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Original Article

Evaluating the Impact of Cardiopulmonary Bypass Priming Fluids on Bleeding After Pediatric Cardiac Surgery: A Systematic Review and Meta-Analysis

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Objectives: Cardiopulmonary bypass (CPB) predisposes young children to coagulopathy. The authors evaluated possible effects of CPB priming fluids on perioperative bleeding in pediatric cardiac surgery.
Design: Meta-analysis and systematic review of previously published studies.
Setting: Each study was conducted in a surgical center or intensive care unit.
Participants: Studies investigating patients <18 years without underlying hematologic disorders were included.
Interventions: The authors evaluated randomized controlled trials (RCTs) published between 1980 and 2020 on MEDLINE, EMBASE, PubMed, and CENTRAL databases. The primary outcome was postoperative bleeding; secondary endpoints included blood product transfusion, mortality, and safety.
Measurements and Main Results: Twenty eligible RCTs were analyzed, with a total of 1,550 patients and a median of 66 patients per study (range 20-200). The most frequently assessed intervention was adding fresh frozen plasma (FFP) to the prime (8/20), followed by albumin (5/20), artificial colloids (5/20), and blood-based priming solutions (3/20). Ten studies with 771 patients evaluated blood loss at 24 hours in mL/kg and were included in a meta-analysis. Most of them investigated the addition of FFP to the priming fluid (7/10). No significant difference was found between intervention and control groups, with a mean difference of −0.13 (−2.61 to 2.34), p = 0.92, I^2 = 69%. Further study endpoints were described but their reporting was too heterogeneous to be quantitatively analyzed.
Conclusions: This systematic review of current evidence did not show an effect of different CPB priming solutions on 24-hour blood loss. The analysis was limited by heterogeneity within the dataset regarding population, type of intervention, dosing, and the chosen comparator, compromising any conclusions.

Key Words: pediatric cardiac surgery; cardiopulmonary bypass; prime; colloid oncotic pressure; bleeding; blood loss; FFP

A LARGE PROPORTION of children affected with congenital heart disease will require cardiac surgery on cardiopulmonary bypass (CPB) at least once in their lifetime and often at a young age. An important aspect for this patient cohort is the treatment for perioperative bleeding, which is associated with hemodynamic instability, prolonged surgery time, chest reexploration, and blood-product transfusion.[1,2] Most children undergoing cardiac surgery receive blood

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products after CPB, with bleeding being a frequent indication. However, the transfusion of any blood product carries risk of fluid overload, electrolyte abnormalities, exposure to transfused foreign antigens (in the short and long term), and risk of infection. Hence, the reduction of bleeding is a relevant target to improve outcomes in this patient group.[2-4]

The causes of perioperative bleeding are multifactorial and so is the range of potential measures for its prevention and early management.[5] The mismatch of CPB circuit volume and body size predisposes infants and young children to hemodilutional coagulopathy. In consideration of this, a variety of modifications of the circuit and the priming solution composition have been investigated.[2,5,6] Although crystalloid solutions are cheap and easily available, these reduce colloidal oncotic pressure (COP) and, hence, promote hemodilution. Adding the natural colloid albumin to the prime potentially better maintains COP and platelet counts and improves perioperative fluid balance. However, high costs, as well as the risks of anaphylaxis and acute kidney injury reported in adults, need to be considered.[6,7] Alternatively, artificial colloids, such as hydroxyethyl starch (HES) preparations and gelatins, are used to augment blood volume to counteract fluid extravasation during cardiac surgery, leading to better cardiac performance and hemodynamics, but adverse effects on renal function and coagulation have been reported in adults.[6,8-10] Blood-based priming solutions containing whole blood, packed red blood cells, and fresh frozen plasma (FFP) often are used in young and small children, for whom there is a greater degree of hemodilution anticipated.[2,6]

The authors aimed to provide a systematic review, and, where possible, quantitative meta-analysis of current data on the effects of different CPB priming composition on clinical outcomes of perioperative blood loss in pediatric cardiac surgery.

Methods

This systematic review was performed using the broad search criteria from a previously performed scoping review of strategies for prevention and management of bleeding in children undergoing cardiac surgery using CPB[5] (Supplement 1). The search was last updated January 31, 2020. For the full review, a study protocol was written guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.[11] As this was a synthesis of previously published literature, ethics committee approval was not required.

