ANESTHESIOLOGY

Postoperative Transfusions after Administration of Delayed Cold-stored Platelets *versus* Room Temperature Platelets in Cardiac Surgery: A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Delayed cold storage of room temperature platelets extends shelf life from 5 days to 14 days, but whether their use in cardiac surgery provides similar transfusion and clinical outcomes compared to room temperature platelets is unknown.

What This Article Tells Us That Is New

- In an observational cohort of 713 adult cardiac surgical patients, 74% received room temperature *versus* 26% delayed cold-stored platelets, those receiving cold-stored platelets had a higher odds of transfusions in the first 24 h postoperatively (44% *vs.* 32%). However, there were no significant differences among those transfused in the total number of units transfused postoperatively, reoperation for bleeding, chest tube output, or clinical outcomes.

ABSTRACT

Background: Delayed cold storage of room temperature platelets may extend shelf life from 5 to 14 days. The study hypothesized that 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-stored 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 allogenic transfusion exposure in the first 24 h postoperatively, were compared between groups.

Results: A total of 713 patient encounters were included: 529 (74%) room temperature-stored platelets and 184 (26%) delayed cold-stored platelets. Median (interquartile range) intraoperative platelet volumes were 1 (1 to 2) units in both groups. Patients receiving delayed cold-stored platelets had higher odds of allogeneic transfusion in the first 24 h postoperatively (81 of 184 [44%] *vs.* 169 of 529 [32%]; adjusted odds ratio, 1.65; 95% CI, 1.13 to 2.39; $P = 0.009$), including both erythrocytes (65 of 184 [35%] *vs.* 135 of 529 [26%]; adjusted odds ratio, 1.54; 95% CI, 1.03 to 2.29; $P = 0.035$) and platelets (48 of 184 [26%] *vs.* 79 of 529 [15%]; adjusted odds ratio, 1.91; 95% CI, 1.22 to 2.99; $P = 0.005$). There was no difference in the number of units administered postoperatively among those transfused. Platelet counts were modestly lower in the delayed cold-stored platelet group (-9×10^9/l; 95% CI, −16 to −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.

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The COVID-19 pandemic has strained medical resources around the world and has exposed vulnerability in blood inventories.[1] Platelets are the blood component most

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vulnerable to shortages. While other products may be stored long-term by freezing or have pharmacologic alternatives such as coagulation factor concentrates, platelets have neither.[2] Typically, platelets are stored at 20 to 24°C with gentle agitation for up to 5 to 7 days.[2] This short outdate has been selected to balance the increased risk of bacterial contamination seen with nonrefrigerated storage and the need to maintain an adequate inventory.[2] The introduction of pathogen reduction technology 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 days.[2] 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 had dramatically shorter lifespans (*i.e.*, 1 to 2 days) after transfusion compared to their room temperature counterparts (*i.e.*, 7 to 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 cold-stored platelets from clinical practice. However, subsequent work has shown that cold-stored platelets may have a more favorable hemostatic profile and improved metabolic characteristics than room temperature platelets, which may potentially be beneficial for the management of acute bleeding.[5–7] Indeed, early clinical work has suggested that cold-stored platelets may at least be equally efficacious in bleeding patients.[8–10] A recent pilot trial in cardiac surgery lends support to the noninferiority of cold-stored platelets compared to room temperature platelets, and a large multicenter randomized trial is currently enrolling participants.[11]

In early 2020, in anticipation of blood shortages and unpredictable platelet usage, the Mayo Clinic in Rochester, Minnesota, notified the U.S. Food and Drug Administration (Silver Spring, Maryland) that it would convert about-to-expire (*i.e.*, day 5 of room temperature storage) pathogen-reduced room temperature platelets to cold storage. These delayed cold-stored platelets would be stored at 1 to 6°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 delayed cold-stored platelets compared to cold-stored platelets, which are immediately refrigerated after collection rather than having a period of room temperature storage.[13] Assuming that delayed cold-stored platelets would display similar features to cold-stored platelets (*i.e.*, shorter circulation duration and potential favorable hemostatic response compared to room temperature platelets), delayed cold-stored platelets were earmarked for use in bleeding patients (*i.e.*, surgical, trauma, massive hemorrhage) when room temperature platelets inventories were low or unavailable.[12] Early clinical review of this practice, including transfusion of 61 units of delayed cold-stored platelets (58% in cardiac surgery), showed signs of hemostatic efficacy without signal for patient harm.

