REVIEW

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Continuous postoperative pericardial flushing to reduce the risk of postoperative bleeding after elective adult cardiac surgery – a studylevel meta-analysis

Shubham N. Jain^{1*}, Hiral S. Jhala^{1*}, Mohsin Uzzaman² and Keith G. Buchan¹

Abstract

Background Retained blood syndrome contributes to higher morbidity and mortality post cardiac surgery. We investigate the benefits of continuous postoperative pericardial flushing (CPPF) over standard care chest drainage in elective adult cardiac surgery patients.

Methods Various online databases were screened for randomised controlled trials (RCTs) and observations studies comparing CPPF to standard care. Primary outcomes: 12-hour and total blood loss, cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times; surgical re-intervention for bleeding, mortality, sternal wound infections and pericardial or pleural fluid re-accumulation at discharge. Secondary outcomes: perioperative blood transfusion, time to extubation and total hospital stay.

Results 586 patients from four studies with matched characteristics were included. CPPF was associated with less blood loss at 12 h and in total: Odds Ratio (OR) (95% CI) 0.71 (-0.91 to 0.51) and 0.49 (-0.67 to -0.32) (both p < 0.00001). CPPF had lower need for transfusion of blood products RR 0.57 (0.36–0.89) (p=0.01)). There were no significant differences in surgical re-intervention rates, overall mortality, CPB, ACC times, length of hospital stay, time until extubation or sternal wound infections. Risk of pericardial or pleural fluid re-accumulation was lower in the CPPF groups RR 0.88 (0.80–0.97) (p=0.01).

Conclusions CPPF has shown promising results in reducing postoperative blood loss and fluid re-accumulation with fewer blood transfusions, and lower surgical re-intervention rates across all ranges of cardiac surgical procedures. It is safe, feasible and effective in all types of cardiac surgery, however further studies are needed to validate these findings.

Keywords Continuous postoperative pericardial Flushing, Pericardial drainage, Mediastinal chest drain

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Introduction

Postoperative bleeding and "retained blood syndrome" in cardiac surgery is a common complication associated with prolonged intensive care unit (ICU) and total hospital stays, higher costs of hospitalization, and higher mortality. It is due to a spectrum of inflammatory and mechanical responses that occur secondary to the failure of the postoperative drainage systems used to adequately evacuate postoperative blood in the pericardium [1, 2].

The conventional method of draining the posterior pericardial and anterior mediastinal spaces postoperatively, consists of chest tubes connected to low-pressure suction systems to aid evacuation of pericardial clots and blood. However, this intermittent drainage system can fail, due to obstruction with clots and blood status, leading to retention of clots in the pericardial space with consequent cardiac tamponade [3, 4]. The presence of blood or clots in the pericardial cavity leads to increased fibrinolytic activity and therefore more bleeding is precipitated.

Warm saline irrigation of the pericardial cavity and evacuation of clots, is routinely performed during reexplorations and can stop bleeding with immediate effect [5]. Hence, continuous postoperative pericardial flushing (CPPF) has emerged as an alternative to standard conventional chest drainage to prevent formation of large clots and chest tube blockage [6].

Whilst CPPF has shown a reduction in postoperative bleeding and its associated inflammatory complications [7, 8], the rationale for adopting CPPF as the new standard of care is not completely clear. In this study-level meta-analysis we present our analysis of outcomes following standard conventional chest tube drainage or CPPF post cardiac surgery.

Methods

This review adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Furthermore, it has been registered on PROSPERO under the registration number CRD42023442025.

Studies published in or translated to the English language from their inception until July 20, 2023, were included in the search. The initial criteria for inclusion involved randomized controlled trials (RCTs) and observational studies that compared CPPF to standard care, for elective adult cardiac surgical patients. Systematic reviews were excluded from the primary analysis, but primary studies included within these systematic reviews were considered for inclusion if they met the predefined inclusion criteria. Only studies focusing on adult cardiopulmonary bypass cardiac surgical patients who were planned for elective interventions, were eligible for inclusion in this review. The primary outcomes of interest encompassed blood loss at 12 h post-operatively; total actual blood loss after surgery; overall mortality; and specific complications: surgical re-intervention for bleeding deep or superficial sternal wound infections and accumulation of pleural or pericardial fluid at discharge.

Secondary perioperative outcomes included the cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times, requirement for transfusion of blood products (packed red blood cell (RBCs) and fresh frozen plasma (FFP)), time to extubation, and length of hospital stay. Supplementary post-operative outcomes included acute kidney injury (AKI) and new atrial fibrillation (AF). It is important to note that all these outcomes were assessed at the endpoint of the respective follow-up periods for the included studies, unless otherwise explicitly specified.