Search Strategy

EMBASE, MEDLINE, PubMed, and the Cochrane Central Register were searched systematically for eligible studies. Gray literature was identified searching clinical trials registries, pharmaceutical company websites, and hand search citations of relevant articles (Supplement 1).

Inclusion and Exclusion Criteria and Outcomes

Studies were eligible if participants were newborn-to-18 years of age undergoing cardiac surgery, using CPB and circuit priming fluids, were evaluated. Studies involving participants with inherited bleeding disorders, sickle cell disease, or other hematologic disorders were excluded, as their risk profile and individual needs are different than the main population. For the final analysis, only controlled trials were eligible, restricted to those published in English between 1980 and 2020. Outcomes of interest were those reflecting perioperative bleeding as expressed by measured blood loss, as well as consequences of bleeding such as pericardial effusion, prolonged chest closure times, transfusion requirements, and mortality. As safety outcomes, the authors analyzed the incidences of thromboses and related complications and renal dysfunction.

Study Selection

Titles and abstracts identified through the initial search were screened by 2 authors (K.S., P.D.), who then independently assessed the full publications of the potentially relevant studies against the formal eligibility criteria. Disagreements were resolved by a third reviewer (S.T., I.M.).

Data from eligible studies were extracted using a standard data collection sheet: country of study origin, patient numbers, mean age, mean weight, mean CPB time, type of surgery, cyanotic versus acyanotic lesions, number of patients undergoing resternotomy, randomization, blinding, reported outcomes, and whether the use of a transfusion policy was reported.

Quality Assessment

Data from eligible studies were reviewed independently and double-appraised by 2 members of the team (K.S., P.D.). For critical appraisal of selected studies, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was applied. Specific areas assessed included randomization, allocation concealment, blinding, outcome assessment, data completion, selective reporting, and any other potential source of bias. The studies were assessed and in cases of disagreement consensus sought in discussion between the 2 researchers (K.S., P.D.) and a third reviewer (S.T., I.M.).[12,13]

Statistical Analysis

A summary of findings table was produced for all included studies using Review Manager 5 software (REVMAN 5, The Cochrane Collaboration, Oxford, UK), as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.[14] Outcome data not allowing for meta-analysis were descriptively reported.

All studies considered for the analysis were assessed for possible risk of bias, using the risk-of-bias tool as described in chapter 8 of the *Cochrane Handbook of Systematic Reviews of Interventions*. Risk of bias was assessed on a 3-point scale: low, high, or unclear.[14]

Quantitative outcomes for bleeding, such as chest tube drainage and transfusion volumes, were reported typically in mL/kg/24 h. Where original data were expressed as continuous

variables, the mean and SD were recorded. Where necessary, SDs were obtained from standard errors, confidence intervals, t values, and p values for differences in means, as described in the Cochrane Handbook.[14]

A random-effects model was used to compute the mean difference. All outcomes were noted as differences compared with the control group. Heterogeneity was assessed using I^2 statistics; according to the Cochrane review guidelines, $I^2 > 40\%$ and $p < 0.01$ were considered threshold values for heterogeneity.[14]

Results

Search Results

Of 7,434 studies identified in the initial search, 41 studies evaluated CPB priming fluid modifications, of which 16 were randomized controlled trials.[5] Repeating the search in 2020 identified a further 3 eligible studies. One study had 2 intervention groups including 2 corresponding control groups and, therefore, was counted as 2 studies, resulting in a total of 20 randomized controlled trials included in the analysis of this review.[15]

Study Quality

The included studies were overall of moderate methodologic quality. Most (19/20) had 1 or more areas at high or unclear risk of bias. Most deficiencies related to the blinding of participants and personnel (18/20), blinding of outcome reporting (9/20), randomization (9/20), and allocation concealment (13/20). In 8/20 included studies, transfusion therapy was not based on a protocol, but left to the clinicians' discretion. For a further 4 studies, the transfusion management was not clearly reported (Fig 1).

