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A pilot randomised clinical trial of cryopreserved vs. liquid-stored platelet transfusion for bleeding in cardiac surgery: the CLIP-NZ Pilot trial.

Short title: Cryopreserved platelets in cardiac surgery: CLIP-NZ pilot

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No data will be available from any public repository. Investigators wishing to collaborate in research of mutual interest may contact the corresponding author for possible access to de-identified individual patient-level data

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MCR drafted the trial protocol, analysed the data, and drafted the manuscript. SMcG, EG, RP and KH finalised the trial protocol, secured ethics approval and funding, recruited patients, collected data, and revised the manuscript for intellectual content. Critical elements of the trial were designed by RD and BH. RC, SM and AA-I prepared the cryopreserved platelets according to a protocol based on procedures developed by LJ and DCM. SMcG and MCR are accountable for all aspects of the work.

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Abstract (250 words, maximum 250 words)

Background and Objectives: Platelets for transfusion have a shelf-life of 7 days, limiting availability and leading to wastage. Cryopreservation at -80°C extends shelf-life to at least one year, but safety and effectiveness are uncertain.
Materials and Methods: This single centre blinded pilot trial enrolled adult cardiac surgery patients who were at high risk of platelet transfusion. If treating clinicians determined platelet transfusion was required, up to three units of either cryopreserved or liquid-stored platelets intraoperatively or during ICU admission were administered. The primary outcome was protocol safety and feasibility.
Results: Over 13 months, 89 patients were randomised, 23 (25.8%) of whom received a platelet transfusion. There were no differences in median blood loss up to 48 hours between study groups, or in the quantities of study platelets or other blood components transfused. The median platelet concentration on the day after surgery was lower in the cryopreserved platelet group ($122 \times 10^3/\mu l$ vs. $157 \times 10^3/\mu l$, median difference $39.5 \times 10^3/\mu l$, p=0.03). There were no differences in any of the recorded safety outcomes, and no adverse events were reported on any patient. Multivariable adjustment for imbalances in baseline patient characteristics did not find study group to be a predictor of 24-hour blood loss, red cell transfusion or a composite bleeding outcome.
Conclusion: This pilot randomised controlled trial demonstrated feasibility of the protocol and adds to accumulating data supporting the safety of this intervention. Given the clear advantage of prolonged shelf-life, particularly for regional hospitals in New Zealand, a definitive non-inferiority phase III trial is warranted.

MeSH Keywords: platelet transfusion; blood transfusion; cryopreservation; cardiac surgical procedures; haemorrhage.

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Introduction

Platelets are essential for haemostasis, providing a mechanical scaffold for blood clot formation and catalysing the generation of thrombin by activation of the coagulation cascade on their phosphatidylserine-rich membrane surface.[1] In New Zealand (NZ), to prolong circulating survival time in recipients, platelets for transfusion are stored in plasma or additive solution at 20-24°C. The disadvantage of 20-24°C storage is possible bacterial growth, limiting shelf-life to 7 days. While most countries discard 10-20% of donated units,[2] in NZ the problem is worse due to a scattered population served by many regional hospitals. In 2019, 29.8% of platelets (>6000 units) were discarded due to expiry, costing NZ$5,260,000 (Charlewood, R., New Zealand Blood Service, 2020, pers comm). Consequently, regional hospitals typically only stock 1-2 platelet units. Patients with life-threatening bleeding can wait many hours for platelets to be delivered from central blood banks, or they do not receive any platelets at all.