Electronic database searches were carried out in Ovid Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews (CDSR). These searches were conducted by a senior information specialist from the library department of the Royal College of Surgeons of Edinburgh on July 3, 2023. Furthermore, an additional search was undertaken through snowballing, referencing relevant articles. A final review was conducted before concluding the literature search on July 20, 2023.

The primary aim of the study was to assess whether CPPF, in elective adult cardiac surgical patients, confers any benefits over standard care in reducing perioperative CPB and ACC times, postoperative blood loss and complications. To guide our search comprehensively, we employed the Patient-Intervention-Control-Outcome (PICO) framework, as outlined in Supplementary Table 1. Thorough search strategy is depicted in Supplementary Tables 2a-b.

Abstract screening and full text review was performed by two independent blinded reviewers [SJ and MU], with conflict resolution by a third senior reviewer, to generate a final list of eligible studies for inclusion in the metaanalysis. Demographic, clinical and outcome data in both treatment arms from individual studies were extracted by one independent researcher and cross-checked with another independent researcher for adequacy and accuracy.

Observational studies were categorized following the criteria established by Mathes and Pieper [9]. The assessment of the risk of bias in randomized controlled trials (RCTs) utilized the revised Cochrane risk-of-bias tool for RCTs (RoB2 Tool) [10], while the Joanna Briggs Institute (JBI) [11] assessment tool was employed for evaluating observational studies. In the case of the JBI appraisal tool, the overall risk of bias for a specific study was determined by the number of questions answered with "yes," "no," or "unclear." Studies were considered to have a low concern

of bias if there was an unfavourable answer to one question or fewer, a moderate concern if there were unfavourable answers to 2 to 3 questions, and a high concern if 4 or more questions received unfavourable answers.

Statistical analysis

Categorical variables were expressed using counts, percentages, and ratios, while continuous data were represented as mean (standard deviation (SD)), as indicated in each individual study. For data initially presented as Median (Inter-Quartile Range (IQR)), a conversion to Mean (SD) was performed, following the formula published by Wan et al. in 2014 [12].

Meta-analysis for categorical variables, such as mortality, surgical site infections, blood products transfusions, surgical re-interventions for bleeding-related complications, fluid accumulation at discharge was conducted using risk ratios (RR) and 95% confidence intervals (CI). Continuous variables, such as CPB and ACC times, postoperative blood loss at 12 h and in total, time to extubation and total length of hospital stay, were represented using standard mean difference (SMD) and 95% CI.

The meta-analysis was carried out employing Review Manager (RevMan) software (version 5.4). Heterogeneity was assessed using I² tests, with significant heterogeneity defined as I² > 50%. In cases of significant heterogeneity, the Mantel–Haenszel (M – H) random-effects model was employed [13].

Handling of confounding factors

Patients and disease characteristics were highlighted and compared in CPFF and standard care comparisons.

Operational definitions

CPPF: Continuous Postoperative Pericardial Flushing – An additional infusion tube inserted into the pericardial space connected to the CPPF connecting line through a volumetric pump and a fluid heating device to deliver 500mL/hour fluid up to a total of 7000mL over a period of 8 h.

Standard Care: Standard chest tube insertions into the pericardial and pleural spaces.

Results

Studies characteristics

Study selection process is demonstrated on the PRISMA diagram (Figure. 1). 937 records were identified on the initial search after excluding duplicates. Out of 25 studies that were eligible for full text review, 13 studies were excluded for either not fulfilling the study question criteria or no comparison performed, five were excluded for incorrect study intervention, two for interventions on paediatric patients and one for incorrect publication type to produce a final list of four studies [6, 8, 14, 15].

Two were randomized controlled trials (RCTs) [8, 14] and two observational studies [6, 15]. All included studies had a homogenous adult population undergoing elective cardiac surgery. However, the control groups in all studies varied with regards to the number and position of chest drains placed postoperatively according to local preference. The included study characteristics are demonstrated in Table 1.

Risk of bias and quality assessment

Risk of bias assessment for RCTs using the RoB2 tool (Supplementary Table 3) showed high concerns [8, 14] and both observational studies using JBI tool (Supplementary Table 4) showed moderate concerns for bias [6, 15].

