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In vitro quality of cold and delayed cold-stored platelet concentrates from interim platelet units during storage for 21 days

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Abstract

Background and Objectives: Based on previous success using apheresis platelets, we wanted to investigate the in vitro quality and platelet function in continuously cold-stored and delayed cold-stored platelet concentrates (PCs) from interim platelet units (IPUs) produced by the Reveos system.

Materials and Methods: We used a pool-and-split design to prepare 18 identical pairs of PCs. One unit was stored unagitated and refrigerated after production on day 1 (cold-stored). The other unit was stored agitated at room temperature until day 5 and then refrigerated (delayed cold-stored). Samples were taken after pool-and-split on day 1 and on days 5, 7, 14 and 21. Swirling was observed and haematology parameters, metabolism, blood gas, platelet activation and platelet aggregation were analysed for each sample point.

Results: All PCs complied with European recommendations (EDQM 20th edition). Both groups had mean platelet content >200 $\times$ 10^9/unit on day 21. The pH remained above 6.4 for all sample points. Glucose concentration was detectable in every cold-stored unit on day 21 and in every delayed cold-stored unit on day 14. The cold-stored group showed a higher activation level before stimulation as measured by flow cytometry. The activation levels were similar in the two groups after stimulation. Both groups had the ability to form aggregates after cold storage and until day 21.

Conclusion: Our findings suggest that PCs from IPUs are suitable for cold storage from day 1 until day 21 and delayed cold storage from day 5 until day 14.

Keywords

blood component storage, cold-stored platelets, delayed cold-stored platelets, interim platelet units, platelet concentrate

Highlights

- High glucose concentrations in platelet concentrates (PCs) from interim platelet units support prolonged cold storage.

- Cold-stored PCs had the ability to form aggregates throughout storage until day 21, measured by light transmission aggregometry.
- Delayed cold-stored PCs had a higher ability to be activated by agonists, measured by flow cytometry.

INTRODUCTION

Platelet concentrates (PCs) have been transfused to patients to reduce bleeding or as prophylaxis to prevent bleeding since the 1950s [1]. Platelets were initially stored cold to prevent bacterial growth. The discovery that room temperature-stored platelets had longer circulation time than cold-stored platelets led to a shift in practice regarding platelet storage temperature [2]. While some hospitals kept a dual platelet inventory, the majority switched to room-temperature storage [2–4]. Whole blood was the primary choice for massively bleeding patients and the need for platelets was primarily for prophylactic transfusions.

PCs are now routinely stored agitated at room temperature for 4–7 days [5, 6]. Transport of PCs from blood service providers to hospitals or from bigger hospitals to smaller hospitals further narrows the window for transfusion. In some cases, blood components are transported across borders to provide military hospitals with lifesaving components. This makes PCs a vulnerable resource, as blood banks and hospitals experience high wastage and a constant threat of bacterial growth from product contamination.

Several recent publications have shown that cold-stored or delayed cold-stored PCs comply with transfusion guidelines and have better in vitro function than room temperature-stored PCs [7–9]. The platelet storage lesion, which occurs during storage as biochemical, structural and functional changes, is mitigated by cold storage [10]. Cold storage reduces the risk of bacterial growth and preserves mitochondrial integrity, which potentially extends shelf life [11–15]. Cold storage shortens platelet circulation time in vivo to 1–3 days post-transfusion; however, the improved in vitro platelet function indicates a more optimal blood product for actively bleeding patients [9, 15].

The majority of PCs are used for prophylactic transfusions for non-bleeding patients, for which room temperature storage is preferred, but high wastage rates challenge platelet inventory management [16]. Wastage could be cut significantly if hospitals initially reserved PCs for prophylactic use and thereafter transferred unused units to cold storage for actively bleeding patients. Implementation of delayed cold-stored PCs may reduce wastage and provide an alternative for actively bleeding patients [17].

Quality control data from our hospital show that as much as 80% of PCs are used for prophylactic transfusions. Following a clinical study of cold-stored platelet transfusion in cardiac surgery patients in 2020, we introduced a dual inventory of PCs where room temperature-stored PCs were supplemented with a small inventory of continuously cold-stored apheresis PCs for actively bleeding patients [18, 19]. This aimed to ensure a sufficient inventory of PCs during the COVID-19 pandemic. In 2021, the dual inventory consisted of 96% room temperature-stored and 4% continuously cold-stored PCs. While the wastage of room temperature-stored PCs was 17%, the figure for cold-stored PCs was 36%.

