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In vitro evaluation of pathogen inactivated platelet quality: An 8 year experience of routine use in Galicia, Spain

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ABSTRACT

Background: Platelet concentrates (PCs) treated by the pathogen inactivation technology (PI) using amotosalen and UVA illumination (PI-PCs) can be manufactured in additive solutions (PAS-III and PAS-IIIM) or in 100% Plasma. Quality control (QC) is an integral part of the production. We capitalized on our ongoing QC program to capture 8 years-worth of data on parameters related to the quality of 116,214 PI-PCs produced under different manufacturing methods.

Materials and methods: Selected in vitro parameters of metabolism, activation, and storage were analyzed for the different manufacturing periods to compare PI-PCs versus conventional PCs (C-PCs) resuspended in different PAS.

Results and discussion: All BC-PCs met quality standards for pH and dose and residual leucocytes. As expected, storage time correlated with increased lactate, LDH, Annexin V, CD62, sCD40 L levels and decreased glucose and pH. With PAS-IIIM, higher levels of glucose were observed toward the end of shelf life ($p < 0.0001$) with lower platelet activation markers Annexin V ($p = 0.038$) and CD62 ($p = 0.0006$). Following PI implementation, a low expire rate of < 0.5% was observed. While a 2.3% mean increase in the production of PCs occurred from 2011 to 2015, the distribution of red blood cell concentrates dropped by 4.4%. A mean incidence of 0.14% for transfusion-related adverse reaction was observed while PI-PCs were distributed, similar to the one observed with C-PCs. Overall, PI-PCs prepared in additive solutions consistently met quality standards. Those prepared in PAS-IIIM appeared to have better retention of in vitro characteristics compared to PAS-III though all demonstrated functionality and clinical effectiveness.

1. Introduction

An important goal in transfusion medicine is to ensure an adequate supply of high quality platelets. Over the past decades, the introduction of pre-storage leukodepletion and the use of additive solutions (AS) contributed toward that goal. The replacement of plasma by AS for the resuspension of platelets reduces the risk of transfusion complications due to potential allergic reactions to proteins present in the donor plasma [1], and it can be modified to further improve platelet storage conditions while generating savings allowing for plasma to be used for other applications [2–5].

In recent decades, storage solutions have been developed to improve platelet function by reducing platelet metabolism, lactate production and glucose consumption [4,6–10]. Indeed glucose exhaustion is associated with platelet apoptosis [11]. Acetate can serve as an alternate energy substrate and its presence in AS decreases glucose consumption. In addition, acetate consumption results in the production of bicarbonate, which helps maintaining pH throughout storage [2]. The addition of magnesium and potassium in PAS-IIIM may further decrease platelet activation [4,12,13].

More recently, to reduce the risks associated with PC transfusion, bacterial testing, sample diversion, point of release testing, and pathogen inactivation technologies were implemented [14,15]. PI technologies were developed to reduce the risk of transfusion-transmitted infections associated with PC components. Storage of PCs at ambient temperature makes them more susceptible to bacterial growth, especially over prolonged period of storage. PCs treated with the INTERCEPT Blood System® for platelets (Cerus Corporation, Concord, CA, USA) can be stored for up to 7 days without incurring the added risk of bacterial contamination even in the absence of bacterial screening.

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Table 1
Composition of PAS-IIIM versus PAS-IIII Additive Solutions.

	PAS-III (InterSol)[a]	PAS-IIIM (SSP+) [37]
NaCl (mM)	77	69
KCl (mM)	–	5
$MgCl_2$ (mM)	–	1.5
Na_3.citrate (mM)	11	10
NaH_2PO_4/ Na_2HPO_4 (mM)	28	26
Na-acetate (mM)	33	30

[a] As per FDA approved package insert [38].

Prolonged PC storage allows for better inventory management and distribution logistics resulting in reduced wastage. Furthermore, because of the robust inactivation of T-cells, INTERCEPT treatment can be used in lieu of gamma irradiation. This greatly reduces the risk of delivering the wrong product to patients with higher risk to develop TA-GVHD as all products in the inventory are safe for at risk recipients such as immune-suppressed patients [16,17].

Our center manufactured C-PCs until 2008. In 2008, the INTERCEPT Blood System was implemented to treat PCs. The use of PI started in April 2008 for the treatment of Apheresis-PCs, while the treatment of BC-CPs was initiated in September of the same year. Until 2012, PI-PCs were produced in PAS-III (InterSol™, Fenwal) but based on our previous experience [18,19] and several studies supporting the positive effect of PAS-IIIM on platelet functionality [8,20], starting in 2012, PI-PCs have been produced in PAS-IIIM (Table 1).

Our blood center supplies blood components for 31 hospitals that serve a community of 2.7 million inhabitants; Approximately 15,000 PCs per year are distributed and those evolved over time from being 57% apheresis and 44% pooled buffy-coats (BC-PCs, derived from 5 buffy-coats) in 2009 to being 37% apheresis and 63% BC-PCs in 2015. PCs quality is assessed on a monthly basis as per the national standards guidelines[21] and the Council of Europe recommendations [22]. This ongoing quality control (QC) program allowed the capture of data on platelet quality and function over a span of eight years corresponding to three time-periods when PI-PCs were manufactured in either PAS-III in 2008, or PAS-IIIM in 2012 and 2015 (Fig. 1) [23]. This study compares PI-PCs manufactured in either PAS-III or PAS-IIIM to C-PCs manufactured in PAS-IIIM.