Given our dual inventory of delayed cold-stored platelets and room temperature platelets 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 delayed cold-stored platelets against traditional room temperature platelets. We hypothesized that delayed cold-stored platelets would be associated with decreased postoperative platelet increments compared to room temperature platelets but comparable transfusion and clinical outcomes.

Materials and 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 (STROBE) guidelines were employed in study design and conduct.[14]

All adults (18 yr or older) 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 cannulation, washout, 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 delayed cold-stored platelet use at our institution.[12]

Delayed Cold-stored Platelet and Room Temperature Platelet 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, in April 2020, we began transitioning pathogen-reduced room temperature platelets 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 delayed cold-stored platelet inventory. The delayed cold-stored platelet inventory was earmarked for use in patients with active bleeding (*i.e.*, surgical, trauma, massive transfusion) when room temperature platelet inventories were low (*i.e.,* less than 10% of optimal levels) or unavailable. Room temperature platelets remained available for bleeding patients when supplies were adequate and were

maintained for patients with nonbleeding 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 delayed cold-stored platelets or room temperature platelets. 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 room temperature platelet or delayed cold-stored platelet 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 protocol.[15] 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, 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, erythrocytes 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 erythrocytes 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 delayed cold-stored platelet *versus* room temperature platelets, with all transfusion episodes extracted from our institutional Transfusion DataMart. Patients in the delayed cold-stored platelet group must have received at least 1 unit of intraoperative delayed cold-stored platelets but could also have received additional units of either platelet type (delayed cold-stored platelet or room temperature platelet) intraoperatively. Patients in the room temperature platelet group only received room temperature platelets intraoperatively.

Outcomes

Both transfusion and bleeding and clinical outcomes were evaluated. The primary outcome was allogeneic transfusion in the first 24 h postoperatively, evaluated as present or absent and by the total number of units transfused. The secondary transfusion and bleeding outcomes included were allogenic transfusions of erythrocytes and platelets in the first 24 and 72 h after surgery, total allogeneic transfusions in the first 72 h postoperatively, unanticipated return to the operating room for bleeding in the first 24 h after surgery, and total chest tube output in the first 24 h 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 after surgery. Stroke was defined by radiographic evidence of acute or subacute infarction during hospitalization after 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, among 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 institutional review board before accessing study data, with any additional analyses labeled as *post hoc*. The statistical analysis plan is provided as Supplemental Digital Content (https://links.lww.com/ALN/D155). Baseline demographic, clinical, and surgical characteristics were described with median (interquartile range) and number (percent) for continuous and categorial data elements, respectively. Unadjusted outcomes were compared between groups with Mann–Whitney U tests and Pearson's chi-square tests for continuous and categorial data elements, respectively. In cases where the expected cell counts were less than five, 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 prespecification of minimum clinically meaningful effect sizes. The results of the zero and the count portions of the hurdle models were reported as follows: (1) an adjusted odds ratio representing the estimated multiplicative increase in odds for receiving any transfusion after surgery for delayed cold-stored platelet compared to room temperature platelet for the zero portion, and (2) an adjusted rate ratio representing the estimated multiplicative increase in total number of units administered after surgery for delayed cold-stored platelet compared to room temperature platelet 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 three 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 h 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 delayed cold-stored platelet group may also receive room temperature platelets, a predefined sensitivity analysis was performed limited to those receiving only delayed cold-stored platelets in the delayed cold-stored platelet group. As a *post hoc* analysis, a runs test was employed to evaluate potential clustering of treatment assignment by calendar time. Subsequently, potential clustering of 24-h transfusion outcomes over time was evaluated with runs tests (*i.e.*, transfusion yes or no) and Durbin–Watson tests (*i.e.*, units transfused). Additionally, among patients receiving a single unit of intraoperative delayed cold-stored platelets, 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 erythrocyte units administered in the first 72 h postoperatively under the hypothetical scenarios in which either all patients in the sample were treated with delayed cold-stored platelets or all patients were treated with room temperature platelets. 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, Austria), and two-tailed P values of less than 0.05 were considered significant.

