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Research paper

Continuous postoperative pericardial flushing method versus standard care for wound drainage after adult cardiac surgery: A randomized controlled trial

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ABSTRACT

Background: Excessive bleeding, incomplete wound drainage, and subsequent accumulation of blood and clots in the pericardium have been associated with a broad spectrum of bleeding-related complications after cardiac surgery. We developed and studied the continuous postoperative pericardial flushing (CPPF) method to improve wound drainage and reduce blood loss and bleeding-related complications.

Methods: We conducted a single-center, open-label, ITT, randomized controlled trial at the Academic Medical Center Amstserdam. Adults undergoing cardiac surgery for non-emergent valvular or congenital heart disease (CHD) were randomly assigned (1:1) to receive CPPF method or standard care. The primary outcome was actual blood loss after 12-hour stay in the intensive care unit (ICU). Secondary outcomes included bleeding-related complications and clinical outcome after six months follow-up.

Findings: Between May 2013 and February 2016, 170 patients were randomly allocated to CPPF method (study group; $n = 80$) or to standard care (control group; $n = 90$). CPPF significantly reduced blood loss after 12-hour stay in the ICU (-41%) when compared to standard care (median differences -155 ml, 95% confidence interval (CI) -310 to 0; $p = \leq 0{\cdot}001$). Cardiac tamponade and reoperation for bleeding did not occur in the study group versus one and three in the control group, respectively. At discharge from hospital, patients in the study group were less likely to have pleural effusion in a surgically opened pleural cavity (22% vs. 36%; $p = 0{\cdot}043$).

Interpretation: Our study results indicate that CPPF is a safe and effective method to improve chest tube patency and reduce blood loss after cardiac surgery. Larger trials are needed to draw final conclusions concerning the effectiveness of CPPF on clinically relevant outcomes.

1. Introduction

Bleeding and bleeding-related complications are common after cardiac surgery and have a negative impact on clinical outcome. Standard postoperative care comprises chest drainage with tubes connected to a low-pressure suction system. However, chest tubes may become obstructed by clots and consequently fail, leading to stasis of blood and clots in the pericardial cavity, with several short and longer term bleeding and bleeding-related complications as a result [8,9]. It has been demonstrated that stasis of blood and clots leads to extremely high fibrinolytic activity in the mediastinum and pericardial space, and may therefore lead to increased or prolonged bleeding [10,11]. This is supported by the frequent finding of negative re-exploration for prolonged or excessive bleeding, where removal of clots and irrigation of the wound with warm saline, is enough to stop the bleeding instantly. Based on this principle, the method of continuous postoperative pericardial flushing (CPPF) has been developed at our institution (Fig. 1). CPPF works by continuously flushing the pericardial cavity with a warm saline irrigation solution, starting towards

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Research in context

Evidence before this study

To our knowledge, this is the first RCT that systematically investigated the efficacy of the CPPF method, intended for routine use in cardiac surgery. In a pilot study, we have demonstrated the CPPF method to be safe and feasible and we found some indication that the method may reduce blood loss [12].

Added value of this study

This study is a first exploratory evaluation of the efficacy of CPPF compared to standard care in reducing postoperative blood loss and bleeding-related complications after elective adult cardiac surgery.

Implications of all the available evidence

Retained blood post cardiac surgery however is a clinical entity well recognised in literature and also the rationale for this study. The introduction of active tube clearance, another innovative method with the same purpose as CPPF, has boosted an interest on the clinical entity of retained blood and its consequences. From a literature review this research group concluded that 14−23% of cardiac surgical patients develop one or more complications of retained blood, for which they introduced the new term 'retained blood syndrome' to label this clinical entity [1,2]. It has been demonstrated that the use of active tube clearance is associated with a reduction of interventions for retained blood [3], new onset postoperative atrial fibrillation [3,4], and reoperation for bleeding and delayed sternal closure after LVAD implantation [5]. On theoretical grounds, one may assume that CPPF should at least be able to equal these results, as active tube clearance has its intermittent action in the chest tube lumen only [6], while CPPF aims to solve intra- and extraluminal formation of clots and continuous complete cleaning of the postoperative pericardial space (Fig. 1). In a recent study it was confirmed that increased inflammation in pericardial fluid persists 48 h after cardiac surgery and they emphasized the possible correlation with postoperative atrial fibrillation. As a solution, they suggested that washing of the pericardial space with or without anti-inflammatory medication could reduce this frequent complication [7]. CPPF could be the ideal method to put this in practice and pave the way to more applications of topical drug treatment in the pericardium post cardiac surgery.

the end of surgery just before sternal closure, and continued during the early postoperative hours after cardiac surgery. Continuous flushing aims to prevent the formation of larger clots, thereby preventing chest tube blockage and promoting the evacuation of blood. In a pilot study, we have demonstrated the CPPF method to be safe and feasible and we found some indication that the method may reduce blood loss [12]. In this study, we evaluated the efficacy of CPPF compared to standard care in reducing postoperative blood loss and bleeding-related complications after elective adult cardiac surgery with a clinical follow-up of six months.