2. Materials and methods

2.1. BC-PC pool preparation

Whole blood (WB) units (450 ± 45 mL) were collected from volunteer donors into quadruple top-and-bottom bags with in-line red blood cell (RBC) filters (MacoPharma Leucoflex LCR). Following donation, the WB units were placed on butanediol plates and processed within the next 14–18 h. Processing included a first centrifugation phase (4497xg, 18 min at 22 °C) followed by component separation using a CompoMat G5 automated blood component separator (Fresenius) to separate plasma from RBCs while the buffy coat (BC) was left in the main bag. Individual BCs were allowed to rest for a minimum of 2 h before pools were prepared; five BCs were pooled(BC-PCs) in PAS (mean volume 53.8 mL with 38.7% hematocrit). BC-PCs were then centrifuged, separated and filtered using the automatic OrbiSac system (TerumoBCT, Lakewood, Co). The final PAS/plasma ratio was approximately 65/35. The final BC-PC product was allowed to rest for 2 h after pooling. All pools were visually inspected before proceeding with amotosalen/UVA treatment.

Air bubbles were systematically removed from all BC-PCs to avoid negative effects on platelet integrity [24] and the BC-PCs were stored in polyolefin bags (PL-2410, 1.3 L) under standard conditions at 22 °C with continuous agitation (Helmer PC 3200 Incubator).

2.2. Pathogen inactivation treatment

Platelets are transferred to the amotosalen container after sterile connection of the platelet bag to the processing kit. Platelets and amotosalen solution then flow by gravity into the illumination container. The original platelet bag and amotosalen container are subsequently removed from the kit. The platelets and amotosalen in the illumination container are mixed end-over-end to ensure thorough homogenization, placed into the illumination device and illuminated (3.0 J/cm^2 UVA). The treated platelets are then transferred into the Compound Adsorption Device (CAD) container. After the illumination container is removed, the treated PCs in the CAD container are kept on a flatbed agitator for 6–16 hours.

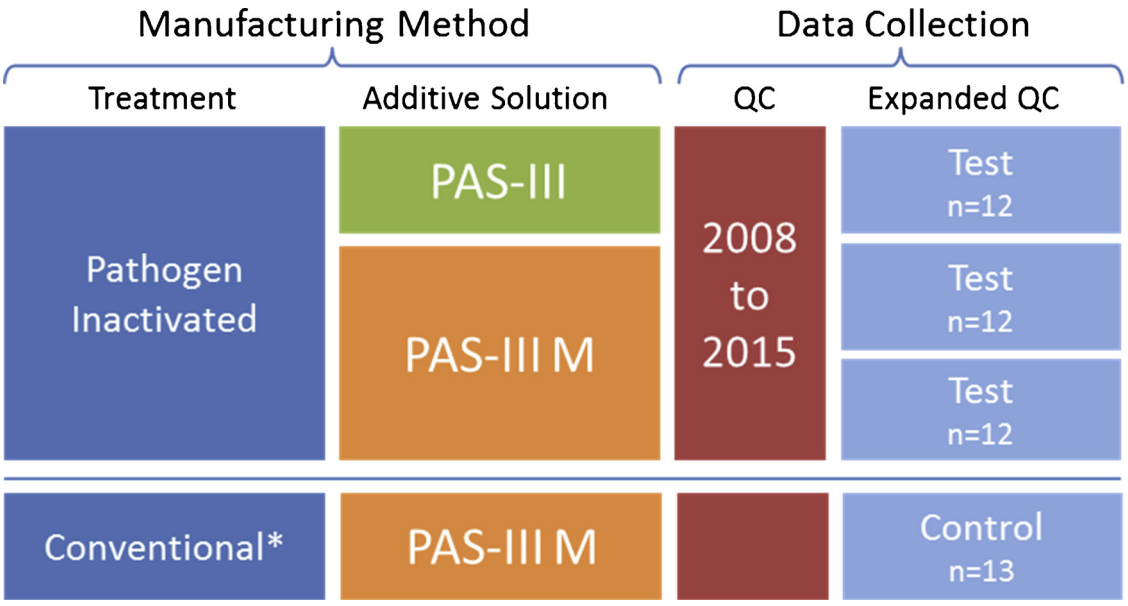

Fig. 1. Assessment of platelet quality and function parameters across 3 time-periods. Data were captured over eight years following the implementation of INTERCEPT Blood System for platelets manufactured in PAS-III in 2008, or in PAS-IIIM in 2012 and 2015. Independently, control data were collected in 2010 on C-PCs resuspended in PAS-IIIM.

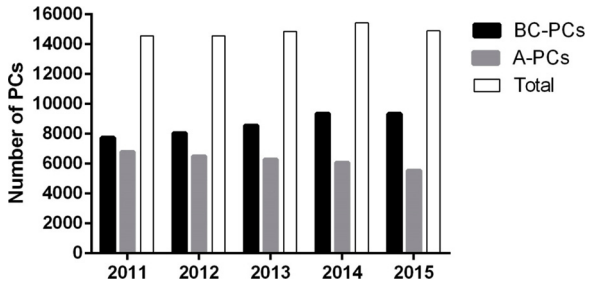

Fig. 2. Supply of PI-PCs over a 5 year period. Numbers of PI treated BC-PCs and A-PCs produced at our blood center are shown for the period from 2011 through 2015.

Subsequently, platelets are transferred by gravity into the storage container. After the CAD container is removed, the storage container is placed on a platelet agitator.