Our research group has performed two laboratory studies, one in preparation for submission, involving delayed cold-stored apheresis PCs on day 7 [8]. We chose day 7, corresponding to the end of shelf life for our routinely stored PCs. This was found to be too late for delayed cold storage [8]. Previous publications indicate that platelets may be delayed cold-stored after 4 days of storage [7, 20]. At our hospital, the main PC production method is from single donation interim platelet units (IPUs). We wanted to explore the effect of relocating IPU PCs from room temperature storage to cold storage near the end of their shelf life aiming to reduce platelet wastage and the workload of our production unit. Additionally, IPU PCs have a slightly higher plasma content than apheresis PCs, which may influence platelet storage lesion [21].

In this study, we investigated the in vitro quality and platelet function from day 1 to day 21 in cold-stored IPU PCs and compared this to delayed cold-stored IPU PCs when transferred from room temperature to cold storage on day 5.

MATERIALS AND METHODS

Study design

This prospective single-centre experimental study was performed at the Department of Immunology and Transfusion Medicine at Haukeland University Hospital, Bergen, Norway from August 2021 to April 2022. The Regional Committee for Medical and Health Research Ethics approved the study (REC id: 2017/157). Blood from healthy regular blood donors, both female and male with blood type A or O were used in the study. The participants consented to their blood samples being used for research purposes.

Production of IPU concentrates

IPU PCs were prepared from five IPU units from whole blood donations. In brief, 450 mL whole blood with 63 mL citrate phosphate dextrose (Reveos, Terumo BCT) was separated using the Reveos system with the 3C program within 3–14 h of donation. Each IPU unit consisted of approximately 30 mL of platelets in autologous plasma. The IPUs rested for 1 h before being moved to a room temperature horizontal agitator for overnight incubation. The next morning five IPUs with an estimated total yield of >300 $\times$ 10^9/unit were sterile connected (TSCDII, Terumo BCT) to a Reveos platelet pooling set (Terumo BCT), and 220 mL platelet additive solution (PAS) (T-PAS+,

Terumo BCT) was then added before the IPU units were passed through a leukocyte filter. The leukocyte-depleted IPU PCs were placed in an agitator for a minimum of 10 min before further manipulation.

Pool-and-split, storage and sampling

The trial included 36 IPU PCs pooled and split into 18 identical pairs. Two ABO-identical IPU PCs were sterile connected and combined in one bag. The bag was mixed gently for a minimum of 5 min before storage bags (Platelet Storage Bag, Terumo BCT) were sterile connected to the pooling bag and the content split into two identical IPU PCs. Each pair was stored for 21 days, where one IPU PC was stored agitated at room temperature (20–24°C) for 5 days before transfer to cold storage without agitation, while the other IPU PC was stored continuously cold without agitation.

Sampling was performed after pool-and-split on day 1 and on storage days 5, 7, 14 and 21. After gentle mixing in an agitator for a minimum of 10 min, we sterile connected sampling bags (BB*T015CM, Terumo BCT) to the storage bags and transferred 25 mL (days 1 and 21) or 15 mL (days 5, 7, and 14) for testing.

Analyses

We tested for residual white blood cells (rWBC) using the BD Leucocount kit and a flow cytometer (BD FACSCanto II with FACSDiva version 8.0.1, BD Biosciences), following established procedures. Swirling was documented at each sample point by gently mixing the storage bags beneath a light source and looking for swirling patterns.

Tubes for haematology analyses contained K2EDTA anticoagulants (BD Bioscience) to obtain single platelets for analysis. Platelet count (PLT) and mean platelet volume (MPV) were analysed on the Sysmex XN-9100 (Sysmex Europe GmbH).

Glucose, lactate, pH, base excess (BE), pO_2 and pCO_2 were analysed at 22°C on a blood gas analyser (ABL825 FLEX, Radiometer Medical ApS).