Cryopreservation using dimethylsulphoxide (DMSO) extends platelet shelf life to at least one year. Extensive preclinical assessments of cryopreserved platelets have been published.[3, 4] Around 50% of the thawed platelets are functional,[5, 6] but these have a higher capacity to bind factor V and produce more thromboxane A2 after ADP stimulation.[7] Platelet-derived microparticles, more abundant and functionally distinct after cryopreservation, are also haemostatically active.[8] In baboons, cryopreserved platelets had better in vivo survival and function than did liquid platelets stored for five days.[6] Phase I human trials of cryopreserved platelets found lower 24-hr platelet recovery counts in comparison to liquid-stored platelets, but with survival times exceeding US Food and Drug Administration requirements.[9]

Only two phase IIb randomised trials of cryopreserved platelets have been published. In 1999, a single-centre trial randomised 73 cardiac surgery patients to receive cryopreserved or liquid-stored platelets.[10] No adverse effects were observed in the 24 patients who received cryopreserved platelets. Blood loss in the patients who received cryopreserved platelets was significantly less, despite lower post-transfusion platelet increments and a tendency towards decreased platelet

survival. Cryopreserved platelets produced more thromboxane A2 and generated more procoagulant activity in response to stimulation, suggesting the freeze/thaw process 'pre-activated' the platelets. However, the sample size was underpowered to assess safety. More recently, the CLIP pilot trial [11] enrolled 121 patients in four Australian hospitals, 41 of whom were transfused platelets. There were no differences in bleeding or adverse events. The accompanying editorial [12] commented on the urgent need for more research in this field and the Australian investigators are now starting a larger study, CLIP-II (NCT03991481). Differences in production methods for cryopreserved platelets used by the New Zealand Blood Service (NZBS) and Australian Red Cross Lifeblood make a binational study impossible. Therefore, two separate studies will be run - one in Australia (CLIP-II) and one in New Zealand (CLIP-NZ). We present here the results of the CLIP-NZ Pilot study testing the NZ method of producing cryopreserved platelets.

Materials and methods

The Cryopreserved vs. Liquid Platelets – New Zealand pilot study (CLIP-NZ Pilot) was a double-blind, parallel-group, single centre pilot trial conducted in a quaternary cardiothoracic surgical unit performing > 1000 operations per year. The protocol was approved by the Northern Region Health and Disability Ethics Committee (16/NTA/89). Written informed consent was obtained preoperatively. The protocol was identical to that which had been prospectively registered for the Australian CLIP pilot trial (ACTRN12612001261808), other than the method of platelet preparation.

Study platelets Group O low antibody titre (universal donor) *Cryopreserved Platelets Apheresis in Plasma (Leucocyte Depleted)* were prepared by secondary processing of the standard NZBS products *Platelets Apheresis in Plasma Leucocyte Depleted* or *Platelets Apheresis in Additive Solution Leucocyte Depleted*. The component is cryopreserved after routine bacterial testing and within 48 hours of collection using 6% w/v DMSO. Such platelets can be stored at ≤ -80°C for up to 1 year. The platelet unit is manufactured in a storage bag that also contains plasma used for reconstitution, separated from the platelets until after thawing (figure 1). When required for transfusion, the platelet / plasma unit is placed in a 37°C water

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bath until reaching a temperature of 30°C, at which point the plasma is gently mixed with the platelets to disperse any clumps. Reconstituted cryopreserved platelets contain more than 40% of the platelets in the original component, and have a 6-hour shelf-life.[13]

Up to three units of study platelets were transfused, after which open-label platelets were provided for any subsequent orders. Study platelets were covered by an opaque shroud to maintain blinding. This shroud was temporarily removed by a clinician not involved in the care of the patient to facilitate correct patient identification prior to transfusion.

Patients randomised to receive liquid-stored platelets were transfused leucocyte-depleted apheresis or pooled whole-blood derived platelets in either additive solution or plasma, according to the available supply. The hospital blood bank selected the ABO and Rh group according to its standard practice.

Inclusion and exclusion criteria Cardiac surgery patients at high risk of platelet transfusion were identified by application of the TRUST score[14]: preoperative haemoglobin < 13.5 g/dl; female; redo surgery; preoperative creatinine >120 μmol/l; non-elective surgery; > 65 years; weight <77kg; and non-isolated surgery. Patients with ≥3 TRUST criteria have a >65% chance of requiring a red cell transfusion. The incidence of platelet transfusion in cardiac surgery is 44% that of red cell transfusion,[15] so a patient with ≥3/8 TRUST criteria has a 44% x 65% = 29% chance of receiving platelets.