For QC data collection, platelets are sampled after mixing of the storage container by gentle agitation followed by expression into the sampling pouch, which is sealed, removed and transferred to the appropriate laboratory.

2.3. Data capture

The usual QC parameters were assessed in PC at 14–18 h after inactivation (volume registration, cell count, swirling visualization and residual leukocytes count). At the end of the component's shelf life (7 days), pH was determined and samples for bacterial culture taken allowing for inoculation of an anaerobic and an aerobic bottle with 10 mL samples for incubation in the BacT/Alert System (Biomerieux) for 7 days. The number of units tested monthly for cell count was 16% of the total component production (as per internal quality indicator ≥15%), and volume registration and visual inspection were carried out in 100% of the PCs. The other parameters were assessed for ~1.7% of PCs (or 12 per months to satisfy the quality control standards recommending to test ≥1% of the production) [21]. Randomization was organized based on the number of platelet component produced on a monthly basis and to insure that approximately 16% were analyzed, 6–7 units were selected daily with representation across blood groups and manufacturing time. Volume was recorded for all units and the swirling was checked for all PCs, Approximately 12 units a month or 3 units a week were randomly selected among units that were not distributed by day 6.

Three storage studies were carried out during the eight years the INTERCEPT® Blood System for platelets was in use. Those were conducted in 2008 on PAS-III PI-PCs (n = 12), and in 2012 (n = 12) and 2015 (n = 12) on PAS-IIIM PI-PCs. Data were collected on days 2, 5, 7, and 9 of storage for 12 PI-PCs. The fractionation method, the device to obtain the PC-pool, the type of platelet filter (LRP6, Pall) and the plasma/PAS ratio did not change between these periods. In 2010, data were collected on C-PCs manufactured in PAS-IIIM (n = 13). The number of PCs distributed and the adverse events (AEs) of transfusion of this component were monitored through passive reporting.

2.4. In vitro parameters

The platelet content and mean platelet volume (MPV) were measured using the XT-2000i Sysmex autoanalyzer. The pH was measured at 22 °C using a pH meter (Crysson MicropH2001). Swirling was assessed visually and given a numerical value of 0–2 (0 = no swirling, 1 = intermediate swirling, and 2 = patent swirling) based on previous work [25]. Residual leukocytes were counted by flow cytometry (FC) using Leukocount™ (FACScalibur, Becton Dickinson). Glucose, lactate and lactate dehydrogenase (LDH) determination were performed on the Olympus AU 400 Chemistry Analyser. For CD62 P and Annexin V marker analysis, samples were diluted to 1×10^6 PLTs/mL and incubated with phycoerythrin (PE)-conjugated CD62 monoclonal antibodies and fluorescein isothiocyanate (FITC)-conjugated Annexin V (Becton Dickinson, Immunocytometry Systems, San Jose, CA, USA) according to the manufacturer protocol before analysis by FC.

Samples harvested in 2008, 2010, and 2012 were centrifuged twice and frozen at −80 °C before duplicate samples were evaluated for cytokine concentration using ELISA kits (R&D Systems, Minneapolis, MN, USA) for sCD62 P, sCD40 L following the manufacturer's instructions.

2.5. Statistical analysis

For each assay, longitudinal data captured on days 2, 5, 7, and 9 were analyzed using a generalized estimating equation (GEE). In addition to the continuous effect of time, a (categorical) treatment group and a time-by-treatment interaction term were also included as covariates into the modelling process. Subsequent inference on the covariate estimates were carried out in order to draw conclusions on the storage and treatment effect. All models were fit in SAS version 9.4 using the Genmod procedure. In addition, an analysis was performed to draw conclusions on the storage effect in each treatment arm comparing values at day 5, 7, and 9 to values at day 2 of storage using GraphPad Prism (GraphPad Software, Inc.); The Friedman test followed by the Dunn's multiple comparison test or the one-way ANOVA followed by the Dunnett's multiple comparison test, or the Kruskal-Wallis test followed by the Dunn's multiple comparison test were used depending on data structure and availability at each time-point.

3. Results

During the 8-year period between April 2008 and April 2016, a total of 116,214 PI-PCs (BC-PCs and Apheresis-PC) were produced. The last five-year PC supply production is detailed in Fig. 2, where the mean increase in the production of PC (from 2011 to 2015) was 2.3%, while over the same period the supply of red blood cell concentrates dropped by 4.4%, suggesting that no excessive bleeding occurred while using PI-PCs. The expiry rate in our center is less than 0.5%.

3.1. Routine QC data demonstrated that PC quality is maintained after INTERCEPT treatment

Table 2 shows the routine QC results for the period 2013-2015. All QC parameters were obtained on PCs 14–18 hours post-inactivation and included platelet content, swirling, residual leucocyte count, and pH measured at 22 °C at the end of shelf life as required by national and European guidelines [21,22]. The mean platelet content per unit was $\geq 3 \times 10^{11}$, leukocyte content in all units was $< 1 \times 10^6$ leukocytes per unit, and pH measured at expiration at 22∘C was ≥7.13. Upon visual inspection, the swirling effect was evident and maintained throughout storage. None of the PCs tested positive for bacterial contamination. In our experience, the mean volume and platelet loss after implementing the INTERCEPT treatment were 7.5% and 8.5%, respectively [26].

3.2. PI-PCs met quality standards for transfusion suitability over time of storage

Three independent studies were conducted to assess in vitro platelet metabolism and activation markers in ***i)***- C-PCs in PAS-IIIM in 2010 and ***ii)***- PI-PCs in PAS-IIIM in 2012 and 2015, to evaluate the effect of PI treatment on platelet metabolism and activation while production methods changed replacing PAS-III with PAS-IIIM.