To measure platelet function, we investigated platelet aggregation responses to 0.5 mM arachidonic acid (AA) and 30 µM thrombin receptor-activating peptide 6 (TRAP-6) (Roche Diagnostics GmbH) with a light transmission aggregometer (Chrono-log Model 700, Chrono-log Corporation). For light transmission analyses (LTA), we centrifuged samples of IPU PCs at 1500*g* for 15 min to obtain platelet-poor plasma (PPP). Platelet-rich plasma (PRP) was prepared by diluting a sample of IPU PC in PPP to a concentration of $\sim 200 \times 10^9$/L platelets. After 3 min of incubation at 37°C, LTA was performed with 1000 rpm stirring at 37°C with either 0.5 mM AA or 30 µM TRAP-6 as agonists until maximum aggregation was achieved. Maximum amplitude (MaxA) indicated distance from PRP (0%) and PPP (100%). The slope indicated maximum speed of aggregation formation (%/min) during analysis. Aggregation response was investigated in duplicate, and results were reported as the mean of the two parallels. We also ran one sample without an agonist to ensure no spontaneous aggregation occurred.

We also recorded the activation response to the same agonists using a flow cytometer (BD FACSCanto II with FACSDiva version 8.0.1, BD Biosciences). For flow cytometry analyses, we diluted IPU PCs with Isoton™ II Diluent (Beckman Coulter Life Sciences) to a concentration of $\sim 200 \times 10^9$/L. Three aliquots of 50 µL from each diluted sample were either added without agonist, 0.5 mM AA or 30 µM TRAP-6. All samples were added 12.5 µL anti-CD61 PerCP and 2.5 µL anti-CD62P PE (BD Biosciences). After mixing, we incubated the samples in the dark at room temperature for 30 min. Before flow cytometer analysis, we adjusted the volume with 2 mL FACSFlow (BD Biosciences) to allow optimal dilution. Samples were run immediately after dilution. The platelets were identified using anti-CD61 (BD Biosciences) and platelet activation response using anti-CD62P (BD Biosciences). A fixed gating setup based on CD61 positivity was used for all samples, irrespective of storage time, and 15,000 events were recorded per sample at a medium flow rate.

Statistics

Our data were analysed using R version 3.5.0 [22] with the NLME package version 3.1-137 [23] (The R Foundation for Statistical Computing). The graphics were derived using GraphPad Prism 9.4.0 for Windows (GraphPad Software). For each outcome, we fitted a linear mixed effect model using time, group and their interaction as predictors. In the time domain, we applied simple contrast (i.e., change from baseline). The interaction describes the change in difference between the groups, with respect to baseline measurements on day 1. Results are presented as mean (95% CI). We considered $p < 0.05$ as significant.

RESULTS

General requirements

The mean ratio of plasma to PAS was 42:58, with plasma concentration ranging from 40% to 43%. All IPU PC units complied with the requirements in the Guide to the Preparation, Use and Quality Assurance of Blood Components (EDQM, 20th edition) after pool-and-split [6]. Mean (95% CI) volume per 60×10^9 platelets was 62 mL (59, 64) in the cold and 62 mL (59, 65) in the delayed cold group ($p = 0.827$). After pool-and-split on day 1, rWBC was 0.04×10^6/unit (0.02, 0.05) in the cold and 0.05×10^6/unit (0.02, 0.07) in the delayed cold group ($p = 0.443$). We graded swirling to 3+ on day 1 in all units. We only downgraded one room temperature-stored unit to 2+ on day 5. No cold-stored or delayed cold-stored units had detectable swirling.

There were no statistically significant differences in any of the analyses on day 1, which indicates that our pool-and-split model resulted in equal pairs. The complete results are presented in Tables S1 and S2.

Haematology and blood gas analyses

There was an overall decline in PLT per unit during storage in both groups (Table 1), however; both groups had PLT > 200 × 10^9/unit on day 21. Cold storage led to shape change and increased MPV (Table 1).

Figure 1a shows that there was a steeper decline in glucose concentration in the delayed cold-stored group, which continued after cold storage ($p < 0.001$). Correspondingly, we saw an increase in lactate concentration (Figure 1b). There was measurable glucose in every unit in the cold-stored group on day 21, while there was one unit without detectable glucose on day 21 in the delayed cold-stored group. This unit had the lowest percentage of plasma from production (40%), that is, a low glucose concentration (6.6 mmol/L) and, due to a high platelet concentration (376 × 10^9/unit), the lowest volume per 60 × 10^9 platelets (52 mL).

