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Postoperative Transfusions following Administration of Delayed Cold Stored Platelets vs. Room Temperature Platelets in Cardiac Surgery: A Retrospective Cohort Study

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Abstract

Background: Delayed cold-storage of room temperature platelets may extend shelflife from 5 to 14 days. We hypothesized the use of delayed cold-stored platelets in cardiac surgery would be associated with decreased postoperative platelet count increments but similar transfusion and clinical outcomes compared to room temperature stored platelets.

Methods: This is an observational cohort study of adults transfused with platelets intraoperatively during elective cardiac surgery between April 2020 and May 2021. Intraoperative platelets were either room temperature or delayed cold-stored based on blood bank availability rather than clinical features or provider preference. Differences in transfusion and clinical outcomes, including a primary outcome of allogeneic transfusion exposure in the first 24 hours postoperatively, were compared between groups.

Results: 713 patient encounters were included: 529 (74%) room temperature, 184 (26%) delayed cold-stored platelets. Median (interquartile range) intraoperative platelet volumes were 1 (1, 2) units in both groups. Patients receiving delayed cold-stored platelets had higher odds of allogeneic transfusion in the first 24 hours postoperatively (81/184 (44%) vs. 169/529 (32%); adjusted odds ratio [aOR], 95% confidence interval [CI], 1.65 (1.13, 2.39); $p=0.009$), including both RBCs (65/184 (35%) vs. 135/529 (26%); aOR 1.54 (1.03, 2.29); $p=0.035$) and platelets (48/184 (26%) vs. 79/529 (15%); aOR 1.91 (1.22, 2.99); $p=0.005$). There was no difference in the number of units administered postoperatively amongst those transfused. Platelet counts were modestly lower in the delayed cold-stored platelet group ($-9 \times 10^9/L$ [95% CI: $-16, -3$]) through the first 3 days postoperatively. There were no significant differences in reoperation for bleeding, postoperative chest tube output, or clinical outcomes.

Conclusions: In adults undergoing cardiac surgery, delayed cold-stored platelets were associated with higher postoperative transfusion utilization and lower platelet counts compared to room temperature stored platelets without differences in clinical outcomes. The use of delayed

cold-stored platelets in this setting may offer a viable alternative when facing critical platelet inventories but is not recommended as a primary transfusion approach.

Summary Statement:

The use of delayed cold-stored platelets during cardiac surgery is associated with modestly higher postoperative blood product utilization and lower platelet counts than room temperature platelets.

Keywords

COVID-19; hemostasis; platelets; surgery; transfusion

Introduction

The COVID-19 pandemic has strained medical resources around the world and has exposed vulnerability in blood inventories. Platelets are the blood component most vulnerable to shortages. While other products may be stored long-term by freezing or have pharmacological alternatives such as coagulation factor concentrates, platelets have neither². Typically, platelets are stored at 20–24 degrees C with gentle agitation for up to 5–7 days². This short outdate has been selected to balance the increased risk of bacterial contamination seen with non-refrigerated storage and the need to maintain an adequate inventory². The introduction of pathogen reduction technology (PRT) in platelet manufacturing has added an element of safety with minimizing bacterial and viral contamination, however this has not yet prolonged the shelf life beyond 5 days². Altogether, this makes platelet inventories dependent on reliable donations and predictable and judicious utilization.

It has long been recognized that refrigeration, or cold storage, may diminish the risk of bacterial contamination, however it comes at a cost. In the 1960s, investigators demonstrated that cold-stored platelets (CSPs) had dramatically shorter lifespans (i.e. 1–2 days) following transfusion compared to their room temperature (RTPs) counterparts (i.e., 7–9 days)^{3,4}. As most platelet transfusions in this time were given to those with hypoproliferative thrombocytopenia in need of prolonged platelet survival, this work essentially excluded CSPs from clinical practice. However, subsequent work has shown that CSPs may have a more favorable hemostatic profile and improved metabolic characteristics than RTPs, which may potentially be beneficial for the management of acute bleeding^{5–7}. Indeed, early clinical work has suggested that CSPs may at least be equally efficacious in bleeding patients^{8–10}. A recent pilot trial in cardiac surgery lends support to the non-inferiority of CSPs compared to RTPs, and a large multicenter randomized trial is currently enrolling participants¹¹.

In early 2020 in anticipation of blood shortages and unpredictable platelet usage, the Mayo Clinic in Rochester, Minnesota notified the United States Food and Drug Administration (FDA) that it would convert about-to-expire (i.e., day 5 of room temperature storage) pathogen-reduced RTPs to cold-storage. These delayed cold-stored platelets (dCSPs) would be stored at 1–6 degrees C without agitation for up to an additional 9 days (i.e., 14 days total storage)¹². Previous work, though limited in nature, has suggested preserved metabolic and activation profiles of dCSPs compared to CSPs, which are immediately refrigerated following collection rather than having a period of room-temperature storage¹³. Assuming

that dCSPs would display similar features to CSPs (i.e., shorter circulation duration and potential favorable hemostatic response compared to RTPs), dCSPs were earmarked for use in bleeding patients (i.e., surgical, trauma, massive hemorrhage) when RTPs inventories were low or unavailable¹². Early clinical review of this practice, including transfusion of 61 units of dCSPs (58% in cardiac surgery), showed signs of hemostatic efficacy without signal for patient harm.