In C-PCs in PAS-IIIM, the mean platelet volume increased slightly from 8.8 to 9.2 fL ($p = 0.0048$) as a function of storage time. The levels of lactate dehydrogenase (LDH) increased from 72.4 on day 2 to 92.6 U/L on day 9 ($p < 0.0001$). Glucose concentration was significantly impacted and decreased from 5.5 to 1.9 mmol/L from day 2 through 9 ($p < 0.0001$) while lactate concentration increased significantly from

Table 2
Quality control mean indices for pathogen inactivated PCs.

	2013 n = 1480 (16.9%)	2014 n = 1591 (16.7%)	2015 n = 1637 (17.2%)
Volume (mL)	331.2 ± 23.4	338.2 ± 19.8	340.5 ± 13.2
Platelet (PLT) count (x10^{11}/unit)	3.38 ± 0.41	3.42 ± 0.41	3.40 ± 0.42
% of units with ≥ 3×10^{11} PLTs	87	86.4	87
"Swirling "score	2	2	2
Residual leukocytes	< 1×10^6/unit	< 1×10^6/unit	< 1×10^6/unit
pH (22 °C)[a]	7.13 ± 0.09	7.18 ± 0.09	7.16 ± 0.10
Tested for bacterial culture[a]	Negative[b]	Negative[b]	Negative[b]

[a] At expiration (Day 7).
[b] Aerobic and anaerobic bottles inoculated with 10 mL samples.

4.9 on day 2 to 13.3 mmol/L on day 9 of storage ($p < 0.0001$) (Fig. 3). Platelet count and pH on the other hand did not change significantly over time of storage (Fig. 3). Platelet activation markers all significantly increased ($p < 0.0001$) as a function of storage time in C-PCs in PAS-IIIM including Annexin V, CD62 after day 7, and sCD40 L sP-selectin after day 5 of storage (Fig. 4).

When PI-PCs in PAS-IIIM were compared to C-PCs in PAS-IIIM, there was no difference in platelet quality parameters such as mean platelet volume ($p = 0.18$), pH ($p = 0.95$), LDH level ($p = 0.12$) or lactate concentration ($p = 0.86$). PI treatment had a slight impact on platelet count decreasing over time ($p = 0.0015$) resulting on day 7 in a ~3.5% platelet loss (compared to < 1% platelet loss in control BC-PCs), though all units met the requirements in term of platelet content per final unit of ≥2.5×10^{11}. While PI-PCs in PAS-IIIM showed a slight increase in glucose consumption over time of storage compared to C-PCs ($p = 0.0002$) (Fig. 3), both PI-PCs and C-PCs had sufficient glucose through day 9 of storage. In PI-PCs, the increase in Annexin V ($p = 0.025$) and CD62 ($p = 0.026$) expression was slightly higher over time of storage compared to C-PCs resuspended in the same AS (Fig. 4).

3.3. PAS-IIIM improves platelet storage conditions after PI treatment

Table 3 shows the evolution of platelet metabolism and activation parameters in PI-PCs resuspended in PAS-III versus PAS-IIIM over time of storage until day 9.

The pH values decreased as a function of time in all PCs (Fig. 3). The pH values were not significantly different between PI-PCs and C-PCs resuspended in PAS-IIIM ($p = 0.95$). The pH decreased more in PI-PCs in PAS-III than in PAS-IIIM ($p < 0.0001$). However in all cases pH values were maintained above 6.8 at day 7 and 9, and therefore both PI-PCs in PAS-III or PAS-IIIM met quality standards with pH well above the 6.4 limit [22].

PI-PCs in PAS-III seemed to have higher mean platelet volume ($p < 0.0001$) and reduced platelet count (resulting in a 4% platelet loss by day 7 of storage) ($p = 0.041$). Glucose consumption ($p < 0.0001$) and lactate production were both accelerated ($p < 0.0001$) over time of storage in PI-PCs in PAS-III compared to those in PAS-IIIM (Table 3 and Fig. 3), suggesting an accelerated platelet metabolism when PCs were manufactured in PAS-III compared to PAS-IIIM. By day 7 of storage, while C-PCs and PI-PCs resuspended in PAS-IIIM had detectable glucose, the PI-PCs in PAS-III had exhausted all the glucose in the bag. PI-PCs in PAS-III also had higher levels of platelet activation markers such as Annexin V ($p = 0.039$), CD62 ($p = 0.0006$), and sP-selectin ($p = 0.0002$) expression over time of storage (Fig. 4), suggesting a better control of platelet activation with PAS-IIIM. A larger increase in the percentage of CD62-positive platelets or secreted cytokines was observed for PI-PCs in PAS-III from day 2 to 5 of storage followed by a more moderate increase from day 5 to 9 of storage, suggesting a stronger platelet activation during the first 5 days of storage.