2. Methods

2.1. Study design

This study was a randomized, two-armed, controlled trial with a clinical follow-up of six months and was conducted exclusively at the Amsterdam University Medical Center, location AMC, the Netherlands (AMC), between May 2013 and August 2016. Patients were assigned, in a 1:1 ratio, to receive either CPPF method (study group) or standard care (control group). This investigator-initiated study was designed to test the hypothesis whether the use of CPPF method decreases postoperative blood loss compared to standard care wound drainage after cardiac surgery. The clinical study protocol was approved on February 15th 2013 by the institutional review board of the AMC (METC 2012_348). The study was conducted according to the principles of the Declaration of Helsinki as stated in the most recent version of Fortaleza, Brazil, October 2013 [13] and the Dutch law of Medical Research Involving Human Subjects (WMO) [14]. The trial is registered with the NederlandsTrialsRegister (NTR5201;http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5201).

2.2. Participants

Consecutive patients undergoing non-emergent elective correction for congenital heart disease (CHD) or valvular surgery were eligible for enrollment. Patients undergoing valvular surgery became eligible for enrollment after an amendment to the protocol dated December 23rd 2013. Patients were excluded if any of the following criteria applied: emergent surgery, age <18 years, inability to understand study information and/or give informed consent, or participation in any study involving an investigational drug or device. Screening was performed by the coordinating investigators. Patients meeting all inclusion criteria and no exclusion criteria gave written informed consent one day prior to surgery. Randomization was performed by the coordinating investigators with the use of ALEA web-based randomization software (block size range 6 to 12) [15]. The treatment allocation was not blinded. The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (supplementary material 1) [16].

2.3. Procedures

Randomization was performed on-site in the operating theater, after surgical hemostasis was achieved, and prior to sternal closure. Patients randomized to the control group had one chest tube inserted into the pericardial space, one in the anterior mediastinum, and one in each surgically opened pleural cavity if applicable. Patients randomized to the study group had an additional infusion tube inserted through a small (3 mm) extra incision hole, placed in between the standard care chest tube incisions. The irrigation solution was delivered to the pericardial and mediastinal space at a constant temperature of approximately 311°K and at a fixed flow rate of 500 ml/hour until the total irrigation volume of 7000 ml had been infused. Standard ICU protocol for chest tube removal was respected in both groups and all inserted tubes were removed simultaneously. Chest radiographs were made in all patients to evaluate pleural effusions at arrival in the ICU five to seven days after randomization, and at hospital discharge. Transthoracic echocardiograms were made before hospital discharge, or at any moment when there was clinical suspicion of pericardial fluid accumulation or cardiac tamponade.

2.4. Clinical assessments and outcomes

Demographic characteristics, medical history, laboratory values, and operative data were registered for all patients according to study protocol and prior to randomization. For the patients who received standard care, postoperative actual blood loss was defined as the total mediastinal chest tube drainage (MCTD) volume originating from the combined pericardial, mediastinal, and pleural cavities. For the patients who received care with the CPPF method, postoperative actual blood loss was calculated by subtracting the total CPPF irrigation volume from the total MCTD volume (Fig. 1). The primary