Patients were excluded if they had received a platelet transfusion earlier during that hospital admission; were women of childbearing age (18-55 years)(to avoid the risk of Rhesus immunisation); death was deemed inevitable in <24hrs (as mortality was a study endpoint); had been enrolled previously in this study or in a clinical trial of a medication (with the exception of aspirin) thought to influence bleeding; had a known

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bleeding diathesis (for example, haemophilia or Von Willebrand Disease) associated with abnormal clotting on investigations taken immediately preoperatively (platelets <100 000, INR>1.5, aPTT > 1.5 x upper limit of normal); allergy to DMSO; objected to receipt of human blood products; had intellectual impairment making them unable to consent to surgery; or if their treating clinician believed participation was not in their best interest.

Trial procedures Patients were randomly allocated 1:1 to study groups using computer-generated permuted block randomisation. Indication for platelet transfusion was not protocolised, but left to the judgement of clinicians informed by standard laboratory tests, thromboelastography (TEG), clinical assessment of bleeding, and national guidelines.[16] Study platelet transfusion could be commenced either in the operating theatre or at any time during the intensive care unit stay.

All trial patients underwent a lower limb duplex venous ultrasound between 48 – 96 hours after surgery. No other aspect of routine clinical care was affected by the trial.

Adverse events Postoperative care involved continuous 1:1 monitoring by qualified ICU nurses in a critical care environment. Every 2 hours for the first 6 hours after platelet administration the presence or absence of 11 anticipated adverse events (skin flushing, rash, abdominal pain, unexplained marked agitation or somnolence, oliguria, 2nd or 3rd degree heart block, systemic vasoconstriction (systemic vascular resistance index >2500 dyne s/cm^5/m^2), hypertension (MAP>100), or sinus tachycardia or bradycardia (HR>120 bpm or <55bpm)) was recorded. As many of these perturbations are common after cardiac surgery, the treating physician was required to judge whether each was an expected effect of the patient's condition or "unexplained" and consequently a possible effect of the platelet transfusion. Possible adverse events to be recorded at any time included venous thromboembolic disease and arterial occlusion. Several other markers of postoperative morbidity were compared between groups (table 6).

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Statistics The primary outcome of this pilot study was the safety and feasibility of the trial protocol, and clinician acceptability assessed by recruitment rate and protocol compliance. Secondary endpoints, assessed for possible use as the primary endpoint to determine the sample size and power in a subsequent phase III trial, included volume of blood in the surgical drains from the time of ICU admission and requirement for postoperative blood component transfusion. Accordingly, no sample size calculation was performed. Rather, it was determined that recruiting 20 patients who were ultimately transfused study platelets would provide sufficient evidence of feasibility.

Data analysis: Categorical outcomes were compared using χ^2 or Fisher exact tests as appropriate, with mean differences in proportions along with the 95% confidence interval (95%CI) of these differences presented. Continuous outcomes were similarly expressed as medians, with the median of differences between individuals in the two groups (and their 95% CI) calculated using the Hodges Lehmann estimate, and compared using Mann-Whitney U tests. To explore the effect of any baseline study group imbalances, multivariable backward stepwise linear and logistic regression modelling using $p<0.1$ for retention of the variables listed in table 1 was undertaken, with 24 hour blood loss, units of red blood cells (RBC) transfused and the Bleeding Academic Research Consortium (BARC) composite bleeding endpoint [17] as outcomes. In all cases, a 2-sided p value of <0.05 was considered significant. No adjustments were made for multiple comparisons. As there were <5% missing data for all reported outcomes, no imputation has been made. Analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas, USA).