During storage, pH declined in both groups with the biggest decline in the continuously cold-stored group on day 21 ($p < 0.001$). However, the lowest value of 6.9 was well above the recommended limit of 6.4 for PCs [6]. pCO_2 and BE declined similarly in both groups, while pO_2 increased with cold storage (Table S1).

Platelet function

Measurements of aggregation response by LTA showed that units not stored cold on day 1 (both groups) and until day 5 (delayed cold-stored group) were unable to produce irreversible aggregation with AA as agonist (Figure 2a). Samples from cold-stored units produced irreversible aggregation, and the cold-stored group had better aggregation by AA, measured by MaxA and slope from day 5 and throughout storage (Figure 2a and Table S2) when compared to the delayed cold-stored platelet group. Room temperature-stored units had better aggregation measured by MaxA and slope with TRAP-6 as agonist. Transfer to cold storage led to a decline in TRAP-induced aggregation in both groups, with a steady decline throughout storage. The continuously cold-stored group showed better aggregation response on days 14 and 21 compared to the delayed cold-stored group (Figure 2b and Table S2). There was no difference in spontaneous aggregation between groups and it did not affect the analysis (Table S2).

Unstimulated platelets had higher CD62P mean fluorescence intensity (MFI) in the continuously cold-stored group from day 5 ($p = 0.010$) and throughout storage (Figure 3a). CD62P MFI when stimulated by AA increased during storage, but the change was not statistically different in the two groups throughout storage (Table S2). CD62P MFI stimulated by TRAP-6 decreased during storage and was similar in both groups until day 7. The continuously cold-stored group had higher MFI from day 14, showing a change between groups ($p = 0.021$). However, the stimulation response measured as difference in MFI between stimulated and unstimulated platelets was higher in the delayed cold-stored group from day 5 to day 21 (Figure 3b).

TABLE 1 Platelet content, platelet count and mean platelet volume.

	Observed values		LME: change	
Outcome	Warm 5 days Mean (95% CI)	Cold no agitation Mean (95% CI)	In time *p*-value	Between groups *p*-value
PLT (10^9/unit)				
Day 1	329 (314, 344)	328 (312, 344)	–	0.724
Day 5	294 (280, 307)	298 (285, 311)	<0.001	0.138
Day 7	274 (261, 288)	280 (267, 293)	<0.001	0.055
Day 14	249 (236, 261)	245 (232, 258)	<0.001	0.482
Day 21	213 (203, 224)	205 (194, 215)	<0.001	0.013
PLT (10^9/L)				
Day 1	982 (936, 1027)	976 (928, 1023)	–	0.307
Day 5	945 (901, 989)	957 (916, 999)	<0.001	0.033
Day 7	938 (891, 985)	941 (896, 985)	<0.001	0.275
Day 14	892 (848, 936)	868 (823, 913)	<0.001	0.028
Day 21	812 (772, 851)	764 (723, 805)	<0.001	<0.001
MPV (fL)				
Day 1	10.0 (9.8, 10.1)	9.9 (9.8, 10.0)	–	0.255
Day 5	10.1 (9.9, 10.2)	10.9 (10.7, 11.0)	0.039	<0.001
Day 7	11.0 (10.9, 11.2)	10.8 (10.7, 10.9)	<0.001	0.024
Day 14	11.2 (11.0, 11.3)	10.7 (10.6, 10.9)	<0.001	<0.001
Day 21	11.2 (11.1, 11.4)	10.7 (10.6, 10.9)	<0.001	<0.001

Abbreviations: LME, linear mixed effect; MPV, mean platelet volume; PLT, platelet count.