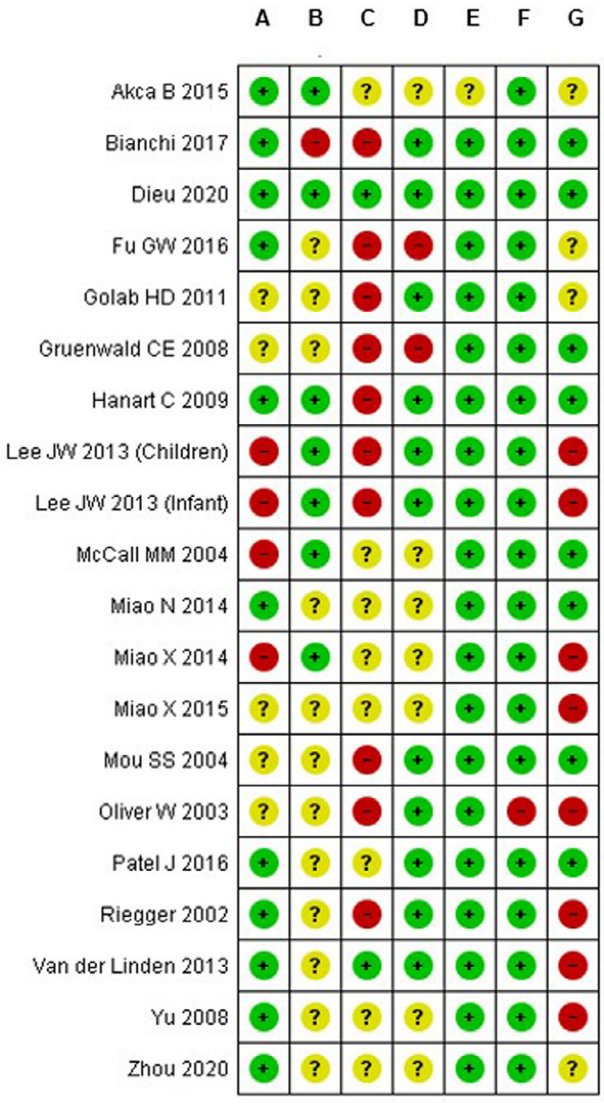

Fig 1. Risk of bias categories: (A) Random sequence generation (selection bias), (B) Allocation concealment (selection bias), (C) Blinding of participants and personnel (performance bias), (D) Blinding of outcome assessment (detection bias), (E) Incomplete outcome data (attrition bias), (F) Selective reporting (reporting bias), (G) other bias.

Study Population

In total, the 20 studies evaluated 1,550 patients. Overall study sizes were small, with a median of 66 patients per study (range 20-200). The number of patients included in the intervention groups ranged from 10-to-96 patients (median 34), with a mean age varying between 15 days and 10 years and a mean weight range of 3.5-to-28.3 kg. More than half of the studies (12/20) investigated a more homogeneous subpopulation, including exclusively neonates or small infants.[15-26]

The participants of most studies underwent a variety of different procedures, with a mean CPB time ranging from 51-to-136 minutes. Two studies included exclusively cyanotic lesions.[27,28] Eight studies excluded children with secondary cardiac surgery;[19,21,24,26-30] 1 study with 2 intervention groups excluded those with delayed sternal closure,[15] and another study excluded children who had been on CPB >120 minutes[18] (Table 1).

Interventions and Comparators

The most frequently assessed intervention was the addition of FFP to the CPB prime (8/20) compared with albumin (n = 5),[15,16,21,23] artificial colloids (n = 2),[28,29] or crystalloid fluids (n = 1).[17]

Albumin was assessed in a total of 5 studies (5/20), using crystalloid fluid (n = 1)[25] or artificial colloids (n = 1)[26] as comparator, comparing albumin against 2 comparators of artificial colloids and crystalloid fluid (n = 1)[24] or comparing high-dose versus low-dose albumin primes (n = 2).[19,30]

Artificial colloid solutions were assessed in a total of 5 studies (5/20), with albumin (n = 3)[31-33] or crystalloid fluid (n = 1)[27] as comparator (in addition to the previously described study comparing artificial colloids, albumin, and crystalloid solution).