Results

Protocol feasibility and acceptability to clinicians All 9 cardiac surgeons in our hospital agreed to patient randomisation. Between 26 June 2018 and 05 August 2019, 89 patients were randomised, of whom 23 (25.8%) underwent surgery and were transfused platelets (figure 2). All 9 surgeons had at least one patient

transfused study platelets. No patients were lost to follow-up. Between-group baseline imbalances were seen in sex, weight and incidence of diabetes (table 1). Intraoperative complexity was equivalent (table S1).

One patient randomised to liquid-stored platelets was transfused one unit of open-label (liquid stored) platelets before subsequently receiving 3 units of study platelets. This patient was retained in the intention-to-treat analysis as part of the liquid-stored platelet group.

All study platelets that were ordered from the hospital blood bank were transfused; no thawed units were wasted because they exceeded their 6-hour post-thaw shelf-life.

Blood loss There were no differences in the median intra- or postoperative blood loss between study groups up to 48 hours (Figure 3 and Table S2). Only one patient returned to the operating theatre to manage bleeding at any time in the first three postoperative days. The Bleeding Academic Research Consortium (BARC) [17] "significant" bleeding outcome was present in a numerically greater proportion of patients in the cryopreserved platelet group, but this difference did not reach statistical significance. Clinicians often only commence postoperative anticoagulation and anti-platelet agents once confident bleeding has settled; hence this can be a surrogate for haemostasis. There was no between-group difference in when these medications were commenced.

Transfusion requirement Tables 2 and S3 compare the transfusion requirements in the two study groups. There were no significant differences in the quantities of blood components transfused. The platelet concentration on the day after surgery was lower in the cryopreserved platelet group (table 3). No other between-group laboratory indices differences were seen on day 1.

Adverse events There were no between-group differences in any of the safety outcomes (tables 4 and S4). None of the 11 prospectively-sought adverse events were recorded in any patient. Two patients in the cryopreserved platelet group, but none in the liquid-stored group, had died by 28-days postoperatively. The causes of

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death were not related to any known adverse effect of cryopreserved platelets. There were no pro-thrombotic arterial or venous complications, including acute myocardial infarction, in either study group. No adverse events were reported to the DSMC.

Coagulation indices Changes in TEG indices were measured in 10 patients in the cryopreserved platelet and 9 patients in the liquid-stored group (table S5), comparing values measured before study platelets were administered with those recorded after the last unit of study platelets that was transfused, however many were required. On average, platelet transfusion shortened R time and K time to a similar extent in both study groups. These parameters are not typically affected by platelet transfusion and it is possible that other blood components being transfused simultaneously might have been responsible. The alpha angle and MA also increased similarly in both groups after platelet transfusion, suggesting more rapid formation of more stable clot (characteristic of platelet function). There was minimal evidence of thrombolysis in either group.

Adjustment for baseline imbalances between groups Multivariable regression modelling found, for 24 hour blood loss, significant ($p<0.05$) predictors of higher blood loss were being blood group B (while group O predicted less blood loss), having been an inpatient prior to surgery, female sex and certain indications for surgery (aortic valve or mitral/tricuspid valve surgery). Urgent surgery, premorbid congestive heart failure, and congestive heart failure as the indication for surgery predicted lower blood loss. Study group allocation did not predict blood loss at 24hrs when adjusted for these factors. Significant predictors of units of RBC transfused were having been an inpatient >24 hours prior to surgery, weight (as a continuous variable) and premorbid chronic lung disease. Congestive heart failure or stable angina as the indication for surgery predicted less RBC transfusion, as did urgent surgery. Study group was not a significant predictor of units of RBC transfused when adjusted for these factors. For BARC bleeding, no significant predictors were identified in multivariable regression.