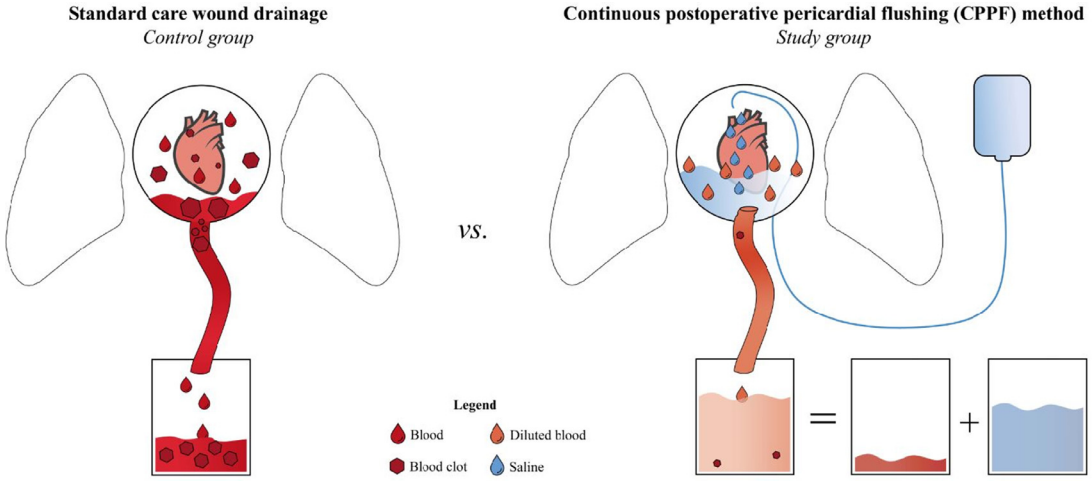


Fig. 1. Continuous postoperative pericardial flushing (CPPF) method versus standard care.

outcome was postoperative actual blood loss after 12-h stay in the ICU after cardiac surgery, assessed by the coordinating investigators. Secondary outcomes included: total postoperative actual blood loss, delta hemoglobin (between randomization and 12-h stay in the ICU and between randomization and hospital discharge), blood transfusions between randomization and hospital discharge, time between randomization and arrival in the ICU, mechanical ventilation duration, chest tube drainage duration, fluid accumulation in the pericardial and/or pleural spaces at hospital discharge, length of stay in the ICU, total hospitalization time, and bleeding-related adverse events. Recorded bleeding-related adverse events included the occurrence of acute (with chest tubes in situ) and late (up to 30-days after chest tube removal) cardiac tamponade, reoperation (for e.g. surgical bleeding, non-surgical bleeding, endocarditis, and other reason), intervention for pericardial or pleural effusion (e.g. subxyphoid pericardial drainage or puncture), infection (e.g. sepsis, pneumonia, superficial wound infection, deep sternal wound infection, and other infection), delirium, acute renal insufficiency, new onset postoperative atrial fibrillation, myocardial infarction, and all-cause mortality. Adverse events were recorded according to the Center for Disease Control criteria for infection [17] and the Society of Thoracic Surgeons Adult Cardiac Surgery Database Data Specifications [18]. Bleeding-related adverse events were adjudicated by a local critical events committee. Interpretation of the imaging was performed by physicians unaware of treatment allocation.

2.5. Statistical analysis

The study was powered to detect a difference of 213 ml postoperative actual blood loss after 12-h stay in the ICU, based on a small pilot study [5], with a power of 95%, a two-sided alpha of 5%, and accommodated for ≈5% drop out. A total required sample of 85 patients per group was requested. The primary analysis was an unadjusted superiority analysis that was performed in the intention-to-treat population. Secondary analyses were performed on per protocol basis and after correction for outliers. Sensitivity analyses were performed using initial primary outcome data (single time point) and expanded data (hourly measurements during the first 12 h in the ICU) with generalized estimating equations. All analysis were done post-hoc based on the observed data. The differences in baseline characteristics between both treatment groups were assessed without imputation for missing data. Normally distributed baseline characteristics were reported as means and standard deviation (SD) and the differences between groups were tested with two-sided t-tests. Non-normally distributed baseline characteristics were reported as medians with interquartile ranges (IQR) and the differences between groups were tested with Mann-Whitney U tests. Categorical data baseline characteristics were reported as numbers and percentages and the differences between groups were tested using Fisher's exact tests. Since we did not want to make any distributional assumptions with respect to the postoperative actual blood loss after 12-hour stay in the ICU, we reported blood loss as medians with IQR, and the between-group difference was tested using the Mann-Whitney U test. Subgroup analyses were performed using Chi-square test. Sample size was calculated using N Query Advisor (version 7.0) software for Windows, study source data were stored in Oracle® Clinical Remote Data Capture (version 4.5.3), analyses were performed using IBM® SPSS® statistics (version 23.0) software for Windows, and curves were plotted using GraphPad Prism® (version 6.0) software for Macintosh.