Results

A total of 713 patient encounters with intraoperative platelet transfusion during cardiac surgery were included (fig. S1 in the Supplemental Digital Content, https://links.lww.com/ALN/D155). Room temperature platelets were administered in 529 cases (74%) and delayed cold-stored platelets in 184 cases (26%), with 154 patients (84%) in the delayed cold-stored platelet group receiving only delayed cold-stored platelets intraoperatively and 30 patients (16%) also receiving intraoperative room temperature platelets. The median age of delayed cold-stored platelet units was 7 (6 to 8) days. The room temperature platelet and delayed cold-stored platelet groups were similar in all baseline demographic, clinical, and surgical characteristics (table 1). Overall, the cohort had a median age of 65 (51 to 73) years with a male predominance (64%) and a median Charlson score of 4 (2 to 6). Half of the cohort underwent complex cardiac surgery, and 34% of operations were redo sternotomies. The most common procedures were as follows: 179 valvular plus other procedures (25%), 140 isolated valvular procedures (20%), and 110 isolated coronary artery bypass graft procedures (15%). The median cardiopulmonary bypass time was 138 (99 to 196) min, and the median cross-clamp time was 102 (67 to 149) min.

Intraoperative transfusions were generally similar between groups (table 2). Patients in both groups received a median of 1 (1 to 2) unit of platelets, representing 777 units of intraoperative room temperature platelets and 292 units of delayed cold-stored platelets. Of those in the room temperature platelet group, 53% received an erythrocyte transfusion, compared to 50% in the delayed cold-stored platelet group, and patients in the delayed cold-stored platelet group received a median of 3 (1 to 4) units of erythrocytes as compared to 2 (1 to 4) units. Cryoprecipitate was given in 49% of cases in the room temperature platelet group and in 37% of cases in the delayed cold-stored platelet group. Cell salvage volumes were modestly higher in the room temperature platelet group (605 [406 to 872] ml *vs.* 527 [347 to 812] ml). Autologous fresh whole blood from acute normovolemic hemodilution was transfused in 12 and 14% of cases for room temperature platelets and delayed cold-stored platelets, respectively, with modestly higher volumes in the room temperature platelet group.

Table 1. Baseline Demographic, Clinical, and Surgical Features

Characteristic	Overall (N = 713)*	Platelet Transfusion Type	
		Room Temperature Platelets (N = 529)*	Delayed Cold-stored Platelets (N = 184)*
Age, yr	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)
Preoperative platelet count (×10^9/l; n = 685)	188 (154, 233)	188 (153, 232)	184 (154, 237)
Preoperative 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†	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%)
Hypertrophic cardiomyopathy/myectomy	40 (6%)	32 (6%)	8 (4%)
Other‡	58 (8%)	43 (8%)	15 (8%)
Pericardiectomy	10 (1%)	8 (2%)	2 (1%)
Transplant	24 (3%)	17 (3%)	7 (4%)
Ventricular assist device and mechanical circulatory support	10 (1%)	4 (1%)	6 (3%)
Valve	140 (20%)	107 (20%)	33 (18%)
Valve + other§	179 (25%)	135 (26%)	44 (24%)
Redo sternotomy	240 (34%)	183 (35%)	57 (31%)
Complex surgery	355 (50%)	267 (50%)	88 (48%)
Cardiopulmonary bypass 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)

*The values are the medians (interquartile range), *n* (%). †Two procedures performed off-pump, both in the room temperature group. ‡Including aneurysm repair, myxoma resections, and pulmonary thromboendarterectomy. §Including the Bentall procedure.

CABG, coronary artery bypass graft.

Unadjusted analyses of postoperative transfusions and other transfusion outcomes revealed significant between-group differences (table S1 in the Supplemental Digital Content, https://links.lww.com/ALN/D155), including a lower incidence of transfusion of platelets (79 of 529 [15%] *vs.* 48 of 184 [26%], $P < 0.001$) and erythrocytes (135 of 529 [26%] *vs.* 65 of 184 [35%], $P = 0.011$) in the first 24 h after surgery in the room temperature platelet group. Among those receiving platelets in the first 24 h after surgery, the proportions of patients receiving a platelet transfusion for active bleeding were 90% (71 of 79) and 96% (46 of 48) for the room temperature platelet and delayed cold-stored platelet groups, respectively ($P = 0.317$). Among those receiving erythrocytes in the first 24 h after surgery, the proportions transfused for active bleeding were 60% (81 of 135) and 71% (46 of 65) for the room temperature platelet and delayed cold-stored platelet groups, respectively ($P = 0.160$). Differences in maximum platelet count on each postoperative day are displayed graphically (fig. 1), showing modestly lower platelet counts on each day in the delayed cold-stored platelet group. There were no significant differences in chest tube output in the first 24 h after surgery (762 [510 to 1,089] ml for room temperature platelets *vs.* 766 [554 to 1,191] ml for delayed cold-stored platelets, $P = 0.215$), return to the operating room for bleeding (24 of 529 [5%] for room temperature platelets *vs.* 11 of 184 [6%] for delayed cold-stored platelets, $P = 0.436$), or clinical outcomes between groups (table 3).