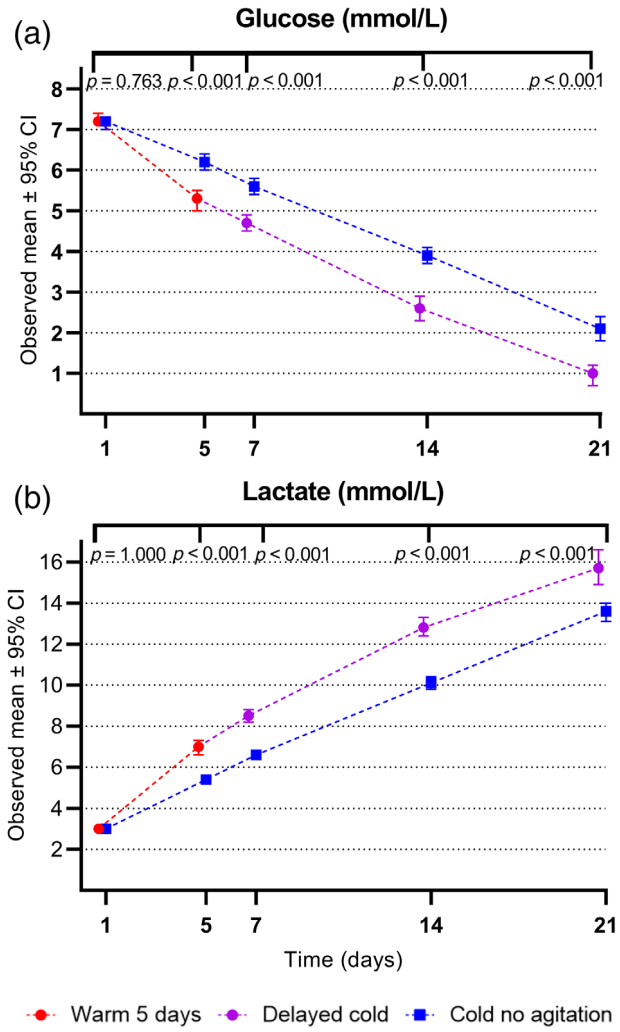

FIGURE 1 Glucose and lactate concentrations. (a) Glucose and (b) lactate in platelet concentrates from interim platelet units stored cold for 21 days (cold-stored, blue) or agitated at room temperature until day 5 and then cold until day 21 (delayed cold-stored, red). The *p* values represent change in difference between groups, with respect to baseline measurements on day 1 (linear fixed-effect model, R version 3.5.0 with the NLME package version 3.1-137). Points show observed mean with 95% CI.