3. Results

Between May 2013, and February 2016, 449 patients were screened for study eligibility of whom 262 were excluded (supplementary material1); 187 patients provided written informed consent; 17 missed inclusions could not be randomized due to process-related issues; 170 patients were randomly allocated to either CPPF method (study group; $n = 80$) or standard care (control group; $n = 90$) and comprise the ITT population. Follow-up at six months was completed for all 170 patients. Baseline clinical characteristics were balanced between groups, except for the preoperative New York Heart Association (NYHA) classification ($p = 0{\cdot}021$) (Table 1). Procedural characteristics were similar between groups (Table 2).

3.1. Intervention details

Infusion tube placement and start of treatment was successfully performed in all 80 patients allocated to the study group. Treatment was completed in 76 (95%) patients and discontinuation was needed in four (5%) patients. One patient required emergency additional coronary angioplasty and three patients with only pericardial and mediastinal chest tubes had accumulation of >200 ml infusion fluid, and treatment was discontinued according to the protocol.

3.2. Primary outcome

The analysis of the primary outcome in the intention-to-treat population showed that median postoperative actual blood loss after 12-h stay in the ICU was reduced with (100% − (225 × 100 /

Table 1
Baseline clinical characteristics[a].

	Study group ($n = 80$)	Control group ($n = 90$)
Age (years)	55·0 ± 15·7	53·7 ± 17·3
Sex (no. males)	54 (68%)	58 (64%)
Body-mass index[b]	27·5 ± 5·0	26·7 ± 4·4
Clinical syndrome diagnoses and associated diseases:		
Congenital heart disease	42 (53%)	51 (57%)
Degenerative valvular disease	38 (48%)	39 (43%)
Coronary artery disease	13 (16%)	14 (16%)
Chronic obstructive pulmonary disease	4 (5%)	5 (6%)
Renal insufficiency (at least moderate)	6 (8%)	8 (9%)
Cerebrovascular accident of transient ischemic attack	6 (8%)	5 (6%)
Previous cardiac surgical procedures:		
None	66 (83%)	73 (81%)
Single previous procedure	12 (15%)	9 (10%)
≥ Two previous procedures	2 (3%)	8 (9%)
EuroSCORE II median (IQR)	1·4 (1·0 to 2·9)	1·3 (1·0 to 2·9)
NYHA class:[c]		
I & II	49 (61%)	39 (43%)
III & IV	31 (39%)	51 (57%)
Left ventricular ejection fraction:		
>50%	67 (84%)	74 (82%)
30–50%	13 (16%)	15 (17%)
<30%	0 (0%)	1 (1%)
hemoglobin (g/dl)	8·7 ± 1·0	8·8 ± 0·9
Preoperative anti-coagulants[d]	35 (44%)	43 (48%)

[a] Data before randomization. Data are presented as numbers (percentages) or mean ± SD, unless otherwise specified.
[b] Data on body-mass index (the weight in kilograms divided by the square of the height in meters).
[c] New York Heart Association (NYHA) classes range from I to IV.
[d] Use of all antiplatelet agents was discontinued 5 days prior to surgery.

Table 2
Procedural data[a].

	Study group ($n = 80$)	Control group ($n = 90$)
Number of surgical procedures		
Single procedure	33 (41%)	43 (48%)
Double procedure	34 (43%)	34 (38%)
Triple procedure	9 (11%)	8 (9%)
Quadruple procedure	4 (5%)	5 (6%)
Procedures per patient median (IQR)	2 (1 to 2)	2 (1 to 2)
Procedure type		
Reoperation	14 (18%)	17 (19%)
Aortic root surgery	25 (31%)	20 (22%)
Operative data		
Cardiopulmonary bypass duration (min)	157 ± 56	154 ± 67
Cross-clamp duration (min)	115 ± 46	103 ± 38
Operation duration (min)	288 ± 90	273 ± 97
Number of surgically opened pleural cavities:		
None	45 (56%)	48 (53%)
One	28 (35%)	33 (37%)
Two	7 (9%)	9 (10%)
Patients transfused before randomization:		
Red cells	12 (15%)	20 (22%)
Fresh-frozen plasma	13 (16%)	10 (11%)
Platelet concentrate	19 (24%)	13 (14%)
Cell-saver blood reinfused (ml) median (IQR)	543 (400 to 721)	477 (250 to 720)
Tranexamic acid (gr) median (IQR)	2·0 (0·0 to 3·0)	2·0 (1·0 to 3·0)

[a] Data before randomization. Data are presented as numbers and percentages or mean ± SD, unless otherwise specified.