In adjusted analyses for the primary outcome, intraoperative delayed cold-stored platelets were associated with higher odds of receiving any allogeneic transfusion (adjusted odds ratio, 1.65; 95% CI, 1.13 to 2.39; $P = 0.009$), any erythrocytes (adjusted odds ratio, 1.54; 95% CI, 1.03 to 2.29; $P = 0.035$), and any platelets (adjusted odds ratio, 1.91; 95% CI, 1.22 to 2.99; $P = 0.005$) in the first 24 h after surgery (table 4). Only an increased odds for platelet transfusion remained statistically significant at 72 h postoperatively. Among those transfused, there were no significant differences in the number of units administered (table 4). In adjusted analyses, patients receiving delayed cold-stored platelets had an estimated −12 (95% CI, −19 to −5) × 10^9/l and −9 (95% CI, −16 to −3) × 10^9/l difference in

Table 2. Intraoperative Transfusion Features

Transfusion Type	Overall (N = 713)*	Platelet Transfusion Type	
		Room Temperature Platelets (N = 529)*	Delayed Cold-stored Platelets (N = 184)*
Any platelets	713 (100%)	529 (100%)	184 (100%)
Platelets (units; n = 713)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Any erythrocyte	371 (52%)	279 (53%)	92 (50%)
Erythrocyte (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)

*n (%), median (interquartile range).

maximum platelet count on postoperative days 0 ($P < 0.001$) and 3 ($P = 0.004$), respectively, compared to those receiving room temperature platelets (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 delayed cold-stored platelets (adjusted odds ratio, 0.85; 95% CI, 0.40 to 1.98; $P = 0.688$), nor was there any significant difference in chest tube output in the first 24 h after surgery (adjusted odds ratio, −31; 95% CI, −168 to 106) ml; $P = 0.660$). Study results were consistent in a predefined sensitivity analysis limited to those receiving only delayed cold-stored platelets in the delayed cold-stored platelet group ($n = 154$; tables S2 to S5 in the Supplemental Digital Content, https://links.lww.com/ALN/D155).

In *post hoc* analyses, there was evidence of clustering of treatment assignment over time (fig. S2 in the Supplemental Digital Content, https://links.lww.com/ALN/D155; runs test $P < 0.001$), but no statistically significant outcome clustering over time was detected for any transfusion (runs test $P = 0.097$), any erythrocyte transfusion (runs test $P = 0.155$), any platelet transfusion (runs test $P = 0.974$), total transfusion units (Durbin–Watson $P = 0.677$), total erythrocyte units (Durbin–Watson $P = 0.580$), or total platelet units (Durbin–Watson $P = 0.606$) in the first 24 h after surgery. Among patients receiving intraoperative delayed cold-stored platelets, 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 h after surgery, each 1-day increase in age of the intraoperative delayed cold-stored platelet unit was associated with a 3.7 times greater rate of platelet transfusions (table S6 in the Supplemental Digital Content, https://links.lww.com/ALN/D155). Similarly, each 1-day increase in intraoperative delayed cold-stored platelet 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 delayed cold-stored platelet unit age and postoperative platelet counts on days 3 and 7. The total model-estimated number of erythrocyte and platelet units administered postoperatively through the first 72 h under the hypothetical delayed cold-stored platelet-only scenario compared to the room temperature platelet-only scenario was 1,060 *vs.* 927 (14% increase with delayed cold-stored platelets) and 411 *vs.* 341 (20% increase with delayed cold-stored platelets), respectively.