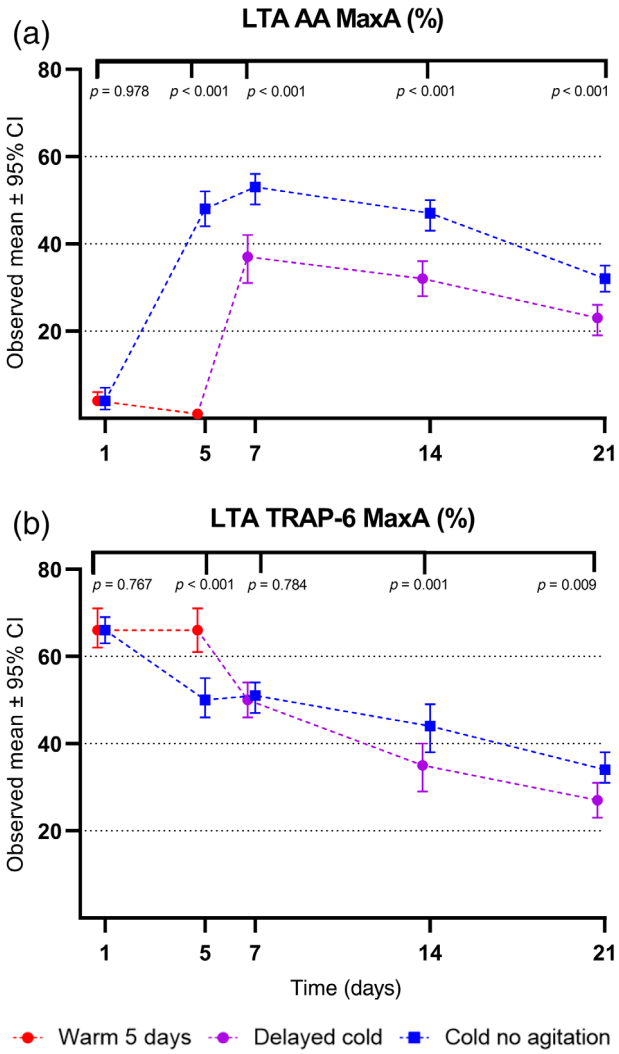

FIGURE 2 Platelet function measured by light transmission aggregometry. Platelet aggregation after stimulation with (a) arachidonic acid (AA) or (b) thrombin receptor-activating peptide 6 (TRAP-6) in platelet concentrates from interim platelet units stored cold for 21 days (cold-stored, blue) or agitated at room temperature until day 5 and then cold until day 21 (delayed cold-stored, red). Maximum amplitude (MaxA) indicates distance from platelet-rich plasma (0%) and platelet-poor plasma (100%). The *p* values represent change in difference between groups, with respect to baseline measurements on day 1 (linear fixed-effect model, R version 3.5.0 with the NLME package version 3.1-137). Points show observed mean with 95% CI. LTA, light transmission analyses.

DISCUSSION

In this experimental study, we found an in vitro quality and function of IPU PCs supporting both cold and delayed cold storage. Throughout storage, PLT per unit was above the recommended regulatory requirements [5, 6].

The study design resulted in 10 different donors in each IPU PC pooled unit. This minimized donor variability between the pooled units. To achieve a high platelet yield per unit, our department uses five IPUs, which provides additional plasma compared to four IPUs in the same amount of PAS. The additional plasma is beneficial for prolonged storage because it entails higher levels of glucose in the units. All units, except one delayed cold-stored, still contained glucose on day 21. Previous findings from studies on apheresis PCs, with delayed cold storage on day 7, showed glucose deprivation as early as on day 14 [8]. Johnson et al. found that glucose exhaustion was associated with apoptotic changes, which indicates that PCs should not be stored beyond glucose deprivation [24]. The lactate concentration found on day 14 in delayed cold-stored PCs and cold-stored PCs on day 21, respectively, is comparable to lactate concentration on day 7 in room temperature-stored PCs in plasma [25]. While pH is a poor predictor of platelet quality due to the presence of acetate and phosphate in the PAS [26], the detection of glucose seems to coincide with platelet function. The one unit without detectable glucose on