380) = 41%) 41% in the study group when compared to the control group (225 ml, IQR −150 to 475 vs. 380 ml, IQR 280 to 560; $p<0·001$) (Table 3). The treatment effect remained consistent in the per-protocol analysis ($p<0·001$) and after correction for outliers ($p = 0·001$). We observed that 19% of patients in the study group had an unexpected calculated and virtual "negative blood loss" at chest tube removal. Negative blood loss was the result of the actual blood loss calculation in the study group, which means that in these cases the total irrigation fluid volume exceeded total MCTD volume. This can only be explained if part of the irrigation fluid had accumulated in the pericardial or pleural space(s) and/or had been absorbed by the epithelial surface in these body cavities. It is important to remark that these negative outcome in the study group may lead to overestimation of the overall results. Based on the explorative character of the study, we didn't perform additional analysis to correct for this unexpected finding.

3.3. Secondary outcomes

Median total postoperative actual blood loss at chest tube removal was 440 ml (IQR 100 to 800) in the study group versus 650 ml (IQR 445 to 938) in the control group ($p = 0·001$). Upon chest tube removal, 15 (19%) patients in the study group had a median irrigation solution volume retention of 200 ml (IQR −980 to −40) of which 11 (73%) had closed pleural cavities and four (27%) had one surgically opened pleural cavity. At hospital discharge, patients in the study group were less likely to have pleural effusion in a surgically opened pleural cavity (22% vs. 36%; $p = 0·043$) compared to the control group (Table 3).

3.4. Sensitivity analyses

For the sensitivity analyses, we used hourly actual blood loss measurements between arrival and 12-h stay in the ICU. Actual blood loss curves over time in both groups were modelled using generalized estimating equations under a working independence assumption (Fig. 2). Results show that *negative blood loss* was not associated with the surgically opened pleural cavity subgroups as it occurred equal in all three groups. In the subgroups with surgically opened pleural cavities, postoperative actual blood loss substantially increased in the control group ($p = 0·050$), the proportion of patients with prior cardiac surgery also increased as there were more surgically opened pleural cavities ($p = 0·004$) (Fig. 3).

3.5. Adverse events

In-hospital adverse events were comparable between groups (Table 4), except for sternal dehiscence, which occurred in only four (5%) patients in the study group. Patients in the study group did not require reoperation for surgical and non-surgical bleeding versus 3 (3%) in the control group. Adverse events between hospital discharge and six months follow-up were not significantly different between groups Table 4.

3.6. Subgroup analyses

The treatment performance, in relation to median 12-h and total postoperative actual blood loss, was more pronounced in the reoperation subgroup (−61% and −48%) when compared with primary surgery (−35% and −27%) (Table 5a). Subgroup analyses further identified coronary artery surgery (hazard ratio 4·05, 95% CI 1·45 to 11·27; $p = 0·007$) and two surgically-opened pleural cavities (hazard ratio 5·90, 95% CI 1·02 to 34·00; $p = 0·047$) as statistically significant risk factors for above median postoperative actual blood loss after 12-h stay in the ICU (Table 5b).