Discussion

In this observational study of intraoperative delayed cold-stored platelets *versus* room temperature platelets for adult cardiac surgery patients, more than 180 patients (25% of the included cases) received delayed cold-stored platelets over the 13-month study period, thereby receiving platelet units that would otherwise have been discarded. Those receiving delayed cold-stored platelets had higher allogeneic transfusion requirements through the first 3 days after surgery. Post-transfusion platelet counts were modestly lower in the delayed cold-stored platelet group (approximately 10×10^9/l less through the first week postoperatively), although 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 delayed cold-stored platelets.

After the discovery in the 1960s that cold-stored platelets exhibited a significantly reduced circulation time after transfusion, cold-stored platelets were nearly abandoned clinically for decades.[3] Collectively, this makes cold-stored

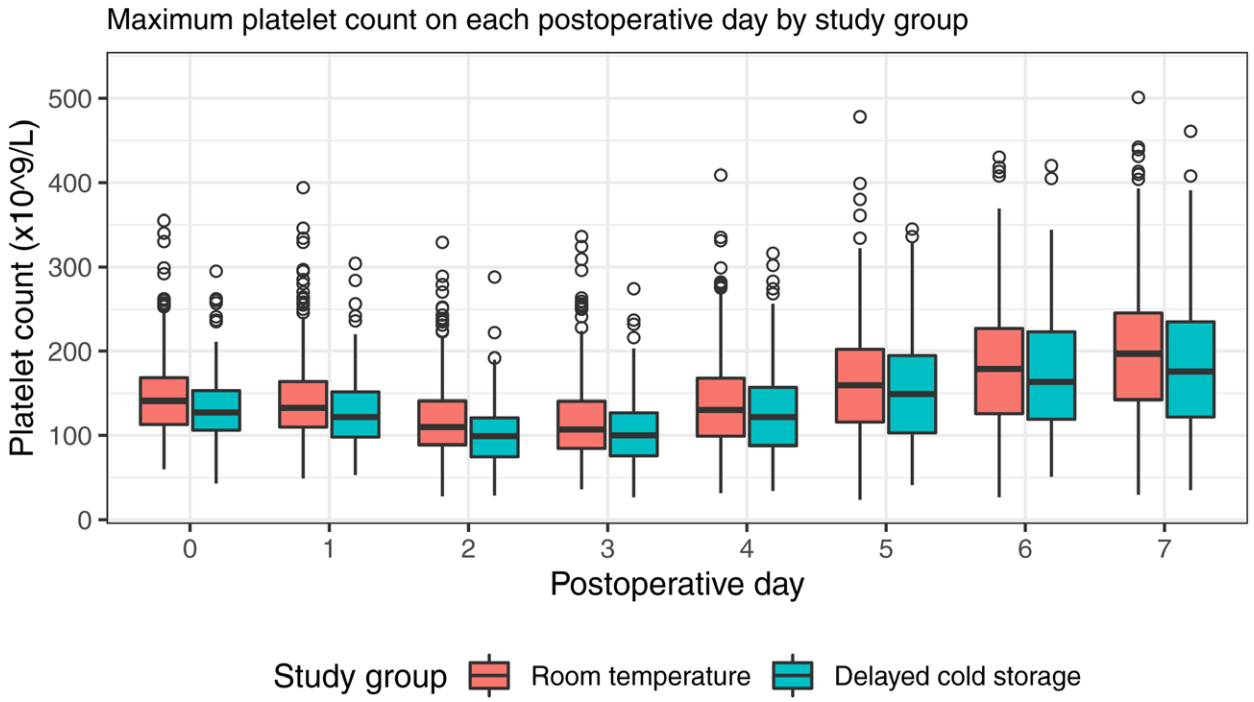

Fig. 1. Maximum platelet counts on each postoperative day. The distribution of maximum platelet count is presented as box-and-whisker plots according to study group and postoperative day. For each box-and-whisker plot, the *bottom*, *middle*, and *top horizontal lines* represent the 25th, 50th, and 75th percentiles, respectively. The difference between the 75th and 25th percentiles is defined as the interquartile range. *Vertical lines* are drawn from the upper and lower quartiles to the maximum and minimum values within 1.5 times the interquartile range, respectively. The values outside of those ranges are plotted as *circles*. Of all patients, 95% had available platelet counts through postoperative day 4, with 89, 74, and 58% having available platelet count on days 5, 6, and 7, respectively.

