difference was observed for any evaluated parameters at any day of storage between PCs incubated with the minimum and then maximum CAD time, results are presented per collection platform (AM and TR) and as combined values.

Significant changes from baseline (day 0/1) during storage included a decrease of platelet concentration, pCO2, bicarbonate, glucose and ATP from day 1 to day 7, and an increase of MPV, pO_2, and lactate also from day 1 to the end of storage, and of LDH on day 5 and day 7.

Comparing products from AM and TR in PCs collected with the AM lower values of pH were measured on day 5 and of pCO2 and bicarbonate on days 5 and 7, whilst pO_2 at days 5 and 7 was higher compared to that in PCs collected with the TR.

Platelet concentration decreased significantly from days 0/1 to 7 with statistical significance for TR from day 1 and for both platforms combined only at day 7. The relatively large standard deviation of the baseline platelet concentration for AM may explain the non-significance of the apparent decrease.

Mean platelet volume (MPV) increased continuously starting from day 1 for products collected by AM and when combining results Values of pH at 22°C remained quite stable from baseline to day 7 (average level varying from 7.1 ± 0.1 to 7.0 ± 0.1). Values of pH were on average 0.2 point higher for TR at days 5 and 7.

Values of pO_2 increased during storage with platelets from both platforms, and were slightly but significantly lower for TR products from day 5. Values of pCO_2 were significantly lower at days 5 and 7 with AM and also bicarbonate and glucose decreased between the pretreatment baseline and days 1, 5, and 7 more rapidly with AM. Similarly, ATP decreased with PI processing and storage, with values being significantly higher for TR products before processing and at every evaluation post-processing. LDH levels tended to increase significantly from day 5 and with lower values throughout storage for TR.

4 | DISCUSSION

In this study, we evaluated standard quality and metabolic parameters of triple-dose PCs collected on two apheresis platforms, suspended in plasma/PAS and treated with amotosalen + UVA with the TS set using two collection platforms. All products met both the EDQM and the Swiss requirements of platelet content, volume and pH values. During a 7-days storage, PCs collected with the AM and TR displayed some statistical differences in metabolic activity, as observed in another recent study.[7]

The procurement and manufacturing of PCs has become increasingly efficient over the years due to multidose platelet collections and the achievement of double-dose products from pooled buffy-coats.[4] At the same time, the safety of components was greatly improved by the use of PAS[8,9] and of PI methods.[1,10] Moreover, many regulatory authorities allow storage for up to 7 days of pathogen inactivated PCs, which leads to a significant reduction of product wastage.[2,4] A more recent development is the use of storage bags and sets with most components manufactured with DEHP-free plastic that allow for improved gas exchange.[11,12]

In Basel, multidose apheresis PCs in plasma/PAS have been produced for more than 20 years. Triple-dose collections amounted to

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TABLE 2 Data of quality and in vitro metabolic parameters as evaluated over 7 days of storage