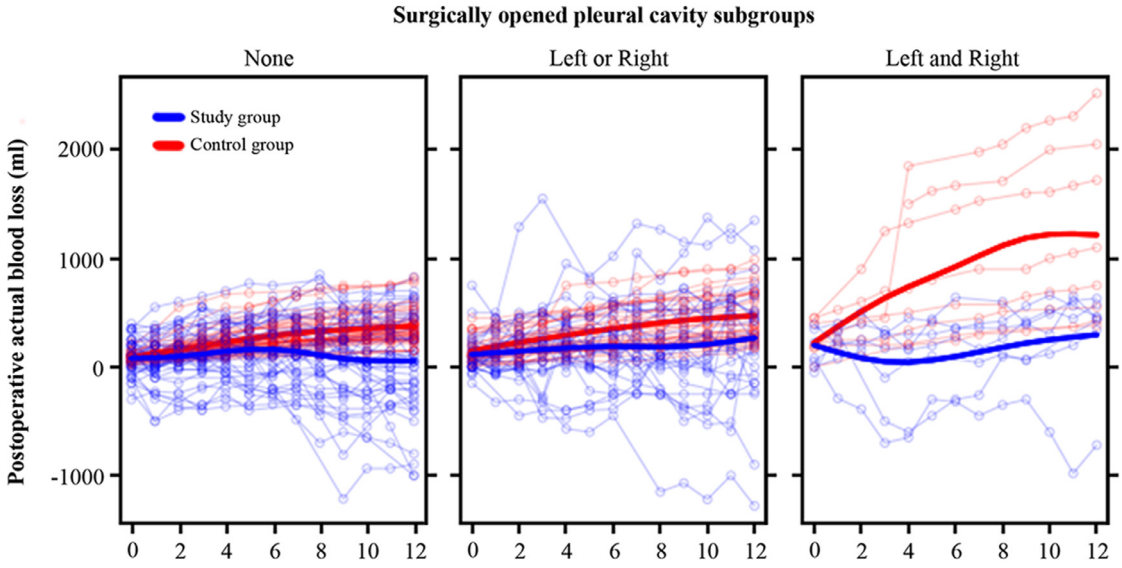
4. Discussion

Our findings indicate that the CPPF method with a saline solution significantly reduces blood loss in the first postoperative hours after cardiac surgical procedures. Analysis of the primary outcome showed

Table 3
Primary and secondary outcomes[a].

	Study group ($n = 80$)		Control group ($n = 90$)		p value[c]
	n/total n[b]		n/total n[b]		
Primary outcome					
12-h postoperative actual blood loss median (IQR)	79/80	225 (−150 to 475)	89/90	380 (280 to 560)	<0·001
Secondary outcomes					
Total postoperative actual blood loss median (IQR)	78/80	440 (100 to 800)	88/90	650 (445 to 938)	0·001
hemoglobin Δ randomization to 12-h stay in the icu (g/dl)	79/80	0·95 ± 0·93	89/90	1·05 ± 0·72	0·45
hemoglobin Δ randomization to hospital discharge (g/dl)	77/80	0·24 ± 0·89	88/90	0·50 ± 0·94	0·07
Patients transfused after randomization:					
Red cells	80/80	10 (13%)	89/90	12 (13%)	0·10
Fresh frozen plasma	80/80	1 (1%)	89/90	3 (3%)	–
Platelet concentrate	80/80	1 (1%)	89/90	3 (3%)	–
Fluid accumulation at discharge[b]					
Pericardial effusion on echocardiogram (≥10 mm)	79/80	10 (13%)	89/90	15 (17%)	0·52
Pleural effusion on chest X-ray	79/80	53 (67%)	89/90	65 (73%)	0·41
in a surgically opened pleural cavity	79/80		89/90	32 (36%)	0·043

[a] Data between randomization and discharge from hospital. Data are presented as numbers and percentages or mean ± SD, unless otherwise specified, Infection according to the Center for Disease Control and Prevention (CDC).
[b] Number of patients included in the analysis.
[c] Mann−Whitney U test.



Number of observations per patient									
Number of measurements	5	6	7	8	9	10	11	12	13
Number of patients	2 (1%)	7 (4%)	12 (7%)	13 (8%)	17 (10%)	22 (13%)	16 (9%)	21 (12%)	59 (35%)

Number of observations per subgroup			
Surgically opened pleural cavities	None	Left or Right	Left and Right
Study group	45 (56%)	28 (35%)	7 (9%)
Control group	48 (53%)	33 (37%)	9 (10%)

Data are presented as numbers (percentages).

Fig. 2. Sensitivity analyses, blood loss in surgically opened pleural cavity subgroups.

that median postoperative actual blood loss after 12-hour stay in the ICU was reduced with 41% in the study group when compared to the control group. The first remark that has to be made is that this relatively high decrease relates to a modest absolute reduction of 155 ml blood loss in this specific cardiac surgical population. However, both study groups had rather low median blood loss, 225 ml in the study group vs. 380 ml in the control group, due to the relatively low risk and younger-aged congenital patients with few comorbidities, and an active blood management strategy, which is the standard at our institution. In addition, subgroup analysis showed that the treatment effect of CPPF seemed more distinct in patients with previous cardiac surgery when compared to those undergoing primary surgery (−61% vs. −35%, respectively) (Table 4). Thus, with regard to blood loss reduction, it may be that the CPPF method is more effective in patients with a higher bleeding tendency, like for instance patients undergoing coronary artery bypass grafting. Secondly, we observed that 19% of patients in the study group had an unexpected calculated and virtual "negative blood loss" at chest tube removal. Apparently, part of the irrigation fluid had accumulated in the pericardial or pleural space(s) and/or had been absorbed by the epithelial surface in