Given our dual inventory of dCSPs and RTPs in which bleeding cardiac surgery patients may receive either product intraoperatively based upon blood bank availability rather than provider preference, there is an excellent opportunity to compare the clinical efficacy of dCSPs against traditional RTPs. We hypothesized that dCSPs would be associated with decreased postoperative platelet increments compared to RTPs but comparable transfusion and clinical outcomes.

Methods

This is a retrospective observational cohort study conducted under appropriate institutional review board approval at the Mayo Clinic in Rochester, Minnesota with a waived requirement for written informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were employed in study design and conduct.¹⁴

All adults (≥ 18 years) undergoing elective cardiac surgery between April 20, 2020 and May 21, 2021 with administration of at least 1 unit of platelets intraoperatively were eligible for inclusion. Patient records were excluded for the following reasons: emergency surgery, primary extracorporeal membrane oxygenation (ECMO) cannulation, wash-out, or weaning, or irrigation and debridement procedures. Additionally, patient records could only be included once, such that the first qualifying cardiac surgery and associated hospital admission was included for each patient. This is a primary analysis of these data, although 28 patients in this investigation were included in an earlier publication regarding dCSP use at our institution¹².

dCSP and RTP availability and blood bank processes

The Mayo Clinic in Minnesota maintains a local blood donor program, with approximately 80% of blood products derived from local donors and an additional 20% received from regional suppliers. All platelets undergo pathogen reduction. As previously described, the in April 2020 we began transitioning pathogen-reduced RTPs on day 5 of their shelf-life to cold-storage for up to an additional 9 days (i.e., 14 days total storage), thereby creating a parallel dCSP inventory. The dCSP inventory was earmarked for use in patients with active bleeding (i.e., surgical, trauma, massive transfusion) when RTP inventories were low (i.e. <10% of optimal levels) or unavailable. RTPs remained available for bleeding patients when supplies were adequate and were maintained for patients with non-bleeding thrombocytopenia. Clinicians were made aware of the dual platelet inventories via various internal communications. No changes were made in blood ordering processes, and clinicians could not request dCSPs or RTPs. When an order for a platelet transfusion was placed from the operating room for a cardiac surgery patient, the Transfusion Medicine team would

distribute either a RTP or dCSP unit based on blood bank availability rather than patient features or provider request.

Transfusion utilization in cardiac surgery

Intraoperative platelet transfusions in cardiac surgery at the study institution are administered to patients with clinical bleeding assessed by the attending anesthesiologist and surgeon in accordance with a previously published protocol¹⁵. Briefly, this includes platelet administration for thrombocytopenia of less than 102×10^9 or a maximal amplitude of less than 48 on kaolin thromboelastography (Haemonetics Corporation, Boston, MA, USA). Thromboelastography use is at the discretion of the anesthesiologist and is not standardized. Supplemental coagulation factor concentrates may be used based on the clinical judgement of the attending anesthesiologist. Similar criteria for platelet transfusion are used postoperatively. During the study time period, RBCs were administered for hemoglobin concentrations less than 8 g/dL, during rapid hemorrhage, or when there was evidence of depressed oxygen delivery on cardiopulmonary bypass. All postoperative transfusion orders for platelets and RBCs must be accompanied by an indication for transfusion entered into the electronic medical record, which may include the presence of bleeding and/or a platelet count or hemoglobin concentration falling below a given threshold.

Exposure

The primary exposure of interest was intraoperative administration of dCSP versus RTPs, with all transfusion episodes extracted from our institutional Transfusion DataMart. Patients in the dCSP group must have received at least 1 unit of intraoperative dCSPs but could also have received additional units of either platelet type (dCSP or RTP) intraoperatively. Patients in the RTP group only received RTPs intraoperatively.

Outcomes

Both transfusion/bleeding and clinical outcomes were evaluated. The primary outcome was allogeneic transfusion in the first 24 hours postoperatively, evaluated as present or absent and by the total number of units transfused. Secondary transfusion/bleeding outcomes included: allogeneic transfusions of red blood cells (RBCs) and platelets in the first 24 and 72 hours after surgery, total allogeneic transfusions in first the 72 hours postoperatively, unanticipated return to the operating room for bleeding in the first 24 hours after surgery, and total chest tube output in the first 24 hours after surgery. Maximum daily postoperative platelet counts were evaluated through postoperative day 7. Secondary clinical outcomes of interest included: venous thromboembolism, stroke or myocardial infarction, infection, transfusion reactions, and hospital mortality. Clinical outcomes were assessed through the first 7 postoperative days, apart from mortality which was evaluated through the duration of hospitalization. Venous thromboembolism was defined by radiographic evidence of acute deep venous thrombosis or pulmonary embolism during hospitalization following surgery. Stroke was defined by radiographic evidence of acute or subacute infarction during hospitalization following surgery and/or clinical diagnosis by Neurology consultation. Myocardial infarction was defined according to the fourth universal definition of myocardial infarction.¹⁶ Infection included those diagnosed clinically during postoperative hospital

admission and treated with systemic antimicrobial therapy (e.g., oral or intravenous antibiotics) with or without positive microbial culture. This could include infections of the bloodstream, urinary tract, lungs, skin or soft tissues, or surgical site, amongst others. Transfusion reactions were those documented in clinical notes and/or reported to the Transfusion Medicine service through our internal reporting system.