4. Discussion

The purpose of this study was to validate the suitability for transfusion of PCs produced using different manufacturing methods. Platelet quality parameters, metabolism and activation markers were compared in 2008, and from 2012 to 2015 for PAS-III and PAS-IIIM, respectively. The results corroborate good platelet quality, and acceptable pH levels until day 7. Platelets stored in PAS-IIIM maintained platelet number and glucose levels with low activation throughout storage, as previously described [8]. Contrary to some of the findings reported in other publications, there was no significant difference between LDH levels in PI-PCs in PAS-IIIM compared to PI-PCs in PAS-III. The CD62 P protein is found in the alpha granules of platelets, and it is expressed on the platelet surface when they are activated. CD62 expression increased over time of storage, however values were lower for PCs in PAS-IIIM than in PAS-III, as previously reported [12]. Although the expression of CD62 P remained low throughout the storage period in PAS-IIIM PCs, its clinical significance is not known; in vitro activation of stored platelets did not correlate with in vivo survival and with platelet hemostatic function after transfusion [27]. Most studies evaluate platelet quality based on in vitro parameters, while only a limited number of studies are able to assess the impact in vivo [12]. We observed a small percentage of Annexin V-positive platelets increasing over time of storage though the increase in phosphatidylserine exposure remained relatively low, less than 10% in all units. This is consistent with previous reports [28]. The level of adhesion molecule expression and cytokine secretion were within expected ranges [29,30]. Soluble CD40 L (sCD40 L) is a powerful immunomodulator that accumulates in the platelets during storage [31], acts as an inflammatory mediator, and has been suggested but not proven to be associated with transfusion adverse reactions [32]. Platelets are the main source of sCD40 L and we observed a gradual increase during storage but, as previously reported by others [33], PI treatment did not significantly increase the accumulation of sCD40 L in PI-PCs versus C-PCs.

In this study, in addition to the monthly quality controls, more comprehensive in vitro studies provided us with additional information on the quality of the produced PCs. PI treatment resulted only in minimal additional changes to the ones in C-PCs. A lower platelet count and a decreased glucose concentration were accompanied by a slightly increased platelet activation toward the end of the platelet shelf life.

Our region's records of haemovigilance (HV) show that transfusion-related AE, related to PI-PCs are mild with a mean incidence over the last 4 years of 0.14%, very similar to the ones observed in the past for C-PCs. Of note all PCs are manufactured in our center using AS since the year 2000. In 2013, a case of TRALI was reported, in relation to antibodies to HLA class II antigens in donor to antigens present in the recipient [34]. No cases of PC transfusion-related sepsis, or post-transfusion GVHD were reported during this period. HV multicenter studies provide information about the safety and efficacy of the treated component in a large population [35]. We have participated in the HV study analysis of 19,175 transfusions of PCs treated with amotosalen-UVA,