platelets 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 room temperature platelets, cold-stored platelets 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, cold-stored platelets appear to be more resistant to bacterial growth than room temperature platelets up to 21 days of cold storage.[2,20,21] These properties have led to a growing interest in apheresis-derived cold-stored platelet concentrates in bleeding patients (mostly trauma), since the introduction of a Food and Drug Administration 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 cold-stored platelets 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.*,[23] 10 volunteers underwent a dual arm crossover and were evaluated for the ability of room temperature platelet or cold-stored platelet autotransfusions to correct aspirin and clopidogrel-influenced bleeding times. While neither group was effective in reversing antiplatelet effects, the two groups were generally comparable.[23] In a recent report of platelet functional recovery, Stolla *et al.*[9] transfused 21 patients with radiolabeled cold-stored platelets stored for 5, 10, 15, or 20 days. 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 storage.[9] Although recovery may be worse *in vivo*, *in vitro* testing shows platelet reactivity is prolonged up to 20 days in cold-stored platelets. A single randomized controlled pilot trial in Norway has directly compared cold-stored platelets to room temperature platelets in complex cardiac surgery.[11] There were no differences in the median chest tube output between the groups, and no differences in total blood product usage, adverse events, or intensive care unit length of stay.[11] The results of this

Table 3. Unadjusted 7-Day Clinical Outcomes

Outcome	Overall (N = 713)*	Platelet Transfusion Type		*P* Value†
		Room Temperature Platelets (N = 529)*	Delayed Cold-stored Platelets (N = 184)*	
Venous thromboembolism	9 (1%)	5 (1%)	4 (2%)	0.247
Stoke 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

*n (%). †All *P* values were from Fisher's exact tests except the *P* value comparing infection between groups, which was from Pearson's chi-square test.

Table 4. Adjusted Postoperative Transfusion Outcomes for Patients Receiving Delayed Cold-stored Platelets *versus* Room Temperature Platelets

Outcome*	Adjusted Odds Ratio		Rate	
	Ratio (95% CI)†	*P* Value	Ratio (95% CI)‡	*P* Value
24 h				
Any allogeneic transfusion	1.65 (1.13 to 2.39)	0.009	0.90 (0.55 to 1.46)	0.665
Erythrocyte transfusion	1.54 (1.03 to 2.29)	0.035	0.93 (0.56 to 1.55)	0.792
Platelet transfusion	1.91 (1.22 to 2.99)	0.005	0.69 (0.326 to 1.45)	0.327
72 h				
Any allogeneic transfusion	1.26 (0.87 to 1.84)	0.217	1.10 (0.73 to 1.66)	0.651
Erythrocyte transfusion	1.30 (0.90 to 1.89)	0.167	1.05 (0.73 to 1.53)	0.776
Platelet transfusion	1.86 (1.20 to 2.89)	0.005	0.76 (0.361 to 1.62)	0.482

*The models were 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 of 713, 96%). †The adjusted odds ratio represents the estimated multiplicative increase in odds of receiving one 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.

trial were used to inform a large multicenter trial of room temperature platelets *vs*. cold-stored platelets in complex cardiac surgery (CHilled Platelet Study [CHIPS]), which is currently recruiting and will likely take several years before results are available (NCT04834414).

Few studies have specifically focused on delayed cold-stored platelets, for which there is at least some period of "typical" storage at room temperature before cooling to 1 to 6°C. Two recent studies have demonstrated preserved metabolic profiles and hemostatic properties of delayed cold-stored platelets for up to 21 days.[13,24] However, Braathen *et al.*[24] demonstrated that although both cold-stored platelets and delayed cold-stored platelets showed reasonable *in vitro* hemostatic profiles and remained functional throughout their storage life, delayed cold-stored platelets showed lower maximal aggregation responses with multiple functional studies compared to cold-stored platelets. Our previously published observational data of 61 delayed cold-stored platelet transfusions for bleeding patients demonstrated adequate hemostasis and no evidence of patient harm, although there was no room temperature platelet comparator.[12]

In this study of delayed cold-stored platelets in adult cardiac surgery, we found that while delayed cold-stored platelets demonstrated clinical efficacy without signal for patient harm, they appear less efficacious than room temperature platelets 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 cold-stored platelets, delayed cold-stored platelets may instead be functionally similar to day 5 room temperature platelets but with shorter circulatory life span. Hence, apart from times of shortages in room temperature platelets, it is unlikely that delayed cold-stored platelets 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, delayed cold-stored platelets may represent a viable option with an encouraging safety and hemostatic profile. However, it is important to