Statistical Analysis

A statistical analysis plan was developed and filed with the IRB prior to accessing study data, with any additional analyses labeled as post-hoc. The statistical analysis plan is provided as supplemental digital content. Baseline demographic, clinical, and surgical characteristics were described with median (interquartile range) and number (percent) for continuous and categorical data elements, respectively. Unadjusted outcomes were compared between groups with Mann-Whitney U tests and Pearson's Chi-square tests for continuous and categorical data elements, respectively. In cases where expected cell counts were less than 5, categorical endpoints were compared with Fisher's exact tests. Surgeries were classified as complex or not, with the complex group including, combination procedures (i.e. coronary artery bypass grafting + valve surgery and/or other procedure; valve surgery + other procedures), adult congenital surgery, ventricular assist device and mechanical circulatory support surgery, and heart transplantation. To account for the large proportion of zero values, multivariable hurdle models were created to assess the association between treatment group and postoperative transfusion outcomes without pre-specification of minimum clinically meaningful effect sizes. The results of the zero and the count portions of the hurdle models were reported as: 1) an adjusted odds ratio (aOR) representing the estimated multiplicative increase in odds for receiving any transfusion after surgery for dCSP compared to RTP for the zero portion, and 2) an adjusted rate ratio representing the estimated multiplicative increase in total number of units administered after surgery for dCSP compared to RTP in those who receive postoperative transfusion for the count portion. Both the zero and count portions of the hurdle models were adjusted for the same covariates. While there was no selection of platelet type by clinicians (i.e., units distributed solely by blood bank inventory), thereby minimizing potential between-group differences in important prognostic and confounding variables, several adjustment variables were selected a priori during study design. These variables included age, sex, preoperative hemoglobin concentration, preoperative platelet count, complex surgery, and total cardiopulmonary bypass time, with 3 additional variables added at the request of peer reviewers including preoperative use of antiplatelet therapy (i.e., aspirin, clopidogrel, or ticagrelor within 7 days of surgery), redo sternotomy, and total number of transfused platelet units intraoperatively. Multivariable linear regression models with the same adjustment variables were employed for the outcomes of postoperative platelet counts and total chest tube output in the first 24 hours postoperatively. For the outcome of return to the operating room for bleeding, a multivariable logistic regression model was utilized and adjusted only for preoperative platelet count and total cardiopulmonary bypass time. No adjustment was performed for clinical outcomes given limited events. Recognizing that some patients receiving more than 1 intraoperative platelet unit in the dCSP group may also receive RTPs, a predefined sensitivity analysis was performed limited to those receiving only dCSPs in the dCSP group. As a post-hoc analysis, runs test was employed to evaluate potential clustering

of treatment assignment by calendar time. Subsequently, potential clustering of 24-hour transfusion outcomes over time was evaluated with runs tests (i.e., transfusion yes or no) and Durbin-Watson (DW) tests (i.e., units transfused). Additionally, amongst patients receiving a single unit of intraoperative dCSPs, we evaluated the relationships between the age of the unit in days and transfusion outcomes using multivariable models as described previously. Finally, we used the coefficients from the final models to estimate the total number of additional platelet and RBC units administered in the first 72 hours postoperatively under the hypothetical scenarios where either all patients in the sample were treated with dCSPs or all patients were treated with RTPs. No power analysis was performed for this hypothesis-generating study, which employed all available clinical data at the time of data extraction. All continuously scaled covariates were included as linear effects in the multivariable models. When not all data were available, complete case analyses were utilized under the assumption that data were missing completely at random. All analyses were performed with R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and two-tailed p-values <0.05 were considered significant.

Results

713 patient encounters with intraoperative platelet transfusion during cardiac surgery were included (Supplemental Figure 1). RTPs were administered in 529 cases (74%) and dCSPs in 184 cases (26%), with 154 patients (84%) in the dCSP group receiving only dCSPs intraoperatively and 30 patients (16%) also receiving intraoperative RTPs. The median age of dCSP units was 7 (6, 8) days. The RTP and dCSP groups were similar in all baseline demographic, clinical, and surgical characteristics (Table 1). Overall, the cohort had a median age of 65 (51, 73) years with a male predominance (64%) and a median Charlson Score of 4 (2, 6). Half of the cohort underwent complex cardiac surgery, and 34% of operations were redo sternotomies. The most common procedures were: 179 valvular plus other procedures (25%), 140 isolated valvular procedures (20%), and 110 isolated CABG procedures (15%). The median CPB time was 138 (99, 196) minutes, and the median cross-clamp time was 102 (67, 149) minutes.