Patient and disease characteristics

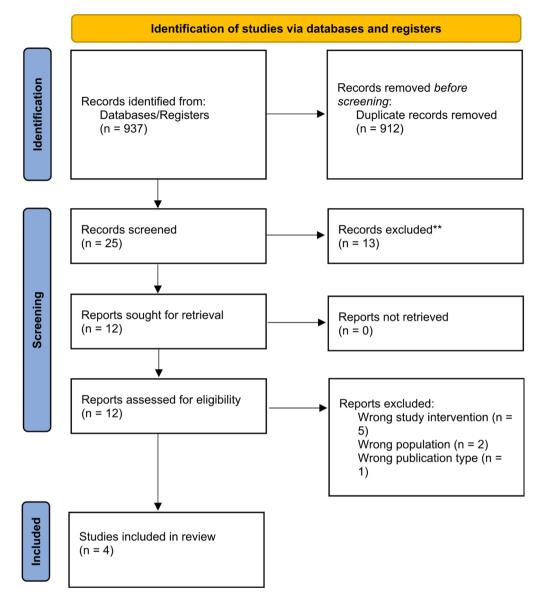
A total of 226 and 360 patients were included in the CPPF and standard care groups respectively. The mean ages of the included populations in the studies were comparable (SMD 0.18; 95%CI (0.00 to 0.35); p-value 0.05). The proportion of male patients in the included studies were comparable in both treatment groups (RR 1.02; 95%CI (0.91 to 1.13); p-value 0.78) with a higher proportion of affected males in all the studies as compared to females. Additionally, the mean body mass index (BMI) values of the patient population was higher in the CPPF treatment group (SMD 0.20; 95%CI (0.02 to 0.37); p-value 0.03).

All studies categorised the echocardiographic left ventricular ejection fraction (LVEF) into > 50%, 30–50% and < 30%. The two groups were comparable in the patient populations in all four studies, with LVEF > 50% (RR 0.92; 95%CI (0.84 to 1.02); p-value 0.11), LVEF 30–50% (RR 1.39; 95%CI (1.00 to 1.92); p-value 0.05) and LVEF < 30% (RR 0.95; 95%CI (0.28 to 3.27); p-value 0.94).

The preoperative haemoglobin (Hb) levels were analysed with random effects model due to a minimal nonsignificant statistical heterogeneity and was found to be statistically significantly lower in the CPPF group (SMD -0.27; 95%CI (-0.52 to -0.01); p-value 0.04). The EUROScore II values were also comparable in both groups (SMD -0.01; 95%CI (-0.20 to 0.19); p-value 0.94). There was equivalence between the groups in all four studies with regards to the preoperative use of anti-platelets or/ anticoagulants (RR 1.03; 95%CI (0.93 to 1.14); p-value 0.59). Patient characteristics are demonstrated in Table 2. Forest plots and funnel plots comparing baseline patient characteristics can be found in Supplementary Figs. 1 and 2 respectively.

Outcomes

Overall assessment of the outcomes measured, favoured CPPF across all studies.





Primary outcomes

Postoperative blood loss

At 12 h: Three of the studies included in the meta-analysis reported on blood loss at 12 h postoperatively [6, 8, 14]. Pooled analysis showed significantly less blood loss in the CPPF group (SMD – 0.71; 95%CI (-0.91 to -0.51); p-value < 0.00001) (Fig. 2a). The blood loss at 12 h after the surgery was < 200mL in the CPPF group in both the studies by Diephuis et al. [8, 14], however, the study by Manshanden et al. showed a higher blood loss in the CPPF group around 376mL on an average almost double that of the other two studies [6]. The blood loss in all the three studies in the standard care groups were comparable. *Total mean actual blood loss*: All four studies measured and reported on the total mean actual blood loss in

both the groups at the time of drain removal [6, 8, 14, 15]. The pooled analysis again showed that the overall blood loss was lower with CPPF (SMD -0.49; 95%CI (-0.67 to -0.32); p-value < 0.00001) (Fig. 2b). The total mean actual blood loss in all studies in the CPPF group was ~ 60–75%.

Postoperative complications

Surgical re-intervention for bleeding The need for surgical re-intervention was proportionally lower in the CPPF group (3.98%) compared to standard care (8.61%) favouring CPPF. However, it was not found to be statistically significant (RR 0.52; 95%CI (0.24 to 1.12); p-value 0.10) (Fig. 3a). The latest study published on CPPF by Diephuis et al. 2020 showed a significant reduction in the need for a surgical re-intervention [14].