Table 1
Study Characteristics and Demographics (All Included Studies)[15-33]

Study	Year	Total No	Treatment Group	Age (mo)*,† (Treatment)	Weight (kg)† (Treatment)	CPB Time (min)† (Treatment)	Control Group	Age (mo)*,† (Control)	Weight (kg)† (Control)	CPB Time (min)† (Control)	Comment	Use of Transfusion Guideline
Akca	2015	20	HES 130/0.4 n = 10	20.7 ± 11.2	9.07 ± 2.13	84.4 ± 34.89	Ringer's lactate n = 10	23.2 ± 15.1	9.97 ± 3.12	97.80 ± 28.18	TOF + TGA only, primary sx only	Unclear
Bianchi	2017	73	FFP n = 36	4.0 (2.0-9.5)	4.8 (3.6-6.6)	119.0 (74.0-151.0)	Albumin n = 37	4.0 (1.0-10.0)	4.8 (3.8-6.1)	125.0 (74.0-158.0)	<10 kg only	Yes
Dieu	2020	59	FFP n = 30	20.0 (11.0-39.0)	9.8 (8.0-13.4)	136.0 ± 59.0	Crystalloid fluid n = 29	18.0 (12.0-32.0)	9.9 (8.2-11.8)	145.0 ± 79.0	7-15 kg only	Yes
Fu	2016	60	0.9% NaCl + RAP n = 26	49.9 ± 20.1	16.23 ± 2.08	51.04 ± 17.76	Bank blood components n = 33	50.09 ± 19.50	16.88 ± 1.90	51.94 ± 19.04	<20 kg only	Unclear
Golab	2011	70	Albumin COP >18 mmHg* n = 34	5.0 ± 4.1	5.9 ± 2.1	89.0 ± 36.0	Albumin COP >15 mmHg* n = 35	5.3 ± 3.8	6.3 ± 1.7	88.0 ± 42.0	<10 kg only, primary sx only	Unclear
Gruenwald	2008	64	RFWB n = 31	15 ± 10 d	3.5 ± 0.6	136.0 ± 58.0	Bank blood components n = 33	14 ± 11 d	3.4 ± 0.4	126.0 ± 41.0	Neonates only	Yes
Hanart	2009	119	HES 130/0.4 n = 60	20 (8-46)	8.3 (5.7-13.5)	112.0 ± 35.0	Albumin n = 59	11.0 (5-42)	6.9 (5.1-13.2)	105.0 ± 40.0	-	Yes
Lee	2013	A: 54 B: 67	FFP A: n = 26 B: n = 34	A: 3.6 (2.1-6.8) B: 121 (42.2-177.9)	A: 5.7 (4.4-7.3) B: 28.3 (14-50)	A: 115 (85-165.3) B: 110 (86-169.5)	Albumin A: n = 28 B: n = 33	A: 2.6 (1.5-3.7) B: 68 (45.3-166)	A: 4.7 (4.1-6.2) B: 20.3 (14.4-38)	A: 96.5 (66-117.8) B: 98 (71.5-134)	A: <1 year only B: 1-16 years	No
McCall	2004	20	FFP n = 10	4.0 ± 3.9	4.0 ± 1.3	105.0 ± 32.0	Albumin n = 10	4.4 ± 1.2	4.6 ± 0.9	110.0 ± 35.0	<10kg only, primary sx only	Yes
Miao N	2014	60	HES 130/0.4 n = 30	243 ± 89 d	7.0 ± 1.5	61.0 ± 15.0	Albumin n = 30	246 ± 86 d	6.9 ± 1.5	61.0 ± 17.0	-	Yes
Miao X	2014	91	FFP n = 46	15.6 ± 7.7	10.8 ± 3.5	123.7 ± 32.3	Gelofusin n = 45	14.7 ± 8.1	10.3 ± 3.7	118.5 ± 37.7	Cyanotic lesions only, primary sx only	No
Miao X	2015	75	FFP A: n = 37	11.8 ± 8.2	9.2 ± 2.3	83.7 ± 32.3	Gelofusin n = 38	12.7 ± 9.5	9.0 ± 2.6	78.5 ± 27.7	Primary sx only	No (intraop) Yes (ICU)
Mou	2004	200	Fresh whole blood n = 96	66.5 d (7.0-178.0)	4.1 (3.3-5.6)	73.0 (59.0-97.0)	Bank blood components n = 104	92.0 d (8.0-193.0)	4.4 (3.3-6.0)	74.5 (56.3-95.0)	<1 year only	Yes
Oliver	2003	56	FFP n = 28	6.9 ± 7.4	5.6 ± 2.0	119.6 ± 52.6	Albumin n = 28	6.6 ± 5.9	5.6 ± 1.6	100.2 ± 38.3	<10 kg only	No
Patel	2016	105	A: albumin n = 35 B: HES 130/0.4 n = 35	A: 15.8 ± 13.1 B: 16.2 ± 14.2	A: 5.8 ± 2.3 B: 6.8 ± 5.1	A: 51.0 ± 29.3 B: 63.8 ± 30.3	C: Ringer's lactate n = 35	4 16.4 ± 16.3	6.9 ± 4.5	57.4 ± 23.9	<15 kg only, primary sx only	Yes
Riegger	2002	86	albumin n = 44	0.53 ± 0.47 yr	6.1 ± 2.4	107.3 ± 43.6	Crystalloid fluid n = 42	0.67 ± 0.8 y	6.1 ± 2.4	106.0 ± 51.3	<14 kg only	No
Van der Linden	2013	55	HES 130/0.4 n = 31	5.0 yr (3.0-7.0)	16.7 (12.9-19.3)	120 (78-144)	Albumin n = 30	4.0 y (2.0-4.0)	14.5 (12.5-17.2)	90 (72-120)	-	No
Yu	2008	151	Albumin 5% n = 68	17.0 ± 8.0	9.0 ± 2.5	78.0 ± 17.0	Albumin 3% n = 83	16.0 ± 9	8.6 ± 1.7	73.0 ± 14.0	Primary sx only	No
Zhou	2020	65	Succinylated gelatin 4% + albumin n = 32	57 d (30-150)	4.0 (4.0-4.9)	100.3 ± 29.0	Succinylated gelatin 4% n = 33	114 d (65-135)	4.7 (4.2-5.0)	88.1 ± 33.3	<5 kg only primary sx only	Unclear