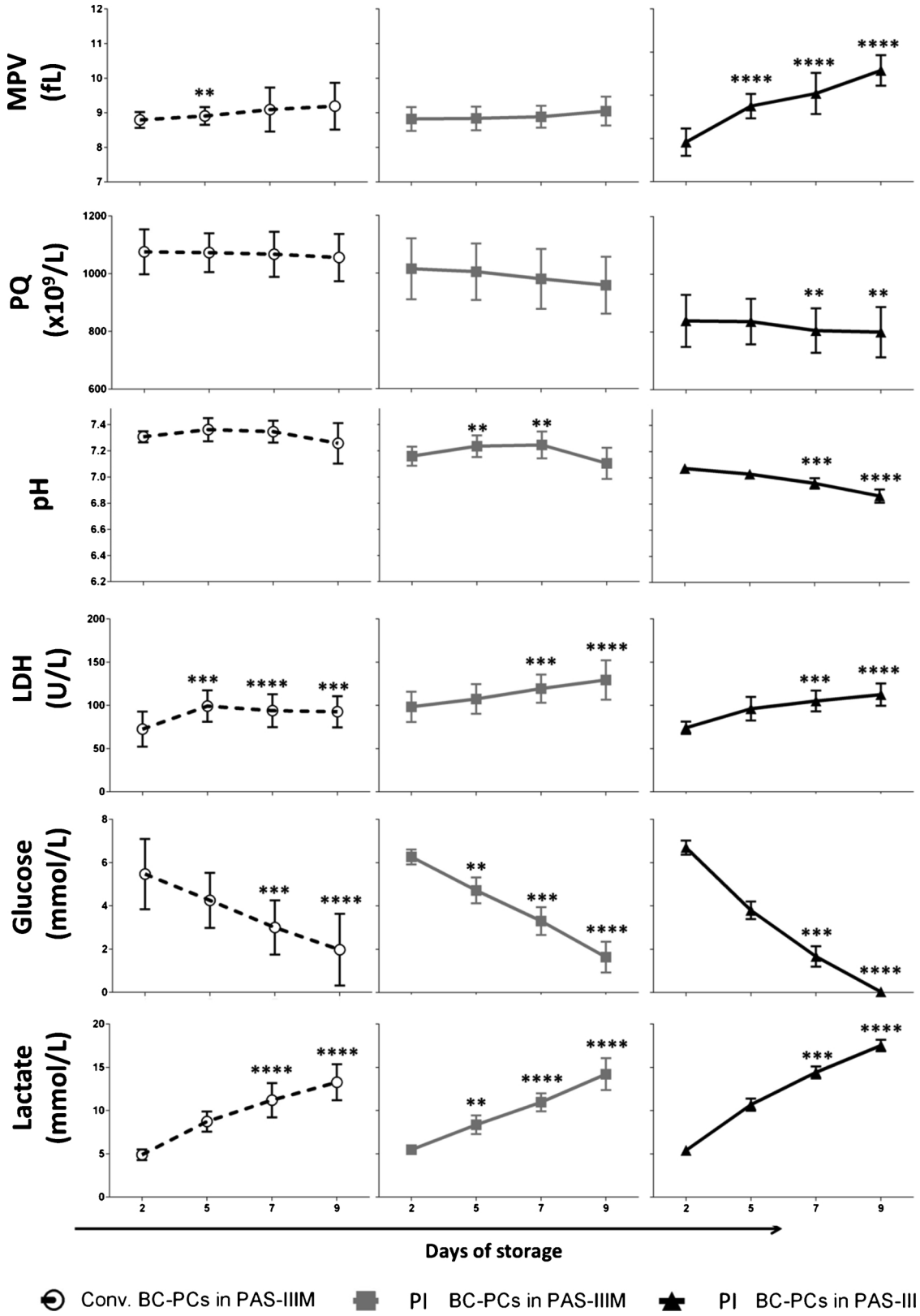

Fig. 3. Evolution of platelet quality parameters during storage depending on PC manufacturing method. Mean platelet volume, platelet count, pH at 22 °C, LDH, glucose and lactate concentrations at day 2, 5, 7, 9 of storage are shown for C-PCs (dotted black lines) and PI-PCs resuspended in PAS-IIIM (solid grey lines) or PAS-III (solid black lines). The graphs show mean ± SEM. P-values by ANOVA < 0.05 are represented by *, < 0.01 by **, < 0.001 by ***, < 0.0001 by **** indicating significant changes compared to day 2 time-point. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

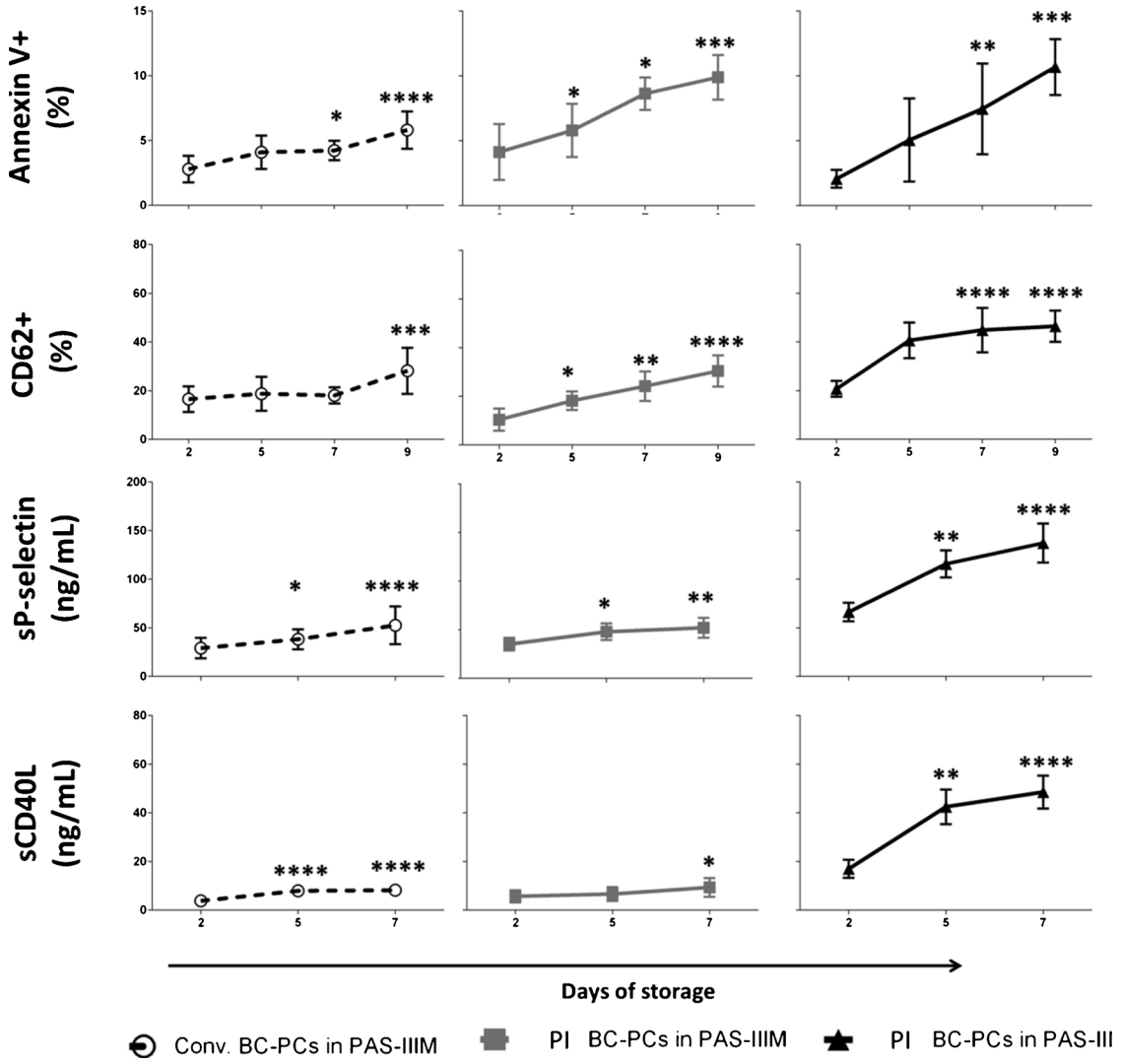

Fig. 4. Platelet activation markers and cytokine levels during storage for different PC manufacturing methods. Frequencies of Annexin V-positive, CD62-positive, sP-selectin-positive platelets and levels of sCD40 L are shown for C-PCs (dotted black lines), and PI-PCs in PAS-IIIM (solid grey lines) or PAS-III (solid black lines) at day 2, 5, 7, and 9 of storage as available. The graphs show mean ± SEM. P-values by ANOVA < 0.05 are represented by *, < 0.01 by **, < 0.001 by ***, < 0.0001 by **** indicating significant changes compared to day 2 time-point. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 3
Mean levels for metabolic and activation parameters shown for pathogen inactivated (PI)-PCs depending on the additive solution used.