Study	Diephuis et al. Nov-2020	Diephuis et al. Mar-2020	Kara and Erden Jul-2019	Manshanden et al. Jul-2015
Study type	RCT	RCT	Prospective	Prospective
Inclusion criteria	Age > 18 years, Elective Cardiac Surgery, Willingness to participate in the study	the study		
Exclusion criteria	previous CABG, emergency surgery and preoperative use of one of the oral anticoagulants; aged < 18 years; inability to understand	emergent surgery, age <18 years, inability to understand study informa-	ventricular assist device use, pregnancy, malignancy, a hema-	emergency surgery, a history of bleeding diathesis or coagulopathy,
	study information, or participation in any study involving an investi- gational drug or device	tion and/or give informed consent, or participation in any study involving an	tologic or autoimmune disease, renal insufficiency, impaired	participation in any study involving an investigational drug or device,
		investigational drug or device.	liver function, additional cardiac surgery, anticoagulant use in the last 5 days, pericardial or pleural adhesions, and history of cardiac	and the inability to understand the study information or give informed consent
			surgery	
Comparisons	CPPF v/s Standard Care			
Total population	169	170	100	147
Power of the study	95%	95%	80%	
Study Period	January 2014 – March 2017	May 2013 – Feb 2016	February 2017 – December 2017	November 2011 – April 2012 (CPPF) January 2010 – December 2011 (Standard Care)
Follow-up period 6 months	d 6 months	6 months		2.9+/-0.1 years (CPPF) 4.1+/-1.0 years (Standard Care)
Withdrawals	11 patients due to not receiving allocated treatment in the group	4 patients. 1 due to need for emer- gency coronary angioplasty and 3 due to accumulation of > 200mL of infusion fluid and hence treatment stopped.		
Outcomes	CPPF may be an effective method to reduce postoperative blood loss after cardiac surgery. Real time hematocrit analysis of MCTD	CPPF is a safe and effective method to reduce blood loss and maintain chest	CPPF after coronary artery bypass grafting surgery is safe, effective,	CPPF after cardiac surgery was found to be safe and feasible in this
	will become essential to overcome the problem of maccurate measurement of blood loss, which is necessary for clinical decision making and implementation of CPPF in a clinical setting.	iube patency aiter cardiac surgery.	reasible, and acceptable.	experimental setting.

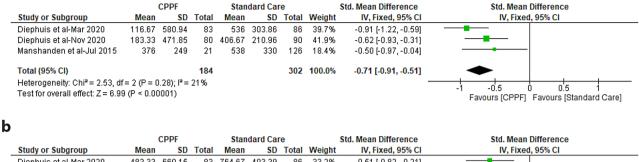
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Study	Population	ion	Age (mean +/- SD)	n +/- SD)	Male Gen-	en-	BMI (kg/m ²)	/m ²)	LVEF						Preoperative Hb	tive Hb	EUROScore2	core2	Antip	Antiplatelet
					der (%)				> 50%		30-50%	%	< 30%		levels				/ Anticoag ulant use	' Anticoag- ulant use
	CPPF Stan- CPPF dard Care	Stan- dard Care	CPPF	Standard Care	СРРЕ	Stan- dard Care	СРРF	Stan- dard Care	CPPF	Stan- dard Care	CPPF	Stan- dard Care	СРРЕ	Stan- dard Care	CPPF	Stan- dard Care	СРРF	Stan- dard Care	СРРF	Stan- dard Care
Diephuis et al. Nov-2020 80			69 +/- 5 68 +/- 6	68 +/- 6	54		27	27 +/- 2	67	74	13	15	0		8.7	9 +/- 0.9 1.41 +/- 1.47	1.41+/-	1.47	35	43
Diephuis et al. Mar-2020	8 83 8	86	55 +/- 15 7	53.7 +/- 173	68	75	+/-	26.7 +/- 4 4	59	64	23	19	.	2	c.u - /+ 8.7 +/- 1	8.8 +/- 0 0	1.04 1.77 +/-143	1.04 +/-1.00 1.77 1.73 +/-1.43 +/-1.43	81	83
Kara and Erden Jul-2019 42		28	-/, - <u>1</u> 67.02 +/- 8.93	64.28 +/- 9.01	34	39	-/, 3 27.69 +/-4.15		28	48	12	6	5	-	13.09 +/- 2.03	13.43 +/- 1.74		р - -	31	43
Manshanden et al. Jul-2015	21 1	126	43.8 +/- 13.6	40.5 +/- 15	11	73	27.5 +/- 7	24.3 +/- 4.6	4	106	7	18	0	5	8.8 +/- 0.7	8.9 +/- 0.9	2.9 +/-2.97	2.9 2.84 +/-2.97 +/-2.63	10	34