Discussion

This pilot randomised controlled trial enrolled an insufficient number of patients to be sure of anything other than its intended primary outcome. By randomising 89 high-

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risk patients at a single hospital over 13 months, of whom 23 (25.8%) received platelet transfusions, the overall acceptability of the protocol to participating clinicians was demonstrated. The single patient transfused a unit of open-label platelets prior to study platelets suggests that clinicians might occasionally believe it is not in a patient's interest to wait the slightly longer time for cryopreserved platelets to be thawed. There were no safety concerns identified either in adverse event reporting during the study, or in quantitative comparisons of study safety outcomes after trial completion. The recruitment rate suggests a phase III trial of an appropriate design would be feasible.

As expected in a study of this size, there were several potentially important baseline imbalances between study groups that might account for trends in differences (or lack thereof) in study outcomes. While multivariable adjustment for these imbalances did not alter the study conclusions, patient numbers are small. Consequently there is a high likelihood that failure to observe significant between-group differences is a type II error. We did not adjust for the possible independent effect of "surgeon" on study outcomes, as this data was omitted from our case report form. However, this is a potentially important outcome predictor that will be important to understand in any subsequent definitive trial. One between-group difference also observed in previous studies [10, 11, 18, 19] is worthy of comment. Patients randomised to cryopreserved platelets had lower platelet count on the first postoperative day. The mechanism of this effect is thought to be the more rapid uptake from the circulation of cryopreserved platelets due to their 'pre-activated' phenotype. In the Australian study, patients randomised to cryopreserved platelets received a greater number of study platelet units. This was possibly explained by clinicians transfusing to a target platelet count (rather than haemostasis endpoints), less effectively achieved with cryopreserved platelets. We did not observe the same effect in the CLIP-NZ Pilot trial, but the numerical trend was in the same direction.

There were several differences between this NZ trial and the Australian study.[11] Fewer patients had medical co-morbidities (total number of recorded comorbidities 11 in 23 patients vs. 54 in 41 patients, p=0.02); more than twice the proportion of

patients (65% vs. 29%, p=0.005) underwent 'urgent' surgery; and a higher proportion of NZ patients (78% vs. 51%, p=0.03) had received aspirin. Slightly over half (57%) NZ patients received their first platelet transfusion in the operating theatre, fewer than in Australia (80%)(p=0.04). These differences reflect the importance of conducting a separate study in NZ, as many of these factors might interact with the safety or effectiveness of cryopreserved platelets.

The extended shelf-life of cryopreserved platelets suggests demonstrating non-inferiority in both safety and effectiveness would be sufficient to change practice. Based on the results of this pilot study, candidate non-inferiority primary outcomes would include blood loss in drains at 24 hours (we observed very little additional bleeding beyond this time point), the BARC composite bleeding endpoint, and the total number of red cell units transfused (noting almost all patients were transfused red cells). Both this study and the Australian CLIP pilot trial found adverse events were either very uncommon or did not occur. A trial would need to be impractically large to have enough power to be sufficiently sure that there were no differences in outcomes that occur very rarely.

Despite its small size, our study has several strengths. Unlike the largest phase IIb trial of cryopreserved platelets,[10] which excluded 11 patients post randomisation for arguably invalid reasons (2 because their cause of death was judged "unrelated" to the transfusion, 3 because they received ε-aminocaproic acid, which was prohibited in the trial, and 6 because their bleeding was judged to have a "surgical" cause), we analysed all randomised patients. We also actively sought and reported all adverse events that might be anticipated based on preclinical knowledge. All patients were screened for leg deep venous thrombosis, and all patients were continuously monitored for possible myocardial ischaemia. As the pilot study for a phase III pragmatic effectiveness trial, we did not protocolise any aspect of patient care, instead allowing physicians to decide when to transfuse platelets and other blood components, and all other aspects of perioperative care.