Intraoperative transfusions were generally similar between groups (Table 2). Patients in both groups received a median of 1 (1, 2) unit of platelets, representing 777 units of intraoperative RTPs and 292 units of dCSPs. Fifty-three percent of those in the RTP group received an RBC transfusion compared to 50% in the dCSP group, and patients in the dCSP group received a median of 3 (1, 4) units of RBCs as compared to 2 (1, 4) units. Cryoprecipitate was given in 49% of cases in the RTP group and 37% of cases in the dCSP group. Cell salvage volumes were modestly higher in the RTP group (605 [406, 872] mL vs. 527 [347, 812] mL). Autologous fresh whole blood from acute normovolemic hemodilution was transfused in 12% and 14% of cases for RTPs and dCSPs, respectively, with modestly higher volumes in the RTP group.

Unadjusted analyses of postoperative transfusions and other transfusion outcomes revealed significant between-group differences (Supplemental Table 1), including a lower incidence of transfusion of platelets (79/529 [15%] vs. 48/184 [26%], $p<0.001$) and RBCs (135/529 [26%] vs. 65/184 [35%], $p=0.011$) in the first 24 hours after surgery in the RTP group.

Amongst those receiving platelets in the first 24 hours after surgery, the proportions of patients receiving a platelet transfusion for active bleeding were 90% (71/79) and 96% (46/48) for RTP and dCSP groups, respectively ($p=0.317$). Amongst those receiving RBCs in the first 24 hours after surgery, the proportions transfused for active bleeding were 60% (81/135) and 71% (46/65) for RTP and dCSP groups, respectively ($p=0.160$). Differences in maximum platelet count on each postoperative day are displayed graphically (Figure), showing modestly lower platelet counts on each day in the dCSP group. There were no significant differences in chest tube output in the first 24 hours after surgery (762 [510, 1089] ml for RTPs vs. 766 [554, 1191] ml for dCSPs, $p=0.215$), return to the operating room for bleeding (24/529 [5%] for RTPs vs. 11/184 [6%] for dCSPs, $p=0.436$), or clinical outcomes between groups (Table 3).

In adjusted analyses for the primary outcome, intraoperative dCSPs were associated with higher odds receiving any allogeneic transfusion (aOR, 95% CI, 1.65 (1.13, 2.39); $p=0.009$), any RBCs (aOR 1.54 (1.03, 2.29); $p=0.035$), and any platelets (aOR 1.91 (1.22, 2.99); $p=0.005$) in the first 24 hours after surgery (Table 4). Only an increased odds for platelet transfusion remained statistically significant at 72 hours postoperatively. Amongst those transfused, there were no significant differences in the number of units administered (Table 4). In adjusted analyses, patients receiving dCSPs had an estimated -12 (95% CI $-19, -5$) $\times 10^9/L$ and -9 (95% CI $-16, -3$) $\times 10^9/L$ difference in maximum platelet count on postoperative days 0 ($p<0.001$) and 3 ($p=0.004$), respectively, compared to those receiving RTPs (Table 5). The difference in platelet counts on postoperative day 7 was similar but not statistically significant. There was no significant difference in odds of returning to the operating room for bleeding with dCSPs (aOR 0.85 (0.40, 1.98), $P=0.688$), nor was there any significant difference in chest tube output in the first 24 hours after surgery (-31 (95% CI $-168, 106$) ml; $p=0.660$). Study results were consistent in a predefined sensitivity analysis limited to those only receiving dCSPs in the dCSP group ($n=154$; Supplemental Tables 2–5).

In post-hoc analyses, there was evidence of clustering of treatment assignment over time (Supplemental Figure 2, runs test $p<0.001$), but no statistically significant outcome clustering over time was detected for any transfusion (runs test $p=0.097$), any RBC transfusion (runs test $p=0.155$), any platelet transfusion (runs test $p=0.974$), total transfusion units (DW $p=0.677$), total RBC units (DW $p=0.580$), or total platelet units (DW $p=0.606$) in the first 24 hours after surgery. Amongst patients receiving intraoperative dCSPs, the age of the unit was not associated with the presence or absence of postoperative transfusion. However, in those receiving a postoperative transfusion of platelets in the first 24 hours after surgery, each 1-day increase in age of the intraoperative dCSP unit was associated with a 3.7 times greater rate of platelet transfusions (Supplemental Table 6). Similarly, each 1-day increase in intraoperative dCSP age was associated with a reduction of -5.7 ($-9.0, -2.3$) in the maximum platelet count on postoperative day 0 ($p<0.001$). There were no significant associations with intraoperative dCSP unit age and postoperative platelet counts on days 3 and 7. The total model-estimated number of RBC and platelet units administered postoperatively through the first 72 hours under the hypothetical dCSP-only scenario compared to the RTP-only scenario was 1060 vs. 927 (14% increase with dCSPs) and 411 vs. 341 (20% increase with dCSPs), respectively.