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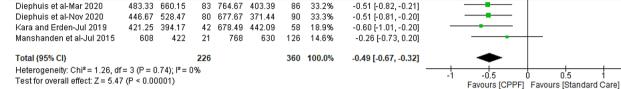


Fig. 2 a: Postoperative blood loss at 12 h b: Total mean actual postoperative blood loss

Overall mortality It was seen that there were only two deaths in the CPPF group out of 226 patients compared to eleven deaths out of 360 patients in the standard care group. However, on pooled analysis it was found that the difference was not statistically different (RR 0.63; 95%CI (0.15 to 2.54); p-value 0.51) (Fig. 3b). No deaths were reported by Diephuis et al. in March 2020 [8], however, there were four deaths reported with two in each group in the study published later in November 2020 by the same author.

Sternal wound infection No statistical difference was found in the rate of sternal wound infections overall between the two groups (RR 1.22; 95%CI (0.57 to 2.62); p-value 0.61) (Fig. 3c). However, there has been an increasing trend noted in the CPPF group [8, 14] compared to a stable rate in the standard care groups.

Pericardial or pleural fluid accumulation at discharge There was a significantly lower incidence of post-operative pericardial and pleural effusions noted with CPPF (n = 142/226) compared to standard care (*n* = 269/360) (RR 0.88; 95%CI (0.80 to 0.97); p-value 0.01) (Fig. 3d). The rates of fluid accumulation reported by Kara and Erden in July 2019 are remarkably low in both the CPPF (n = 2/42) and standard care groups (n = 3/58) which can potentially be explained because of the active drainage of any fluid in these cavities in this study before the removal of chest drains to reduce the incidence of accumulation [15].

Secondary outcomes

CPB and ACC times The CPB and ACC times were shown to be equivalent in all four studies in both the groups with a pooled analysis result showing no statistical difference (SMD 0.06; 95%CI (-0.12 to 0.23); p-value 0.52) [6, 8, 14, 15] & (SMD 0.09; 95%CI (-0.08 to 0.27); p-value 0.30) respectively (Fig. 4). However, the study by Manshanden et al. 2015 showed non-significant albeit higher times in the standard care group for both parameters [6].

0.5

Transfusion of blood products There was no significant difference in the number of patients needing postoperative RBC transfusions in all four studies [6, 8, 14, 15] with similar proportions of approximately 26% patients needing a transfusion (RR 0.87; 95%CI (0.66 to 1.15); p-value 0.34) despite a lower preoperative haemoglobin level in the CPPF group (Fig. 5a) Three of the four studies [8, 14, 15] reported on their need for postoperative FFP transfusions which were significantly lower in the CPPF group compared to standard care (RR 0.57; 95%CI (0.36 to 0.89); p-value 0.01) (Fig. 5b). The two RCTs by Diephuis et al. showed a remarkable reduction in the rates in both the groups [8, 14].

Time until extubation Although there was a faster extubation in patients receiving standard care in 2 of the studies [6, 8], there was no statistically significant difference between the two groups on pooled analysis (Fig. 5c) (SMD 0.14; 95%CI (-0.08, 0.35); p-value 0.22).

Total length of hospital stay The total length of hospital stay even though not statistically significant was lower in the CPPF group in at least two [6, 15] out of the three studies that reported it (Fig. 5d) (SMD -0.07; 95%CI (-0.29, 0.14); p-value 0.50) [6, 8, 15].

а		CPP	F	Standard	Care		Risk Ratio	Risk Ratio
•••	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
	Diephuis et al-Mar 2020	4	83	5	86	25.1%	0.83 [0.23, 2.98]	
	Diephuis et al-Nov 2020	2	80	6	90	28.8%	0.38 [0.08, 1.81]	
	Kara and Erden-Jul 2019	2	42	6	58	25.7%	0.46 [0.10, 2.17]	
	Manshanden et al-Jul 2015	1	21	14	126	20.4%	0.43 [0.06, 3.09]	
	Total (95% CI)		226		360	100.0%	0.52 [0.24, 1.12]	
	Total events	9		31				
	Heterogeneity: Chi ² = 0.74, df	= 3 (P = 0).86); l²	= 0%				
	Test for overall effect: Z = 1.67	(P = 0.10))					0.05 0.2 1 5 20 Favours [CPPF] Favours [Standard Care]