Day of storage		2	5	7	9	p-value[¥]
pH	A	7.07 ± 0.02	7.03 ± 0.03	6.96 ± 0.04	6.86 ± 0.05	
(22 °C)	B	7.16 ± 0.07	7.24 ± 0.09	7.25 ± 0.1	7.10 ± 0.12	*< 0.0001*
Glucose	A	6.7 ± 0.3	3.8 ± 0.4	1.7 ± 0.5	0.03 ± 0.04	
(mmol/L)	B	6.3 ± 0.4	4.7 ± 0.6	3.3 ± 0.6	1.64 ± 0.7	*< 0.0001*
Lactate	A	5.4 ± 0.4	10.7 ± 0.7	14.4 ± 0.7	17.5 ± 0.7	
(mmol/L)	B	5.5 ± 0.5	8.3 ± 1.1	11.0 ± 1.04	14.2 ± 1.84	*< 0.0001*
CD62p (%)[a]	A	20.7 ± 3.3	40.6 ± 7.3	44.9 ± 9.2	46.4 ± 6.4	
	B	9.3 ± 6	17.2 ± 1.9	19.7 ± 5.9	25 ± 10	*< 0.0006*
sP-selectin	A	66.3 ± 9.5	115.7 ± 13.9	137.1 ± 20	NT	
(ng/mL)	B	35.5 ± 8.5	51.8 ± 12	57.7 ± 15.1	77.5 ± 23.2	*0.0002*
LDH	A	74.1 ± 7.2	96.1 ± 13.6	105.1 ± 12.1	112.5 ± 13.0	
(U/L)	B	98.4 ± 17.6	107.5 ± 17.3	119.4 ± 16.4	129.6 ± 22.9	0.0753
Annexin V[a]	A	2.1 ± 0.7	5.0 ± 3.2	7.4 ± 3.5	10.7 ± 2.2	
(%)	B	3.0 ± 2.0	4.7 ± 1.8	6.0 ± 2.8.	7.3 ± 3.3	0.0389

A = PI-PCs in PAS-III in 2008 (n = 12).
B = PI-PCs in PAS-IIIM in 2012 and 2015 (n = 24).
NT = not-tested.
[a] By flow cytometry.
[¥] p-value by GEE comparing A and B over time of storage.

where a low rate of AE and a safety profile similar to the one for C-PCs were reported [36].

5. Conclusions

Our QC program allowed for the evaluation of PI-PCs quality over a 8 year-period while PI-PCs were manufactured in PAS-III or PAS-IIIM. Overall the results demonstrate that all PI-PCs met good quality criteria with platelet quality parameters and metabolism and activation markers maintained throughout platelet storage. PI-PCs prepared in PAS-IIIM appeared to have better retention of in vitro characteristics compared to PAS-III though all demonstrated functionality and clinical effectiveness. This study highlights the fact that the PI technology using amotosalen and UVA can be implemented to improve blood safety while maintaining platelet quality and efficacy.

Authorship contributions

A.C.F. contributed to study design, data collection, data analyses, and manuscript writing and editing. M.C.L. contributed data analyses and manuscript writing and editing. C.A.O., A.D.P., and M.A.P. contributed data collection, data analyses, and manuscript editing.

Disclosure of conflicts of interest

Marion C. Lanteri is an employee of Cerus Corporation.
The other authors have declared no conflict of interest.