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The major limitation of our pilot trial is its small size. No conclusion can be drawn from the lack of between-group differences observed. While we identified no safety concerns with cryopreserved platelets, absence of evidence is not equivalent to evidence of safety. Nonetheless, our results enlarge the body of trial evidence in support of safety: no trial [9-11, 18-20] or observational series [5] has found evidence of coronary graft occlusion, myocardial ischaemia, venous thrombosis, infection, respiratory complications or any other hypothesised adverse effect of cryopreserved platelets. Clinicians in our trial were blinded using an opaque shroud that could be removed easily. We would have preferred to relabel study platelets, but regulatory requirements prevented this. The opaque shroud method has been used successfully in a 5000-patient trial of red cell storage duration,[21] and was used in the Australian CLIP study.[11] The dose of platelets in one unit received by each trial group might not have been comparable. Cryopreserved platelets prepared by the NZBS contain “>40% of the pre-freeze platelet content” of a unit of apheresis platelets.[13] Patients in the liquid-stored group received either whole blood-derived platelets or apheresis platelets, which both contain “a minimum platelet content of 2.4×10^{11} per pooled unit”.[22] This difference in platelet count might explain the differences in day 1 platelet concentrations observed. Finally, transfusion of a unit of cryopreserved platelets was accompanied by the mandatory transfusion of plasma (109 mL) in which the platelets were resuspended. The trial could therefore be a comparison of platelets plus plasma vs. platelets alone. This is a feature of the study that must be understood rather than dismissed. In most counties, cryopreserved platelets are resuspended in plasma. It would be incorrect to attempt to separate the independent effects of the plasma from the platelets in any clinical effectiveness trial. Similarly, the time taken to thaw the plasma means a cryopreserved platelet unit takes approximately 25 minutes longer to prepare than a liquid-stored unit. It would be incorrect to attempt to separate the independent effect of this delay from the therapeutic efficacy of the cryopreserved platelet unit. Nonetheless, quantifying this delay is important. This has not been possible in this pilot study as the time platelets were requested from the blood bank was not recorded. This additional information should be collected in a subsequent definitive trial.

Conclusion

Given the clear advantage of prolonged shelf-life of cryopreserved platelets, particularly in the dispersed regional hospitals of New Zealand, a definitive phase III trial using a non-inferiority design is warranted.

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References

1 Reddy EC, Rand ML: Procoagulant Phosphatidylserine-Exposing Platelets in vitro and in vivo. Front Cardiovasc Med 2020; 7: 15.

2 Flint AW, McQuilten ZK, Irwin G, Rushford K, Haysom HE, Wood EM: Is Platelet Expiring Out of Date? A Systematic Review. Transfus Med Rev 2020; 34: 42-50.

3 Johnson L, Reade MC, Hyland RA, Tan S, Marks DC: In vitro comparison of cryopreserved and liquid platelets: potential clinical implications. Transfusion 2015; 55: 838-47.

4 Johnson L, Coorey CP, Marks DC: The hemostatic activity of cryopreserved platelets is mediated by phosphatidylserine-expressing platelets and platelet microparticles. Transfusion 2014; 54: 1917-26.

5 Lelkens CC, Koning JG, de KB, Floot IB, Noorman F: Experiences with frozen blood products in the Netherlands military. Transfus Apher Sci 2006; 34: 289-98.

6 Valeri CR, Giorgio A, MacGregor H, Ragno G: Circulation and distribution of autotransfused fresh, liquid-preserved and cryopreserved baboon platelets. Vox Sang 2002; 83: 347-51.

7 Valeri CR, MacGregor H, Ragno G: Correlation between in vitro aggregation and thromboxane A2 production in fresh, liquid-preserved, and cryopreserved human platelets: effect of agonists, pH, and plasma and saline resuspension. Transfusion 2005; 45: 596-603.

8 Johnson L, Raynel S, Seghatchian J, Marks DC: Platelet microparticles in cryopreserved platelets: Potential mediators of haemostasis. Transfus Apher Sci 2015; 53: 146-52.