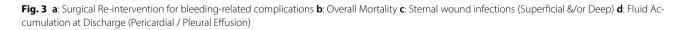
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	CPP	F	Standard	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Diephuis et al-Mar 2020	0	83	0	86		Not estimable	
Diephuis et al-Nov 2020	2	80	2	90	33.3%	1.13 [0.16, 7.80]	_
Kara and Erden-Jul 2019	0	42	1	58	22.4%	0.46 [0.02, 10.96]	
Manshanden et al-Jul 2015	0	21	8	126	44.4%	0.34 [0.02, 5.67]	
Total (95% CI)		226		360	100.0%	0.63 [0.15, 2.54]	
Total events	2		11				
Heterogeneity: Chi ² = 0.57, df:	= 2 (P = 0).75); l²	= 0%				
Test for overall effect: Z = 0.65	(P = 0.51)					0.02 0.1 1 10 50 Favours [CPPF] Favours [Standard Care]

C

	CPP	F	Standard	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Diephuis et al-Mar 2020	3	83	2	86	17.1%	1.55 [0.27, 9.07]	· · · · · · · · · · · · · · · · · · ·
Diephuis et al-Nov 2020	9	80	5	90	40.9%	2.02 [0.71, 5.79]	│
Kara and Erden-Jul 2019	0	42	4	58	33.0%	0.15 [0.01, 2.76]	·
Manshanden et al-Jul 2015	0	21	3	126	9.0%	0.82 [0.04, 15.42]	
Total (95% CI)		226		360	100.0%	1.22 [0.57, 2.62]	-
Total events	12		14				
Heterogeneity: Chi ² = 3.02, df	= 3 (P = 0	0.39); I ^z	= 1 %				
Test for overall effect: Z = 0.5	l (P = 0.61	1)					Favours [CPPF] Favours [Standard Care]

	CPP	F	Standard	Care		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% Cl	
Diephuis et al-Mar 2020	60	83	71	86	38.7%	0.88 [0.74, 1.03]				
Diephuis et al-Nov 2020	63	80	80	90	41.7%	0.89 [0.77, 1.01]				
Kara and Erden-Jul 2019	2	42	3	58	1.4%	0.92 [0.16, 5.27]		-		
Manshanden et al-Jul 2015	17	21	115	126	18.2%	0.89 [0.72, 1.10]			-	
Total (95% CI)		226		360	100.0%	0.88 [0.80, 0.97]		•		
Total events	142		269							
Heterogeneity: Chi ² = 0.02, df	= 3 (P = 1	.00); I ^z	= 0%				_		<u> </u>	<u> </u>
Test for overall effect: Z = 2.53) (P = 0.01)					0.2	0.5 1 Favours [CPPF]	Favours (Stan	dard Care]



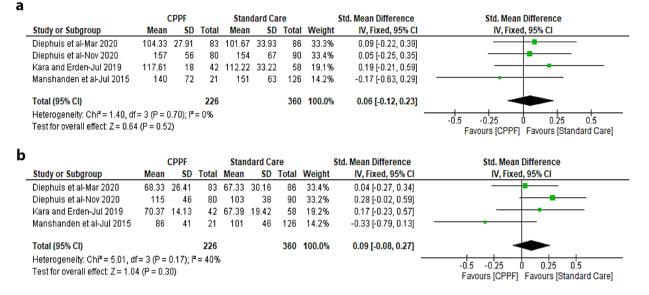


Fig. 4 a: CPB Time b: ACC Time

Discussion

In our meta-analysis, we see comparable demographics and risk scores amongst the CPPF and the conventional care group. The CPPF group had significantly lower rates of post-operative blood loss at 12 h (p-value < 0.00001) and total mean blood loss (p-value < 0.00001), with a reduced rate of surgical re-intervention by 4.7% (p-value 0.10). This is possibly attributable to the higher incidence of anti-platelet and anti-coagulant use in the standard care group compared to the CPPF group, despite having no statistical significance. However, this demonstrates promising results for the safety and feasibility of using CPPF in order to improve bleeding outcomes in the immediate post-operative period.

The post-operative blood loss never exceeded four hundred millilitres in either study, however, Manshanden et al. [6] demonstrated a higher blood loss in both groups compared to the other studies suggesting a role of surgeon dependent haemostasis in the requirement for CPPF vs. standard care chest drainage. Additionally, whether one or both pleural cavities were opened can prolong chest drainage, and the duration of drains in situ could clarify whether clot retention in the pleural cavities could have caused a larger drainage compared to the other studies.