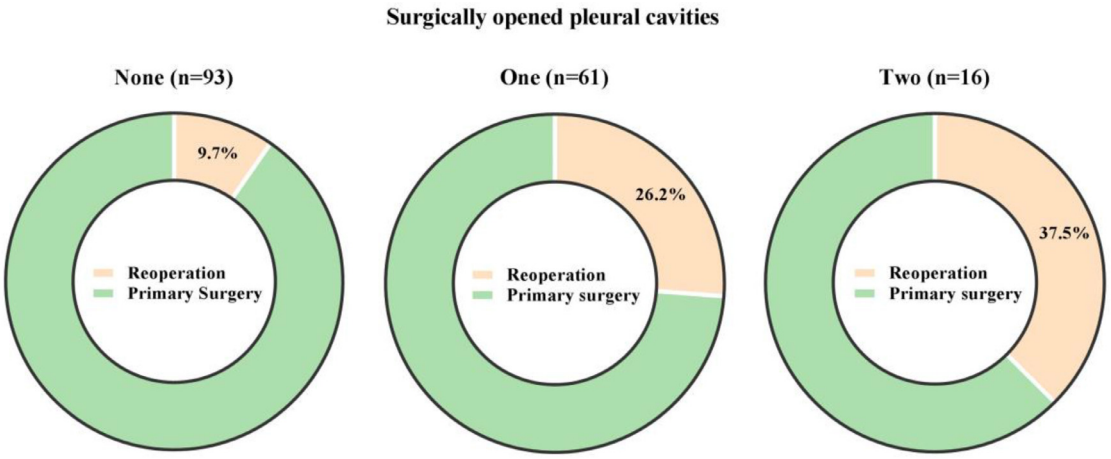


Fig. 3. Sensitivity analyses, surgically opened pleural cavity in reoperation and primary operation subgroups.

Table 4
Bleeding-related adverse events between randomization and six months follow-up.

	In-hospital		Six months follow-up	
	Study group (n = 80)	Control group (n = 90)	Study group (n = 80)	Control group (n = 90)
Cardiac tamponade (acute / late)	0/2 (3%)	1/1 (2%)	0/1 (1%)	0/0 (0%)
Reoperation				
For non-surgical bleeding	0 (0%)	1 (1%)	–	–
For surgical bleeding	0 (0%)	2 (2%)	–	–
For other reasons	1 (1%)	2 (2%)	–	–
For endocarditis	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Intervention for fluid accumulation				
Pericardial intervention	4 (5%)	2 (2%)	3 (4%)	3 (3%)
Pleural intervention	–	–	0 (0%)	2 (2%)
Infections[a]				
Sepsis	1 (1%)	3 (3%)	–	–
Pneumonia	5 (6%)	1 (1%)	–	–
Pericarditis	1 (1%)	1 (1%)	–	–
Deep sternal wound infection	3 (4%)	2 (2%)	1 (1%)	2 (2%)
Surgical wound infection	–	–	5 (6%)	1 (1%)
Sternal dehiscence	4 (5%)	0 (0%)	–	–
Delirium	7 (9%)	4 (4%)	–	–
Acute renal insufficiency	3 (4%)	2 (2%)	0 (0%)	1 (1%)
New onset postoperative atrial fibrillation	20 (25%)	19 (21%)	2 (3%)	2 (2%)
Myocardial infarction	2 (3%)	2 (2%)	0 (0%)	1 (1%)
Mortality	1 (1%)	1 (1%)	1 (1%)	1 (1%)

Data are presented as numbers and percentages or mean ± SD, unless otherwise specified.
[a] Number of patients included in the analysis.

Table 5A
Postoperative actual blood loss in reoperation and primary surgery subgroups.

		Study group (n = 80)		p value[a]
		patients		
Reoperation	12-h postoperative actual blood loss median (IQR)	14	220 (−169 to 470)	0·006
	Total postoperative actual blood loss median (IQR)	14	490 (−56 to 856)	0·019
Primary surgery	12-h postoperative actual blood loss median (IQR)	66	225 (−150 to 488)	0·002
	Total postoperative actual blood loss median (IQR)	66	438 (100 to 800)	0·006

[a] Mann-Whitney U test.

these body cavities. However, median negative blood loss was 200 ml and no clinical consequences were observed in the first postoperative days. Besides, patients in the study group were less likely to have pleural effusion in a surgically opened pleural cavity at hospital discharge while the incidence of pericardial and pleural effusions at hospital discharge were comparable between groups. Nevertheless, blood loss was underestimated in the study group since negative blood loss is non-existent post-cardiac surgery.