References

[1] Cohn CS, Stubbs J, Schwartz J, Francis R, et al. A comparison of adverse reaction rates for PAS C versus plasma platelet units. Transfusion 2014;54:1927–34.
[2] Gulliksson H. Additive solutions for the storage of platelets for transfusion. Transfus Med 2000;10:257–64.
[3] Gulliksson H. Defining the optimal storage conditions for the long-term storage of platelets. Transfus Med Rev 2003;17:209–15.
[4] Gulliksson H. Platelet storage media. Vox Sang 2014;107:205–12.
[5] Kacker S, Ness PM, Savage WJ, Frick KD, et al. The cost-effectiveness of platelet additive solution to prevent allergic transfusion reactions. Transfusion 2013;53:2609–18.
[6] Gawaz M, Ott I, Reininger AJ, Neumann FJ. Effects of magnesium on platelet aggregation and adhesion. Magnesium modulates surface expression of glycoproteins on platelets in vitro and ex vivo. Thromb Haemost 1994;72:912–8.
[7] Gulliksson H, AuBuchon JP, Cardigan R, van der Meer PF, et al. Storage of platelets in additive solutions: a multicentre study of the in vitro effects of potassium and magnesium. Vox Sang 2003;85:199–205.
[8] Gulliksson H, AuBuchon JP, Vesterinen M, Sandgren P, et al. Storage of platelets in additive solutions: a pilot in vitro study of the effects of potassium and magnesium. Vox Sang 2002;82:131–6.
[9] Gulliksson H, Sallander S, Pedajas I, Christenson M, et al. Storage of platelets in additive solutions: a new method for storage using sodium chloride solution. Transfusion 1992;32:435–40.
[10] Sheu JR, Hsiao G, Shen MY, Fong TH, et al. Mechanisms involved in the antiplatelet activity of magnesium in human platelets. Br J Haematol 2002;119:1033–41.
[11] Johnson L, Schubert P, Tan S, Devine DV, et al. Extended storage and glucose exhaustion are associated with apoptotic changes in platelets stored in additive solution. Transfusion 2016;56:360–8.
[12] Diedrich B, Sandgren P, Jansson B, Gulliksson H, et al. In vitro and in vivo effects of potassium and magnesium on storage up to 7 days of apheresis platelet concentrates in platelet additive solution. Vox Sang 2008;94:96–102.
[13] Leitner GC, List J, Horvath M, Eichelberger B, et al. Additive solutions differentially affect metabolic and functional parameters of platelet concentrates. Vox Sang 2016;110:20–6.
[14] Webert KE, Cserti CM, Hannon J, Lin Y, et al. Proceedings of a Consensus Conference: pathogen inactivation-making decisions about new technologies. Transfus Med Rev 2008;22:1–34.
[15] Alter HJ. Pathogen reduction: a precautionary principle paradigm. Transfus Med Rev 2008;22:97–102.
[16] Corash L, Lin L. Novel processes for inactivation of leukocytes to prevent transfusion-associated graft-versus-host disease. Bone Marrow Transplant 2004;33:1–7.
[17] Irsch J, Lin L. Pathogen inactivation of platelet and plasma blood components for transfusion using the INTERCEPT blood system. Transfus Med Hemother 2011;38:19–31.
[18] Castrillo A, Arcas C. Castro Aea. In vitro function of PC stored in ssp + platelet additive solution. Vox Sang 2009;96:246–7.
[19] Castrillo A, Arcas C. Castro Aea. In vitro quality of platelet concentrate from buffy coat and apheresis in additive solution, treated with two pathogen inactivation systems. Vox Sang 2010;99:249–50.
[20] Tynngard N, Trinks M, Berlin G. In vitro properties of platelets stored in three different additive solutions. Transfusion 2012;52:1003–9.
[21] Estándares en transfusión sanguínea. 4ª edición CAT; 2012.
[22] Guide to the preparation, use and quality assurance of blood components. 19th edition Strasbourg: Council of Europe; 2017.
[23] Levin E, Jenkins C, Culibrk B, Gyongyossy-Issa MI, et al. Development of a quality monitoring program for platelet components: a report of the first four years' experience at Canadian Blood Services. Transfusion 2012;52:810–8.
[24] Sandgren P, Saeed K. Storage of buffy-coat-derived platelets in additive solution: in vitro effects on platelets of the air bubbles and foam included in the final unit. Blood Transfus 2011;9:182–8.
[25] Bertolini F, Murphy S. A multicenter evaluation of reproducibility of swirling in platelet concentrates. Biomedical Excellence for Safer Transfusion (BEST) Working Party of the International Society of Blood Transfusion. Transfusion 1994;34:796–801.
[26] Rasongles P, Angelini-Tibert MF, Simon P, Currie C, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Reunion. Transfusion 2009;49:1083–91.
[27] Leytin V, Allen DJ, Gwozdz A, Garvey B, et al. Role of platelet surface glycoprotein Ibalpha and P-selectin in the clearance of transfused platelet concentrates. Transfusion 2004;44:1487–95.
[28] Abonnenc M, Sonego G, Kaiser-Guignard J, Crettaz D, et al. In vitro evaluation of pathogen-inactivated buffy coat-derived platelet concentrates during storage: psoralen-based photochemical treatment step-by-step. Blood Transfus 2015;13:255–64.
[29] Vetlesen A, Mirlashari MR, Akkok CA, Kelher MR, et al. Biological response modifiers in photochemically pathogen-reduced versus untreated apheresis platelet concentrates. Transfusion 2013;53:147–55.
[30] Tauszig ME, Picker SM, Gathof BS. Platelet derived cytokine accumulation in platelet concentrates treated for pathogen reduction. Transfus Apher Sci 2012;46:33–7.
[31] Cognasse F, Boussoulade F, Chavarin P, Acquart S, et al. Release of potential immunomodulatory factors during platelet storage. Transfusion 2006;46:1184–9.
[32] Wenzel F, Gunther W, Baertl A, Gruber W, et al. Platelet transfusion alters CD40L blood level and release capacity in patients suffering from thrombocytopenia. Transfusion 2012;52:1213–20.
[33] Cognasse F, Osselaer JC, Payrat JM, Chavarin P, et al. Release of immune modulation factors from platelet concentrates during storage after photochemical pathogen inactivation treatment. Transfusion 2008;48:809–13.
[34] Arcas C, Castrillo A. Adelantado Mea. A case of probable TRALI from pooled buffy coat platelets containing anti-HLA antibodies. Transfusion 2014;54:140A.
[35] Corash L, Benjamin RJ. The role of hemovigilance and postmarketing studies when introducing innovation into transfusion medicine practice: the amotosalen-ultraviolet A pathogen reduction treatment model. Transfusion 2016;56(Suppl 1):S29–38.
[36] Knutson F, Osselaer J, Pierelli L, Lozano M, et al. A prospective, active haemovigilance study with combined cohort analysis of 19,175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. Vox Sang 2015;109:343–52.
[37] Alhumaidan H, Sweeney J. Current status of additive solutions for platelets. J Clin Apher 2012;27:93–8.
[38] Indications and Usage: InterSol solution. Available at https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/UCM193796.pdf. Accessed on 03/12/2018.