Table 5. Adjusted Platelet Recovery and Bleeding Outcomes for Patients Receiving Delayed Cold-stored Platelets *versus* Room Temperature Platelets

Outcome*	Estimate†	95% CI	*P* Value
Platelet count on postoperative day 0, × 10^9/l (n = 669)	−12	−19 to −5	<0.001
Platelet count on postoperative day 3, × 10^9/l (n = 667)	−9	−16 to −3	0.004
Platelet count on postoperative day 7, × 10^9/l (n = 396)	−11	−29 to 6	0.199
Return to operating room for bleeding (n = 681)	0.85	0.40 to 1.98	0.688
Chest tube output in first 24 h after surgery, ml (n = 678)	−31	−168 to 106	0.660

*The models were 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. The number of observations with complete outcome and covariate information and included in each analysis is summarized. †The estimates represent the estimated differences 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 to 19) × 10^9/l lower immediate postoperative platelet count compared to room temperature platelets.

consider the implications of using a blood inventory management strategy that may reduce wastage of platelet units before surgery but may come at a cost of increased platelet and erythrocyte utilization after surgery. In this study, the use of delayed cold-stored platelets intraoperatively was associated with model-predicted absolute increases in postoperative erythrocyte and platelet units through the first 72 h of 133 and 70 units, respectively. These utilization numbers are substantially lower than the 292 delayed cold-stored platelet 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 $1,360 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 erythrocytes administered postoperatively in the delayed cold-stored platelet 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. Second, 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 toward increased transfusion of platelets in the delayed cold-stored platelet 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 delayed cold-stored platelet group also received room temperature platelets intraoperatively, which may bias outcome estimates. We performed a predefined sensitivity analysis excluding patients receiving both delayed cold-stored platelets and room temperature platelets 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 delayed cold-stored platelets and room temperature platelets. Sixth, although delayed cold-stored platelet *versus* room temperature platelet 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 pathogen reduction technology platelets used for cold storage have slightly altered clotting dynamics compared to those cold stored without pathogen reduction technology treatment, and the results of this study may not be generalizable to non–pathogen reduction technology platelets.[28] 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 delayed cold-stored platelets in bleeding cardiac surgery patients. Despite reasonable clinical efficacy as highlighted by no differences in chest tube output or reoperation for bleeding, delayed cold-stored platelets were associated with increased odds of allogenic transfusion through the first

3 postoperative days. Since delayed cold-stored platelets undergo a period of typical room temperature storage before refrigeration, determining the clinical efficacy and safety of cold-stored platelets, 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 delayed cold-stored platelet 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 delayed cold-stored platelet use in bleeding patients, especially when the alternative may be to forego platelet transfusion due to lack of inventory.

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Competing Interests

Dr. Klompas serves as the site principal investigator for the CHilled Platelet Study (CHIPS) randomized controlled trial (NCT04834414). Dr. Stubbs serves as coinvestigator for the CHIPS randomized controlled trial (NCT04834414). Dr. Kor has received research support from the National Institutes of Health and consulting fees from National Institutes of Health, UpToDate (Philadelphia, Pennsylvania), and Dynocardia (Cambridge, Massachusetts). Dr. Warner receives research support from the National Institutes of Health and serves on the board of directors for the Society for the Advancement of Patient Blood Management (Mt. Royal, New Jersey). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content, https://links.lww.com/ALN/D155
Supplemental Figure 1. Consort diagram.
Supplemental Figure 2. Treatment allocation over time.
Supplemental Table 1. Unadjusted postoperative transfusion and bleeding outcomes.
Supplemental Table 2. Baseline demographic, clinical, and surgical features limited to those with only a single type of platelet transfusion intraoperatively.
Supplemental Table 3. Intraoperative transfusion features limited to those with only a single type of platelet transfusion intraoperatively.
Supplemental Table 4. Unadjusted clinical outcomes limited to those with only a single type of platelet transfusion intraoperatively.
Supplemental Table 5. Adjusted postoperative transfusion outcomes for patients receiving delayed cold-stored platelets *vs.* room temperature platelets, limited to those with only a single type of platelet transfusion intraoperatively.
Supplemental Table 6. Adjusted postoperative transfusion outcomes in patients receiving intraoperative delayed cold-stored platelets for each 1-day increase in age of the platelet unit.
Data Analysis Plan

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