Discussion

In this observational study of intraoperative dCSPs versus RTPs for adult cardiac surgery patients, more than 180 patients (25% of included cases) received dCSPs over the 13-month study period, thereby receiving platelet units that would otherwise have been discarded. Those receiving dCSPs had higher allogeneic transfusion requirements through the first 3 days after surgery. Post-transfusion platelet counts were modestly lower in the dCSP group (approximately $10 \times 10^9/L$ less through the first week postoperatively), though this was not accompanied by an increased rate of reoperation for bleeding or higher chest tube output. There was no signal for adverse clinical outcomes such as transfusion reactions or thrombotic events in those receiving dCSPs.

Following the discovery in the 1960s that CSPs exhibited a significantly reduced circulation time after transfusion, CSPs were nearly abandoned clinically for decades³. Collectively, this makes CSPs a relatively rare product in modern clinical practice outside of the military and clinical trial situations^{12,17,18}. Despite this rarity, accumulating evidence has suggested although they remain in circulation for less time than RTPs, CSPs have improved metabolism and reduced oxidative stress, demonstrate ‘prohemostatic’ characteristics due to improved aggregation and clot strength, and release fewer proinflammatory markers during storage^{5-7,19}. In addition, CSPs appear to be more resistant to bacterial growth than RTPs up to 21 days of cold storage^{2,20,21}. These properties have led to a growing interest in apheresis derived CSP concentrates in bleeding patients (mostly trauma) since the introduction of an FDA variance in 2015 and a renewed interest in studying their clinical efficacy and safety in actively bleeding patients in other clinical areas^{12,17,18}.

Although few studies have evaluated CSPs clinically, those that have generally demonstrate comparable early post transfusion efficacy in actively bleeding patients with no significant safety concerns and consistently demonstrate a decreased post-transfusion circulation time^{4,8,10,22}. In a recent study by Cohn *et al.*, 10 volunteers underwent a dual arm crossover and were evaluated for the ability of RTP or CSP autotransfusions to correct aspirin and clopidogrel-influenced bleeding times²³. While neither group was effective in reversing antiplatelet effects, the two groups were generally comparable²³. In a recent report of platelet functional recovery, Stolla *et al.* transfused 21 patients with radiolabeled CSPs stored for 5, 10, 15, or 20 days⁹. They found a continuous decline in post-transfusion platelet recovery with increasing storage duration with the low nadir platelet recovery occurring after 10 days of storage, however in vitro assessments showed preserved metabolic profiles, integrin activation and mitochondrial membrane integrity up to 20 days of cold storage⁹. Although recovery may be worse in vivo, in vitro testing shows platelet reactivity is prolonged up to 20 days in CSPs. A single randomized controlled pilot trial in Norway has directly compared CSPs to RTPs in complex cardiac surgery¹¹. There were no differences in the median chest tube output between the groups, and no differences in total blood product usage, adverse events, or ICU length of stay¹¹. The results of this trial were used to inform a large multicenter trial of RTPs vs. CSPs in complex cardiac surgery (CHIPs), which is currently recruiting and will likely take several years before results are available (NCT04834414).

Few studies have specifically focused on delayed CSPs, where there is at least some period of “typical” storage at room temperature before cooling to 1–6 degrees C. Two recent studies have demonstrated preserved metabolic profiles and hemostatic properties of dCSPs for up to 21 days^{13,24}. However, Braathen *et al.* demonstrated that although both CSPs and dCSPs showed reasonable in vitro hemostatic profiles and remained functional throughout their storage life, dCSPs showed lower maximal aggregation responses with multiple functional studies compared to CSPs²⁴. Our previously published observational data of 61 dCSP transfusions for bleeding patients demonstrated adequate hemostasis and no evidence of patient harm, though there was no RTP comparator¹².

In this study of dCSPs in adult cardiac surgery, we found that while dCSPs demonstrated clinical efficacy without signal for patient harm, they appear less efficacious than RTPs within their first 5-day storage window for the prevention of postoperative transfusions or maintenance of postoperative platelet counts. Rather than having greater hemostatic efficacy as has been previously postulated for CSPs, dCSPs may instead be functionally similar to day 5 RTPs but with shorter circulatory life span. Hence, apart from times of shortages in RTPs, it is unlikely that dCSPs should play a major role in the management of thrombocytopenia-related acute bleeding during cardiac surgery. That being said, in times of severe inventory shortages, dCSPs may represent a viable option with an encouraging safety and hemostatic profile. However, it is important to consider the implications of using a blood inventory management strategy that may reduce wastage of platelet units prior to surgery but may come at a cost of increased platelet and RBC utilization after surgery. In this study, the use of dCSPs intraoperatively was associated with model-predicted absolute increases in postoperative RBC and platelet units through the first 72 hours of 133 and 70 units, respectively. These utilization numbers are substantially lower than the 292 dCSP units administered intraoperatively that otherwise would have been discarded, suggesting positive net benefit on inventory. Regarding financial implications, employing estimated acquisition costs of \$585 and activity-based costs of \$1360 per unit of platelets,²⁵ saving 222 units in net platelet utilization would translate to approximately \$129,870 to \$301,920 in cost savings over the 13-month study period based on acquisition and activity-based costs, respectively. Considering the additional 133 units of RBCs administered postoperatively in the dCSP group with estimated acquisition and activity-based costs of \$210 and \$761,^{26,27} these savings would be offset by approximately \$27,930 to \$101,213, yielding total transfusion-related cost savings of \$101,940 (acquisition costs only) to \$200,707 (activity-based costs). Importantly, these estimates do not include potential costs related to the management of a dual-platelet inventory.