The CPPF group received fewer blood products despite having a lower pre-operative haemoglobin, which could be a result of blood priming rather than crystalloid priming of the cardiopulmonary bypass circuit for these patients to pre-emptively control blood loss [16]. Moreover, surgeons may have opted against using cell-salvage for lower risk cases to prevent impaired coagulation as a result of residual heparin which would necessitate postoperative blood product usage [17].

Moreover, point of care testing of active clotting time (ACT) for heparin reversal [18], thromboelastography (TEG) [19] and intra-operative rotational thromboelastometry (ROTEM) [20, 21], can independently predict high blood loss and guide reversal of coagulopathy post cardiac surgery, and perhaps additional doses of protamine and platelets were administered but not included in the final analysis in these studies. Intraoperative ROTEM for example, can identify those patients at high risk of post-operative bleeding who may confer a much greater benefit from CPPF.

The CPB (p-value 0.52) and ACC (p-value 0.30) times were not statistically significant for either groups, however there was variability in the type of operations that were performed across the studies from isolated coronary artery bypass grafts (CABG) [15] to valve procedures and major aortic surgery [6, 14]. Whilst this demonstrates the applicability of CPPF across the spectrum of cardiac surgical procedures, the temperature of cooling on cardiopulmonary bypass can impact the likelihood of coagulopathy, which in turn can cause an accumulation of mediastinal blood and increased drain output [22].

Kara and Erden 2019 [15] reported lower rates of fluid accumulation in both groups, compared to the other studies, potentially due to the active drainage of any fluid in these cavities in this study prior to chest drain removal in order to reduce the incidence of accumulation. This would suggest that active evacuation in addition to CPPF can reduce the rates of surgical chest drain insertion owing to a reduced chance of fluid re-accumulation as this would be ensured prior to drain removal.

	CPP	F	Standard	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Diephuis et al-Mar 2020	27	83	23	86	31.3%	1.22 [0.76, 1.94]	
Diephuis et al-Nov 2020	10	80	12	90	15.7%	0.94 [0.43, 2.05]	
Kara and Erden-Jul 2019	20	42	39	58	45.5%	0.71 [0.49, 1.02]	
Manshanden et al-Jul 2015	1	21	19	126	7.5%	0.32 [0.04, 2.24]	
Total (95% CI)		226		360	100.0%	0.87 [0.66, 1.15]	•
Total events	58		93				
Heterogeneity: Chi ² = 4.27, df	= 3 (P = 0).23); l²	= 30%				0.05 0.2 1 5 20
Test for overall effect: Z = 0.98	δ (P = 0.34	4)					0.05 0.2 1 5 20 Favours [CPPF] Favours [Standard Care]

b

а

	CPP	F	Standard	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Diephuis et al-Mar 2020	1	83	3	86	8.6%	0.35 [0.04, 3.25]	
Diephuis et al-Nov 2020	1	80	3	90	8.2%	0.38 [0.04, 3.53]	
Kara and Erden-Jul 2019	15	42	34	58	83.2%	0.61 [0.38, 0.96]	
Total (95% CI)		205		234	100.0%	0.57 [0.36, 0.89]	◆
Total events	17		40				
Heterogeneity: Chi ² = 0.41,	df = 2 (P :	= 0.81);	l² = 0%				
Test for overall effect: Z = 2	.47 (P = 0	.01)					0.05 0.2 1 5 20 Favours [CPPF] Favours [Standard Care]

C

		CPPF		Stan	dard C	аге		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Diephuis et al-Mar 2020	7	4.53	83	6	3.02	86	49.7%	0.26 [-0.04, 0.56]	
Kara and Erden-Jul 2019	10.72	3.17	42	11.18	6.14	58	28.9%	-0.09 [-0.49, 0.31]	
Manshanden et al-Jul 2015	7.6	6.1	21	6.8	5.2	126	21.4%	0.15 [-0.31, 0.61]	
Total (95% CI)			146			270	100.0%	0.14 [-0.08, 0.35]	
Heterogeneity: Chi ² = 1.88, df	= 2 (P =	0.39);	$ ^{2} = 0\%$	5				-	
Test for overall effect: Z = 1.24	4 (P = 0.2	22)							-0.5 -0.25 0 0.25 0.5 Favours [CPPF] Favours [Standard Care]

d

		CPPF		Stand	dard C	are		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Diephuis et al-Mar 2020	8.33	2.26	83	8.33	2.26	86	50.0%	0.00 [-0.30, 0.30]	+
Kara and Erden-Jul 2019	7.3	3.44	42	7.72	2.86	58	28.8%	-0.13 [-0.53, 0.26]	
Manshanden et al-Jul 2015	7.7	2.4	21	9	8.6	126	21.3%	-0.16 [-0.62, 0.30]	
Total (95% CI)			146			270	100.0%	-0.07 [-0.29, 0.14]	
Heterogeneity: Chi² = 0.45, df Test for overall effect: Z = 0.65	•	~ ~ ~	I ² = 0%						-0.5 -0.25 0 0.25 0.5 Favours [CPPF] Favours [Standard Care]