9 Dumont LJ, Cancelas JA, Dumont DF, Siegel AH, Szczepiorkowski ZM, Rugg N*, et al.*: A randomized controlled trial evaluating recovery and survival of 6% dimethyl sulfoxide-frozen autologous platelets in healthy volunteers. Transfusion 2013; 53: 128-37.

10 Khuri SF, Healey N, MacGregor H, Barnard MR, Szymanski IO, Birjiniuk V*, et al.*: Comparison of the effects of transfusions of cryopreserved and liquid-preserved platelets on hemostasis and blood loss after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1999; 117: 172-83.

11 Reade MC, Marks DC, Bellomo R, Deans R, Faulke DJ, Fraser JF*, et al.*: A randomized, controlled pilot clinical trial of cryopreserved platelets for perioperative surgical bleeding: the CLIP-I trial (Editorial, p. 2759). Transfusion 2019; 59: 2794-804.

12 Cohn CS, Williams S: Cryopreserved platelets: the thaw begins ... (Article, p. 2794). Transfusion 2019; 59: 2759-62.

13 NZBS BLOOD COMPONENT MONOGRAPH: Platelets Apheresis in Plasma Leucocyte Depleted Cryopreserved; Auckland, New Zealand. New Zealand Bloor Service, 2021.

14 Alghamdi AA, Davis A, Brister S, Corey P, Logan A: Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. Transfusion 2006; 46: 1120-9.

15 Weightman WM, Gibbs NM, Weidmann CR, Newman MA, Grey DE, Sheminant MR*, et al.*: The effect of preoperative aspirin-free interval on red blood cell transfusion requirements in cardiac surgical patients. J Cardiothorac Vasc Anesth 2002; 16: 54-8.

16 *Patient Blood Management Guidelines Module 2 - Perioperative*. Canberra, ACT, Australia: National Blood Authority; 2012.

17 Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J*, et al.*: Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123: 2736-47.

18 Bohoněk M, Kutáč D, Landová L, Kořánová M, Sládková E, Stašková E*, et al.*: Kryokonzervované trombocyty v klinické praxi: srovnávací studie s nativními trombocyty. Transfuze Hematol 2016; 22: 268-78.

19 Bohonek M, Kutac D, Landova L, Koranova M, Sladkova E, Staskova E*, et al.*: The use of cryopreserved platelets in the treatment of polytraumatic patients and patients with massive bleeding. Transfusion 2019; 59: 1474-8.

20 Slichter SJ, Dumont LJ, Cancelas JA, Jones M, Gernsheimer TB, Szczepiorkowski ZM*, et al.*: Safety and efficacy of cryopreserved platelets in bleeding patients with thrombocytopenia. Transfusion 2018; 58: 2129-38.
21 Cooper DJ, McQuilten ZK, Nichol A, Ady B, Aubron C, Bailey M*, et al.*: Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults. N Engl J Med 2017; 377: 1858-67.
22 Platelet components. Auckland, New Zealand, New Zealand Blood Service. https://www.nzblood.co.nz/clinical-information/transfusion-medicine/health-professionals-medicine-datasheets/platelet-components/ (Last accessed 2021).

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Tables

Table 1. Baseline characteristics

	Cryopreserved (n=10)	Liquid (n=13)
Sex, male	9 (90)	5 (38.5)
Age, years, median (IQR)	69 (59-77)	73 (64-77)
Blood group		
O	3 (30)	7 (54)
A	6 (60)	4 (31)
B	1 (10)	2 (15)
AB	0 (0)	0 (0)
Rhesus D positive	8 (80)	10 (77)
Weight, kilograms, median (IQR)	82 (72-93)	72 (63-78)
Comorbidity		
Previous myocardial infarction	0 (0)	1 (8)
Congestive heart failure	2 (20)	1 (8)
Chronic lung disease	2 (20)	1 (8)
Chronic renal impairment	1 (10)	0 (0)
Diabetes	4 (40)	1 (8)
Main indication for surgery		
Aortic valve	4 (40)	6 (47)
Congestive heart failure	1 (10)	1 (8)
Endocarditis	1 (10)	0 (0)
Mitral / Tricuspid disease	1 (10)	4 (31)
Stable angina	2 (20)	1 (8)
Aortic root replacement	1 (10)	1 (8)
Surgery included coronary artery bypass grafts	7 (70)	6 (47)
Inpatient for >24hrs prior to surgery	7 (70)	6 (46)
Urgent surgery	7 (70)	8 (62)