To our knowledge, this is the first RCT that systematically investigated the efficacy of the CPPF method, intended for routine use in cardiac surgery. The choice for blood loss as primary outcome was based on pilot study findings [12] and under the assumption that blood loss reduction would demonstrate clinical effectiveness at the smallest sample size, whereas most retained blood-related acute adverse events have a relatively low incidence rate of only a few percentage points. Re-exploration for acute cardiac tamponade or (non)

Table 5B
Above median 12-h postoperative actual blood loss in predefined subgroups.

	Study group (n = 80) patients/events	Control group (n = 90) `patients/events	p value[a]
Preoperative NYHA class			
Class 3–4	49/24	39/17	0·615
Class 1–2	31/16	31/29	0·000
Reoperation			
Yes	14/7	17/14	0·055
No	66/33	73/32	0·467
Surgery for congenital heart disease			
Yes	42/15	51/29	0·042
No	38/25	39/17	0·050
Aortic root surgery			
Yes	25/10	20/13	0·095
No	55/30	70/33	0·411
Coronary surgery			
Yes	13/10	14/10	0·745
No	67/30	76/36	0·756
At least one surgically opened pleural cavity			
Yes	35/22	42/27	0·897
No	45/18	48/19	0·967
Two surgically opened pleural cavities			
Yes	7/6	9/8	0·849
No	73/34	81/38	0·966
Intraoperative administration of tranexamic acid			
Yes	59/29	73/37	0·861
No	19/9	17/9	0·738
Intraoperative red cell transfusion			
Yes	12/6	20/13	0·403
No	68/34	70/33	0·737
Intraoperative fresh frozen plasma transfusion			
Yes	13/8	10/7	0·673
No	67/32	80/39	0·905
Intraoperative platelet concentrate transfusion			
Yes	19/10	13/11	0·061
No	61/30	77/35	0·663

[a] Chi-square test.

surgical bleeding occurred a few times in the control group versus none in the study group. Although this supports the principle of the CPPF method, larger numbers are needed to reach statistical significance. We anticipated the possibility of fluid retention and incorporated pre-specified sensitivity analyses on the number of surgically opened pleural cavities. Negative blood loss was not associated with the number of surgically opened pleural cavities and the phenomenon also occurred in some patients with closed pleural cavities (Fig. 2). This suggests that part of the CPPF irrigation fluid volume may have been absorbed by pericardial or mediastinal tissue surfaces as a significant intrapericardial fluid accumulation was never demonstrated. Thus, we did not find an explanation for the mechanism causing fluid retention and the extent to which this phenomenon influences the primary outcome needs further investigation. Besides this, it is very likely that in a number of patients in the control group certain amounts of blood and clots were retained in the opened body cavities, with no direct clinical manifestations but also leading to an underestimation of blood loss. Four patients in the study group developed sternal dehiscence during hospitalization over none in the control group. However, two patients had hyperactive delirium and one patient, with high body-mass index and chronic obstructive pulmonary disease, developed pneumonia with a productive cough, which are independent risk factors for sternal dehiscence [19,20]. In any case, a causal relationship with the CPPF method seems unlikely. Our study has some limitations. Randomization was slightly unbalanced. Secondly, because of the inevitable un-blinded study design, the involved caregivers were aware of treatment-group assignment. In the initial study protocol of this exploratory, investigator initiated, evaluation of CPPF a first planned analysis of the statistical paragraph was described (https://www.trialregister.nl/trial/5070). Further elaboration of the analysis for this early phase evaluation has taken shape in a post-hoc analysis. Finally, the unexpected phenomenon of negative blood loss on the primary outcome needs to be investigated and clarified before we can draw final conclusions about the degree of blood loss reduction. In conclusion, this study indicates that CPPF is a safe and effective method to reduce blood loss and maintain chest tube patency after cardiac surgery. Future studies are needed to draw final conclusions concerning the effectiveness of CPPF on clinically relevant outcomes.

Declaration of Competing Interest

Based on the experiences from this study and for the safe application of the CPPF method, authors DK and JM invented and patented a new medical device (WO2015086857A1). Author DK is a member of a start-up company (Haermonics B.V.) that will develop this device. In this capacity he may have future benefits from this. Author ED was a member of a start-up company Haermonics B.V. and has received personal fees from Haermonics. All other authors have nothing to declare.

Data sharing

For purposes of reproducing the results or replicating the method, the corresponding author will make the data, analytic methods, and study materials available to other researchers on request, with investigator support.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2020.102744.

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