Fig. 5 a: PRBC Transfusions (postoperative) b: FFP Transfusions c: Time Until Extubation d: Total Length of Hospital Stay

The CPPF group interestingly had a slower extubation time compared to the standard care group in two studies (p-value 0.22) [6, 8], which cannot be attributable to blood loss alone, as criteria for extubation is multifactorial owing to inotropic support, metabolic and respiratory parameters. The reported EuroScore II values were comparable across all studies between both study groups, however the presence of pre-existing lung disease, specifically chronic obstructive pulmonary disease (COPD) will impact extubation parameters and perhaps require a more cautious approach to extubation [23]. The increased rate of sternal infections seen among the CPPF group could be attributable to the extra tubing required to perform CPPF compared to standard chest tube drainage (p-value 0.61), however notably the CPPF group *also had* a higher pre-operative BMI (p-value 0.03). High BMI is a *recognised risk factor for postoperative wound infections* [24] which could further explain the increased rates in the CPPF patients, although the effect is more pronounced beyond a BMI of 30 kg/ m² [25]. CPPF reduced 30-day mortality by 2.2% overall (p-value 0.51), possibly owing to the fewer surgical re-interventions in the CPPF group, where each surgical re-intervention adds a further mortality risk.

Limitations

The sample size included was small, only analysing 4 studies. The two RCTs mentioned in the systematic review have also shown high risk of bias which may affect the strength of the overall metanalysis. The reports on complications, length of ICU stay, and coagulation parameters were limited. In order to identify those at risk of bleeding and those who may benefit the most from CPPF compared to standard care, further randomised controlled trials with these pre-operative and post-operative coagulation parameters need to be performed, to determine whether CPPF can be introduced as the new standard practice or whether it needs to be targeted to specific individuals who may confer the most benefit.

Conclusion

In this meta-analysis, CPPF has shown promising results in reducing postoperative blood loss and subsequent fluid re-accumulation, cardiac tamponade with fewer blood transfusions requirements and a reduced need for surgical re-interventions across the studied cardiopulmonary bypass cardiac surgical procedures. This suggests it is potentially safe, feasible and effective in cardiopulmonary bypass cardiac surgery. However, further larger, multicentre, randomised controlled trials with rigorous analysis need to be performed. We recommend that further studies on this technique assess the long-term outcomes and use of this technique in emergency surgeries.

Abbreviations

Abbreviat	lons
ACC	Aortic Cross Clamping
ACT	Active Clotting Time
AF	Atrial Fibrillation
AKI	Acute Kidney Injury
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disorder
CPB	Cardio-Pulmonary Bypass
CPPF	Continuous Postoperative Pericardial Flushing
FFP	Fresh Frozen Plasma
Hb	Hemoglobin
ICU	Intensive Care Unit
IQR	Inter-Quartile Range
JBI	Joanna Briggs Institute
LVEF	Left Ventricular Ejection Fraction
M-H	Mantel-Haenszel
OR	Odds Ratio
PICO	Patient-Intervention-Control-Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and
	Meta-Analyses
RBCs	Packed Red Blood Cells
RCT	Randomised Control Trials
RR	Risk Ratio
ROTEM	Rotational Thromboelastometry
SD	Standard Deviation
SMD	Standard Mean Difference
TEG	Thromboelastography

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Supplementary Material 1

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Author contributions

S.J. and M.U. were involved in the conception OR design of the work; the acquisition, analysis, and interpretation of data; S.J. and H.J. drafted the work or substantively revised it S.J. prepared all tables and figures K.B. revised and validated the manuscript as a senior author. All authors approved the submitted version.

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None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

As this is a study-level meta-analysis no ethics approval was needed from the local institution body and neither did we need any patient consent.

Consent for publication

All authors consented to the publication of this manuscript. No patient related data is included in this study as it is a study-level meta-analysis and hence no consent was needed.

Competing interests

The authors declare no competing interests.

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