Our report has several limitations worth highlighting. First, these findings are representative of a single tertiary referral center performing cardiac surgery with a large in-house blood donor and product manufacturing capability. As such, the approach presented therein (i.e., maintenance of dual platelet inventory) may be impractical for many centers. Secondly, our study is observational which may introduce relevant biases related to residual confounding or incomplete data. Third, our institution utilizes transfusion algorithms based on standard blood counts. Without correcting for the expected differences in post transfusion platelet recovery, there may be a bias towards increased transfusion of platelets in the dCSP group despite no difference in hemostatic efficacy. Our practice also allows the individualized

use of coagulation factor concentrates that were not captured herein. Fourth, some patients (16%) in the dCSP group also received RTPs intraoperatively, which may bias outcome estimates. We performed a predefined sensitivity analysis excluding patients receiving both dCSPs and RTPs with similar results. Fifth, as an observational design, adverse events are identified and evaluated by bedside clinicians rather than prospective surveillance, which may predispose to under-reporting. As such, similar clinical outcomes between groups does not necessarily imply comparable safety of dCSPs and RTPs. Sixth, although dCSP versus RTP use was based on blood bank availability and not directly related to patient acuity, important measured or unmeasured confounders might exist and could contribute to a missing covariable bias, although we attempted to limit this with thoughtful adjustment for clinically relevant confounders. Further, as a post hoc analysis we evaluated for clustering of treatment over time based on inventory levels, which could introduce bias in treatment assignment. Despite evidence of clustering of treatment assignment over time, there was no evidence of outcome clustering. However, the study was not designed to assess outcome clustering, therefore the nonsignificant findings should not be considered definitive. Seventh, a small proportion of observations were excluded due to missing covariate information, and bias may be introduced by using a complete case approach to missing data. Eighth, it is known that PRT platelets used for cold storage have slightly altered clotting dynamics compared to those cold stored without PRT treatment, and the results of this study may not be generalizable to non-PRT platelets²⁸. Finally, the data presented herein pertain specifically to cardiac surgical patients and therefore cannot be extrapolated to other bleeding clinical situations.

In summary, our data demonstrate the utility of dCSPs in bleeding cardiac surgery patients. Despite reasonable clinical efficacy as highlighted by no differences in chest tube output or reoperation for bleeding, dCSPs were associated with increased odds of allogenic transfusion through the first 3 postoperative days. Since dCSPs undergo a period of typical room temperature storage before refrigeration, determining the clinical efficacy and safety of CSPs, which undergo immediate refrigeration, will require well designed, randomized controlled trials, of which one is currently underway. Finally, these results show that nearly 300 units of platelets that would have otherwise been discarded were able to be utilized in clinical practice, which far outweighs any increase in downstream platelet utilization related to intraoperative dCSP use. In the face of ongoing blood shortages and financial concerns related to the maintenance of adequate platelet inventories due to their short outdate and high wastage rates, further discussion is needed regarding the potential utility of dCSP use in bleeding patients, especially when the alternative may be to forego platelet transfusion due to lack of inventory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

- Allan Klompas: Serves as the site principal investigator for the CHIPS randomized controlled trial (NCT04834414)
- Simon Zec: No conflicts of interest to disclose
- Andrew Hanson: No conflicts of interest to disclose
- Tim Weister: No conflicts of interest to disclose
- James Stubbs: Serves as a co-investigator for the CHIPS randomized controlled trial (NCT04834414)
- Daryl Kor: Has received research support from the NIH and consulting fees from NIH, UpToDate, and Dynocardia.
- Matthew Warner: Receives research support from the National Institutes of Health. Serves on the board of directors for the Society for the Advancement of Patient Blood Management.