		Pretreatment day 0/day 1	Day 1	Day 5	Day 7
PLT concentration[a] (10^3/μl)	AM	1424 ± 353	1544 ± 179	1366 ± 154	1258 ± 150
	TR	1557 ± 120	1529 ± 128*	1462 ± 148*	1440 ± 165*
	Combined	1491 ± 261	1536 ± 148	1414 ± 152	1349 ± 178*
PLT MPV (fL)[b]	AM	7.3 ± 0.5	7.5 ± 0.6*	7.9 ± 0.5*	8.1 ± 0.5*
	TR	7.9 ± 1.0	7.9 ± 1.1	8.0 ± 1.0	8.1 ± 1.0
	Combined	7.6 ± 0.9	7.7 ± 0.8*	7.9 ± 0.7*	8.1 ± 0.7*
pH (22°C)[b]	AM	7.1 ± 0.1	7.0 ± 0.1*	6.9 ± 0.0*	6.9 ± 0.1
	TR	7.1 ± 0.1	7.0 ± 0.1	7.1 ± 0.1#	7.1 ± 0.1
	Combined	7.1 ± 0.1	7.0 ± 0.1*	7.0 ± 0.1	7.0 ± 0.1
pO_2 (kPa)[b]	AM	12.0 ± 2.2	17.2 ± 1.6*	20.8 ± 0.7*	20.6 ± 1.8*
	TR	10.6 ± 2.6	16.1 ± 1.3*	16.7 ± 1.4*#	15.9 ± 3.1*#
	Combined	11.3 ± 2.4	16.6 ± 1.5*	18.7 ± 2.3*	18.3 ± 3.5*
pCO_2 (kPa)[b]	AM	4.2 ± 0.7	4.7 ± 0.9	1.2 ± 0.3*	0.9 ± 0.2*
	TR	4.0 ± 1.0	4.5 ± 1.0*	2.1 ± 0.3*#	2.1 ± 0.3*#
	Combined	4.1 ± 0.8	4.6 ± 0.9*	1.7 ± 0.6*	1.5 ± 0.7*
Bicarbonate (mmol/L)[b]	AM	6.9 ± 1.0	5.5 ± 1.0*	1.4 ± 0.5*	1.2 ± 0.5*
	TR	6.3 ± 1.1	5.6 ± 0.9*	4.1 ± 0.2*#	3.6 ± 0.7*#
	Combined	6.6 ± 1.1	5.6 ± 0.9*	2.8 ± 1.5*	2.5 ± 1.4*
Glucose (mmol/L) [b]	AM	5.2 ± 1.2	4.2 ± 1.3*	0.5 ± 0.8*	0.1 ± 0.0*
	TR	6.1 ± 1.1	5.2 ± 1.2	2.7 ± 1.1*#	0.7 ± 0.5*#
	Combined	5.6 ± 1.2	4.7 ± 1.3*	1.6 ± 1.5*	0.4 ± 0.4*
Lactate (mmol/L)[b]	AM	3.6 ± 1.9	5.4 ± 1.8*	11.7 ± 1.8*	12.1 ± 1.7*
	TR	3.6 ± 1.7	5.0 ± 2.6	9.6 ± 1.7*	12.2 ± 1.3*
	Combined	3.6 ± 1.7	5.2 ± 2.1*	10.6 ± 2.0*	12.1 ± 1.5*
ATP (nmol/10^8 PLTs)[b]	AM	2.7 ± 0.4	2.5 ± 0.4	1.8 ± 0.6*	1.3 ± 0.6*
	TR	4.1 ± 0.7#	3.9 ± 0.7*#	3.9 ± 0.7*#	3.7 ± 0.7*#
	Combined	3.4 ± 0.9	3.2 ± 0.9*	2.8 ± 1.3*	2.5 ± 1.4*
LDH (U/L)	AM	292 ± 73	237 ± 78	417 ± 133*	508 ± 99*
	TR	87 ± 5#	98 ± 9#	137 ± 20*#	141 ± 11*#
	Combined	201 ± 119	167 ± 90	277 ± 172*	324 ± 203*

Note: Results are expressed as mean ± SD.

#*p*-values <0.05 indicate significant difference for Amicus (AM) versus Trima (TR).

**p*-values <0.05 indicate significant difference compared to the baseline. [a]Values refer to the triple-dose apheresis products ($n = 12$).

[b]Values refer to the final single-dose platelet units tested during storage (A on day 1, B on day 5, and C on day 7) for both the minimum and the maximum CAD incubation.

approximately 20% of procedures until the INTERCEPT® blood system for platelets was implemented in January 2011. Due to the unavailability of sets suitable for PI treatment of products with such large volume and high platelet content, triple-dose apheresis was no longer performed. At the same time, the demand of PCs from the clinic increased steadily[2] and the procurement of sufficient numbers of units became challenging at times. Thus, the new TS set is of particular interest for our centre, since it allows for the re-introduction of the manufacturing of PCs from triple-dose collections in compliance with the current quality and safety standards.

Overall, data on the quality of triple-dose PCs are limited. Triple-dose products stored for 7 days in PAS 5, PAS 5/plasma or in 100% plasma collected with the AM and the TR were equivalent for in vitro storage parameters.[13] To date, only one other study assessed the quality of PCs manufactured with comparable methods as described in our study. Lotens et al.[7] analysed standard quality and metabolic parameters up to day 7 in PCs treated with amotosalen + UVA using large volume sets or TS sets and prepared with three different platforms (AM, TR, and pooled buffy-coats). In that study, PCs stored in TS sets had a higher volume and platelet recovery and higher residual amotosalen (although within the required limits), and displayed less platelet activation during storage compared to PCs processed with large volume sets. Differences in metabolic parameters were observed both between AM and TR and between apheresis-derived and buffy

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coat derived components. Compared to the results of Lotens et al. on apheresis-derived PCs treated with the TS set (the study products with the same characteristics as ours), platelet content, pH at 22°C, glucose and bicarbonate of our products remained higher throughout storage and lactate was lower. On day 7, pO_2 was higher and pCO_2 lower, whilst ATP levels were comparable to the day 7 values reported by Lotens et al. for the units collected with AM. Thus, we observed an overall slightly better metabolic profile of stored platelets from apheresis, but with differences between AM and TR along the same line.