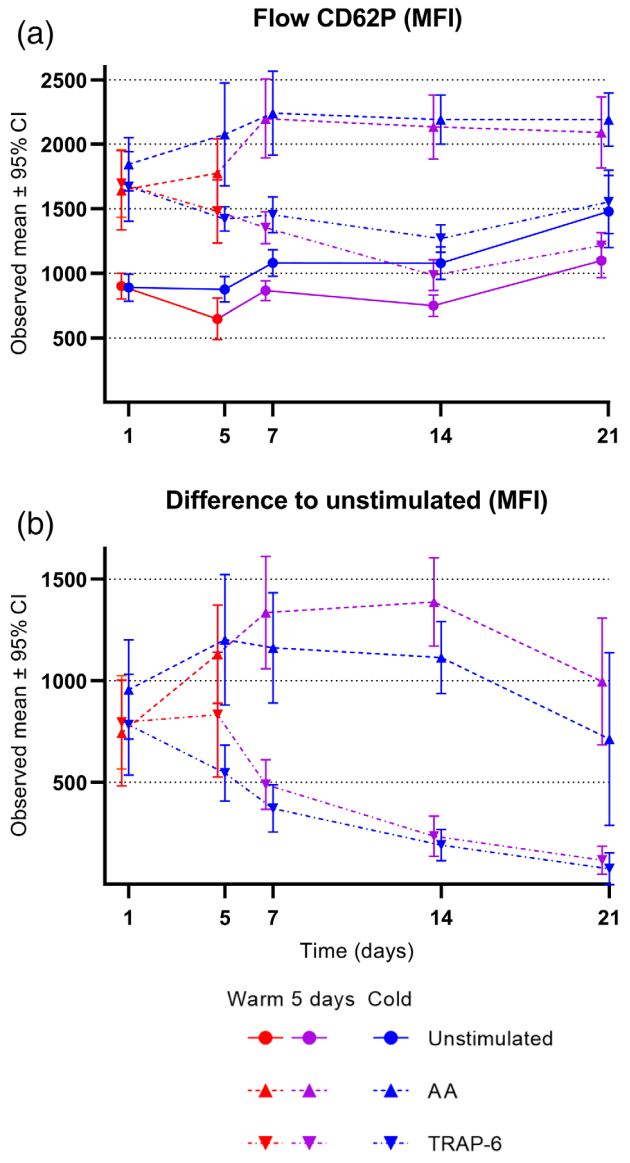

FIGURE 3 Platelet function measured by flow cytometry. (a) Activation response by use of anti-CD62P measured as mean fluorescent intensity (MFI) with flow cytometry in platelet concentrates from interim platelet units stored cold until day 21 (cold-stored, blue) or agitated at room temperature until day 5 and then cold until day 21 (delayed cold-stored, red). Points show observed mean with 95% CI. Circles indicate unstimulated platelets, triangles pointing upward indicate platelets stimulated with arachidonic acid (AA) and triangles pointing downward indicate platelets stimulated with thrombin receptor-activating peptide 6 (TRAP-6). The platelets were identified by use of anti-CD61 and platelet activation response by use of anti-CD62P. (b) MFI difference to unstimulated (baseline) after stimulation with AA (triangles pointing upwards) or TRAP-6 (triangles pointing downwards).

day 21 lacked the ability to aggregate with AA or TRAP-6 measured with LTA and also the ability to be stimulated with AA in flow analysis compared to the other units in the same group. We have found corresponding results in our previously published study of apheresis PCs [8].

Our flow cytometry analyses indicate that the cold and delayed cold-stored platelets have continuous high activation potential, especially with AA as agonist. We also found that the cold and delayed-cold platelets had the ability to form aggregates throughout storage with both AA and TRAP-6 as agonists. Room temperature-stored platelets did not form aggregates with AA as agonist (Figure 2a). Increasing the concentration of agonist in the study might enhance aggregate formation. The shape change that occurs after cold storage leads to clustering of GPIbα [27], which may enhance the effect of AA on the activation of platelet aggregation [28]. Tohidi-Esfahani et al. report that cold-stored PCs are more activated than room temperature-stored PCs [29]. The increased CD62P MFI of unstimulated platelets in the continuously cold-stored units indicates an in vitro activated state [30]. Due to lower activation levels in the unstimulated samples, there was a higher ratio between unstimulated and stimulated CD62P MFI in the delayed cold-stored platelets. However, CD62P MFI levels were similar in the two groups after stimulation.

The MPV of delayed cold-stored units where the volume continued to increase during storage may indicate a storage lesion not seen in the continuously cold-stored units. The cold-stored units decreased in size from day 5, which may be due to microparticle formation. The presence of microparticles in the units may contribute to enhanced in vitro function [31].

Logistically, IPU PCs are feasible for cold and delayed cold storage. It is easier to organize the production of cold-stored IPU PCs from the previous day's whole blood donations than to find suitable apheresis donors, and collect and produce a specific amount of apheresis PCs. In addition, IPU PCs may be stored cold immediately after production while, in our department, apheresis PCs may need to rest until the following day at room temperature to reduce aggregates from the apheresis process, which may delay cold storage. Another benefit of using platelets from whole blood is the resting period before production, where leukocytes are able to phagocytose possible bacteria.

Implementation of a dual inventory of platelets with a small cold-stored inventory with a prolonged shelf life for actively bleeding patients may reduce wastage [17]. The prolonged shelf life of cold-stored PCs may simplify logistics for blood providers and hospitals. If a new pandemic, or another severe event, occurs, a dual inventory may mitigate wastage and improve the availability of platelets as part of overall measures to establish control over blood supply and demand [32, 33]. Unagitated, cold-stored PCs may be suitable for transport to military hospitals or rural civilian hospitals and thereby ensure the availability of a platelet-containing product for the resuscitation of bleeding patients in a logistically challenging setting [34].

In conclusion, our results suggest that IPU PCs are suitable for cold storage from day 1 until day 21 and delayed cold from day 5 until day 14. The cut-offs expressed here are based on levels of glucose measured in the PCs and the results of platelet function analysis. Further studies are encouraged to further examine the optimal storage time of cold-stored platelets.

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H.B., T.O.A., T.H.F.L. and G.S. designed the research study; H.B. and T.H.F.L. collected the data; J.A. designed statistical analyses, tables and figures; H.B., T.H.F.L. and T.O.A. analysed and interpreted the data; H.B and T.O.A. wrote the manuscript, while all the other authors reviewed and approved the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Norwegian Armed Forces Joint Medical Services.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and online supporting tables.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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