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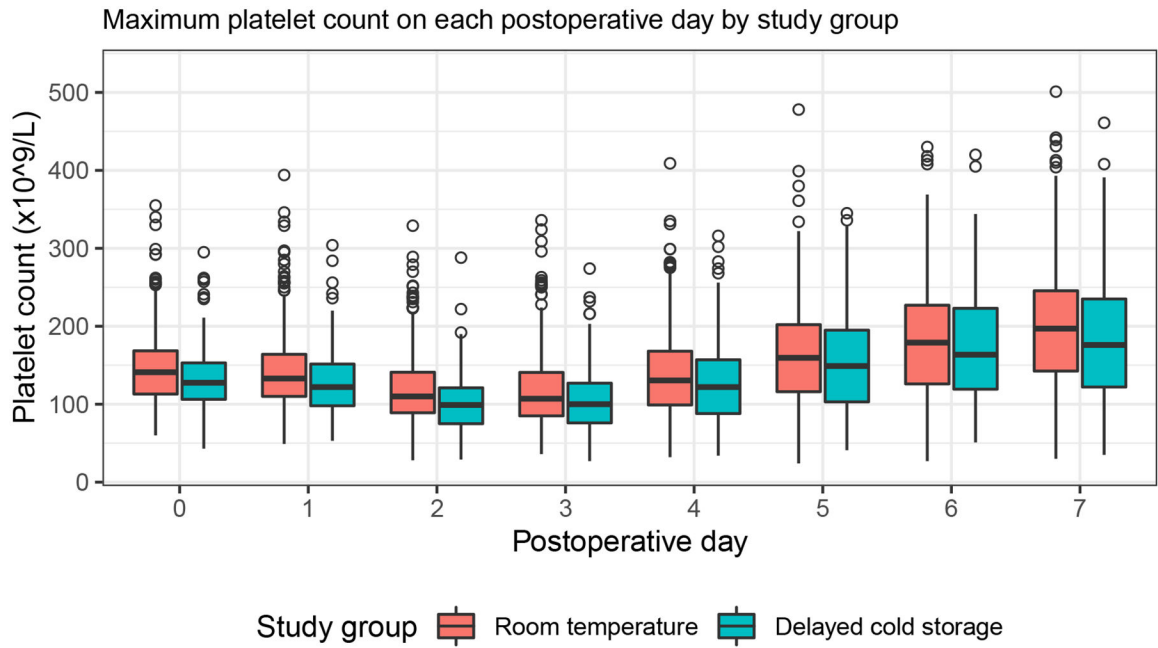


Figure 1.

Maximum platelet counts on each postoperative day.

Distribution of maximum platelet count presented as box-and-whisker plots according to study group and postoperative day. For each box-and-whisker plot, the lower, middle, and upper horizontal lines represent the 25th, 50th, and 75th percentiles. The difference between the 75th and 25th percentiles is defined as the interquartile range (IQR). Vertical lines are drawn from the upper and lower quartiles to the maximum and minimum values within 1.5 IQR respectively. Values outside of those ranges are plotted as circles. Ninety-five percent of patients had available platelet counts through postoperative day 4, with 89%, 74%, and 58% having available platelet count on days 5, 6, and 7 respectively.

Table 1.

Baseline demographic, clinical, and surgical features

Characteristic	Platelet Transfusion Type		
	Overall N = 713 ^I	RTPs N = 529 ^I	dCSPs N = 184 ^I
Age (yrs)	65 (51, 73)	64 (51, 73)	66 (56, 74)
Sex			
Female	255 (36%)	191 (36%)	64 (35%)
Male	458 (64%)	338 (64%)	120 (65%)
Charlson Score	4 (2, 6)	4 (2, 6)	4 (3, 7)
Preop Platelet count (×10⁹/L; n=685)	188 (154, 233)	188 (153, 232)	184 (154, 237)
Preop Antiplatelet Use	357 (50%)	257 (49%)	100 (54%)
Aspirin	346 (49%)	248 (47%)	98 (53%)
Clopidogrel/Ticagrelor	82 (12%)	57 (11%)	25 (14%)
Procedure Type			
CABG Only ^a	110 (15%)	72 (14%)	38 (21%)
CABG + Other	12 (2%)	10 (2%)	2 (1%)
CABG + Valve	50 (7%)	42 (8%)	8 (4%)
CABG + Valve + Other	13 (2%)	9 (2%)	4 (2%)
Congenital	67 (9%)	50 (9%)	17 (9%)
HCM/Myectomy	40 (6%)	32 (6%)	8 (4%)
Other ^b	58 (8%)	43 (8%)	15 (8%)
Pericardiectomy	10 (1%)	8 (2%)	2 (1%)
Transplant	24 (3%)	17 (3%)	7 (4%)
VAD and MCS	10 (1%)	4 (1%)	6 (3%)
Valve	140 (20%)	107 (20%)	33 (18%)
Valve + Other ^c	179 (25%)	135 (26%)	44 (24%)
Redo Sternotomy	240 (34%)	183 (35%)	57 (31%)
Complex surgery	355 (50%)	267 (50%)	88 (48%)
CPB time (min; n=709)	138 (99, 196)	141 (100, 199)	129 (96, 185)
Cross-clamp time (min; n=646)	102 (67, 149)	104 (66, 152)	99 (70, 138)

^IMedian (IQR); n (%)^aTwo procedures performed off-pump, both in the room-temperature group^bIncluding aneurysm repair, myxoma resections, pulmonary thromboendarterectomy^cIncluding Bentall procedure.

Abbreviations: CABG; coronary artery bypass graft, HCM; hypertrophic cardiomyopathy, VAD; ventricular assist device, MCS; mechanical circulatory support

Table 2.