Platelet loss after treatment (%) was in line with the volume loss. Quality parameters were not different in PCs treated with the minimum versus the maximum CAD time (results not shown) recommended in the instructions for use. This observation does not indicate a substantial influence of different CAD times on platelet metabolism after treatment with amotosalen + UVA, as also reported by others.[14,15]

Storage containers made of DEHP-free plastics, as in the TS sets, display improved gas permeability. Platelets of double-dose buffy coat derived PCs treated with amotosalen + UVA and stored in the same type of containers had reduced glucose and bicarbonate consumption and less lactate production.[5] DEHP-free containers are particularly interesting for the storage of multidose, highly concentrated PCs, since the improved gas exchange can reduce the negative effects of a relative O_2 deprivation on platelet metabolism and energy supply.[16]

Effects on platelet quality were described for highly concentrated products,[16,17] for PI,[18,19] and for prolonged storage,[20] which are also the manufacturing conditions of our study components.

High platelet concentrations were associated with decreased swirling and glucose content and increased lactate in double-dose, pathogen inactivated PCs from apheresis.[17]

Because anaerobic metabolites accumulate in these components, Feys et al. suggested that the upper guard band ranges for amotosalen + UVA treatment of such apheresis products be revalidated,[17] but in that study products were stored in one or two containers post-PI treatment, whilst they were split into three storage containers in our study, leading to a lower platelet content per bag. Indeed, despite a higher platelet concentration, we did not observe a significant increase in anaerobic metabolisms in our PCs.

We observed in all products after collection. Glucose, lactate and pH at 22°C values and the changes of the other parameters from day 1 to day 7 of storage were overall comparable to those reported previously for apheresis-derived double-dose PCs (having a lower platelet concentration).[21]

High concentrations of platelets, like those of multidose products, and further processing of PCs impact in vitro platelet biology and function to a different extent,[22–24] even if standard quality parameters comply with regulations. However, changes in platelet function are in part reversible after transfusion to the patient, and overall do not seem to impair transfusion efficacy in vivo.[2,25]

A 7 days storage of pathogen inactivated PCs from triple-dose apheresis collections would further improve cost efficiency of PC manufacturing, as described for double-dose buffy-coat derived products.[4] Besides reducing material consumption and workload, and allowing for a rapid replenishment of stores, this strategy could facilitate the procurement of PCs for patients with particular requirements (e.g., HLA-matched PCs or platelets negative for specific HPA antigens).

Limitations of the present study include the small number of products evaluated and that no assessment of biologic platelet functions (e.g., aggregation tests) was performed. Further studies to analyse the in vivo transfusion efficacy would also be required.

In conclusion, our study demonstrates apheresis-derived triple-dose PCs treated with amotosalen + UVA with the TS sets fulfilled the quality requirements and exhibited metabolic activity during 7-day storage. Some differences were observed with metabolic parameters when comparing both platforms, but not large enough to expect differences in platelet quality. The INTERCEPT TS sets would both allow further savings in materials and labour time for PI treatment of PCs and facilitate the procurement of platelet products.

AUTHOR CONTRIBUTIONS

LI and JMP designed the study. LI and VP recruited the study donors. SM performed the laboratory tests. SA and JSL performed the data analysis. LI and JMP wrote the manuscript. AH and AB revised the manuscript.

ACKNOWLEDGMENT

Open access funding provided by Universitat Basel.

FUNDING INFORMATION

The study was partly financially supported by Cerus Corporation under a service agreement.

CONFLICT OF INTEREST

Silke Andresen, Jean-Marc Payrat, and Jin-Sying Lin are employees of Cerus Corporation.

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How to cite this article: Infanti L, Pehlic V, Mitrovic S, et al. Pathogen inactivation treatment of triple-dose apheresis platelets with amotosalen and ultraviolet a light. *Transfusion Medicine*. 2022;32(6):505-511. doi:10.1111/tme.12913

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