Aspirin given within 7 days of surgery	7 (70)	11 (85)

Data are expressed as number (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range.

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Table 2. Efficacy outcomes: transfusion and haemostasis interventions required

	Cryopreserved (n=10)	Liquid (n=13)	Median of differences between groups (95% CI)	p
Patients transfused RBC at any stage	8 (80)	12 (92)	-12% (-41% – 16%)	0.38
Number of RBC units transfused total, median (IQR)	2 (1-7)	1 (1-3)	0.5 (-1 – 5)	0.47
Patients transfused FFP at any stage	6 (60)	8 (62)	2 (-42 – 39)	0.94
Number of FFP units transfused total, median (IQR)	2 (0-4)	2 (0-3)	0 (-2-2)	0.95
Patients transfused cryoprecipitate at any stage	4 (40)	4 (31)	9 (-30 – 49)	0.65
Number of cryoprecipitate units transfused total, median (IQR)	0 (0-5)	0 (0-2)	0 (0 – 2)	0.40
Patients transfused study platelet units				
1 unit	4 (40)	8 (62)		
2 units	4 (40)	4 (31)		
3 units	2 (20)	1 (8)		
Median number of study platelet units (IQR)	2 (1-2)	1 (1-2)	0 (0 – 1)	0.27

Data are expressed as number (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range.

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Table 3. Efficacy outcomes: laboratory indices

	Cryopreserved (n=10)	Liquid (n=13)	Median of differences between groups (95% CI)	p
Platelet concentration day 1, x10^3/μl, median (IQR)	122 (92-154)	157 (140-178)	-40 (-73 – 3)	0.03
Haemoglobin concentration day 1, g/dL, median (IQR)	86 (79-101)	91 (82-100)	-3 (-14 – 12)	0.75
INR day 1, median (IQR)	1 (1-1)	1 (1 – 1)	0 (0 – 0)	0.36
APTT day 1, median (IQR)	37 (35-45)	35 (33-39)	2 (-4 – 9)	0.49
Fibrinogen day 1, g/L, median (IQR)	2 (2 – 3)	2 (2-3)	0 (-0-1)	0.83

Abbreviations: INR, international normalised ratio; APTT, activated partial thromboplastin time

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Table 4. Safety outcomes

	Cryopreserved (n=10)	Liquid (n=13)	Median of differences between groups (95% CI)	p
PaO_2/FiO_2 ratio 3hrs post transfusion, median (IQR)	284 (152-324)	280 (257-325)	-17 (-154 – 65)	0.73
Wound infection	0 (0)	0 (0)	0% (0%-0%)	-
Systemic infection	0 (0)	0 (0)	0% (0%-0%)	-
Deep venous thrombosis	0 (0)	1 (8)	8% (-22%-7%)	0.37
Acute myocardial infarction postoperatively	0 (0)	0 (0)	0% (0%-0%)	-
Hospital length of stay, days, median (IQR)	9 (7-12)	12 (8-19)	-4 (-10 – 0)	0.07
28-day mortality, died	2 (20)	0 (0)	20% (-5% – 45%)	0.09

Data are expressed as number (%) unless otherwise indicated.

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Figure Legends

Figure 1. Cryopreserved platelet and plasma unit prior to reconstitution.

Figure 2. Patient flow diagram

Figure 3. Blood loss through chest drains in the 48 hours after ICU admission.

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