Intraoperative transfusion features

Transfusion Type	Platelet Transfusion Type		
	Overall, N = 713 ^I	RTPs, N = 529 ^I	dCSPs, N = 184 ^I
Any Platelets	713 (100%)	529 (100%)	184 (100%)
Platelets (units; n=713)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Any RBC	371 (52%)	279 (53%)	92 (50%)
RBC (units; n=371)	2 (1, 4)	2 (1, 4)	3 (1, 4)
Any Plasma	314 (44%)	233 (44%)	81 (44%)
Plasma (units; n=314)	2 (1, 2)	2 (1, 2)	2 (2, 3)
Any Cryoprecipitate	329 (46%)	261 (49%)	68 (37%)
Cryoprecipitate (units; n=329)	2 (1, 2)	2 (1, 2)	2 (1, 2)
Any Cell Salvage	675 (95%)	498 (94%)	177 (96%)
Cell salvage (mL; n=675)	578 (388, 846)	605 (406, 872)	527 (347, 812)
Any Fresh whole blood	92 (13%)	66 (12%)	26 (14%)
Fresh whole blood (mL; n=92)	742 (451, 902)	775 (454, 902)	642 (449, 826)

^I
n (%); Median (IQR)

Abbreviations: dCSPs; delayed cold-stored platelets, RBC; red blood cell, RTPs; room-temperature platelets

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Table 3.

Unadjusted seven-day clinical outcomes

Outcome	Platelet Transfusion Type			P-value ²
	Overall N = 713 ¹	RTPs N = 529 ¹	dCSFs N = 184 ¹	
Venous thromboembolism	9 (1%)	5 (1%)	4 (2%)	0.247
Stroke or myocardial infarction	10 (1%)	8 (2%)	2 (1%)	0.999
Infection	52 (7%)	37 (7%)	15 (8%)	0.603
Hospital mortality	16 (2%)	12 (2%)	4 (2%)	0.999
Transfusion Reaction (n=712)	6 (1%)	4 (1%)	2 (1%)	0.650

¹n (%)²All p-values were from Fisher's exact tests except the p-value comparing infection between groups which was from Pearson's Chi square test

Abbreviations: dCSFs; delayed cold-stored platelets, RBC; red blood cell RTPs; room-temperature platelets

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Table 4.

Adjusted postoperative transfusion outcomes for patients receiving dCSPs vs RTPs

Outcome [*]	aOR [#] (95% CI)	P-value	Rate Ratio [^] (95% CI)	P-value
<i>24 hours</i>				
Any allogeneic transfusion	1.65 (1.13, 2.39)	0.009	0.90 (0.55, 1.46)	0.665
RBC transfusion	1.54 (1.03, 2.29)	0.035	0.93 (0.56, 1.55)	0.792
Platelet transfusion	1.91 (1.22, 2.99)	0.005	0.69 (0.33, 1.45)	0.327
<i>72 hours</i>				
Any allogeneic transfusion	1.26 (0.87, 1.84)	0.217	1.10 (0.73, 1.66)	0.651
RBC transfusion	1.30 (0.90, 1.89)	0.167	1.05 (0.73, 1.53)	0.776
Platelet transfusion	1.86 (1.20, 2.89)	0.005	0.76 (0.361, 1.62)	0.482

* Models adjusted for age, sex, preoperative hemoglobin concentration, preoperative platelet count, preoperative use of antiplatelet agents, complex surgery, redo sternotomy, total number of transfused intraoperative platelet units, and total cardiopulmonary bypass time. Analysis limited to observations with complete covariate information (n=681/713, 96%).

aOR represent estimated multiplicative increase in odds of receiving 1 or more of the given transfusion associated with receipt of cold-stored platelets intraoperatively compared to room temperature platelets.

[^] Rate ratios represent the estimated multiplicative increase in the number of units administered postoperatively (limited to those who received a given postoperative transfusion type) associated with receipt of cold platelets intraoperatively compared to room temperature platelets.

Abbreviations: dCSPs; delayed cold-stored platelets, RBC; red blood cell, RTPs; room-temperature platelets

Table 5.

Adjusted platelet recovery and bleeding outcomes for patients receiving dCSPs vs RTPs

Outcome [*]	Estimate [#]	95% CI	P-value
Platelet count on postoperative day 0, $\times 10^9/L$; n=669	-12	-19, -5	<0.001
Platelet count on postoperative day 3, $\times 10^9/L$; n=667	-9	-16, -3	0.004
Platelet count on postoperative day 7, $\times 10^9/L$; n=396	-11	-29, 6	0.199
Return to operating room for bleeding; n=681	0.85	0.40, 1.98	0.688
Chest tube output in 1 st 24 hours after surgery, ml; n=678	-31	-168, 106	0.660

* Models adjusted for age, sex, preoperative hemoglobin concentration, preoperative platelet count, preoperative use of antiplatelet agents, complex surgery, redo sternotomy, total number of transfused intraoperative platelet units, and total cardiopulmonary bypass time, except for return to the operating room for bleeding which is adjusted for preoperative platelet count and total cardiopulmonary bypass time. Number of observations with complete outcome and covariate information and included in each analysis is summarized.

[#] Estimates represent the estimated difference in outcome associated with receipt of cold platelets intraoperatively compared to room temperature platelets. For example, receipt of cold platelets was associated with an estimated 12 (95% CI: 5, 19) $\times 10^9/L$ lower immediate postoperative platelet count compared to room temperature platelets.

Abbreviations: dCSPs; delayed cold-stored platelets, RBC; red blood cell, RTPs; room-temperature platelets

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