NOTE. Studies included in the meta-analysis are marked in yellow.
Abbreviations: COP, colloid osmotic pressure; FFP, fresh frozen plasma; RAP, retrograde autologous blood; RFWB, reconstituted fresh whole blood; sx, surgery.
* Age given in months unless stated otherwise.
† Numbers given in mean ± SD or median (IQR).

A further 3 studies (3/20) investigated blood-based priming solutions using retrograde autologous blood priming (RAP; n = 1),[18] fresh whole blood (n = 1),[22] and reconstituted fresh whole blood (n = 1)[20] compared against priming based on bank-blood components (Table 2).

Safety Outcomes

Safety data were sparse, with only 8 of 20 studies commenting on relevant endpoints. No significant between-group differences were reported for thromboembolic events, renal impairment, allergic reactions, and general adverse events.[16,17,22,24-26,28,33]

Efficacy Outcomes

The reporting of most study endpoints was too heterogeneous to be quantitatively analyzed. Hence, these results are summarized descriptively, with transfusion outcomes reported from n = 18, coagulation parameters from n = 15, and safety outcomes from n = 11 studies (Supplement 2).

Blood loss in mL/kg/24 hours was the most frequently and most homogeneously reported outcome, which allowed a quantitative evaluation through a meta-analysis including 10 studies with a total of 770 patients. No significant difference was found between intervention and control groups, with a mean difference of −0.13 (−2.61 to 2.34), p = 0.92 and an indication for substantial heterogeneity within the dataset (I^2 = 69%, p = 0.0007) (Fig 2).

Removing studies investigating albumin (n = 1) and HES (n = 2) from the meta-analysis left a more homogeneous group of 7 studies (I^2 = 50%, p = 0.06) that assessed the addition of FFP.

Dosing and Efficacy Outcomes: FFP Intervention Groups

Dosing

Among studies, the amount of FFP added to the prime was variable from fixed amounts in the range of 150-to-300 mL, to weight-dependent dosing ranging between 10 and 20 mL/kg, none of them being guided by fibrinogen levels or functional fibrinogen. None of the included studies directly compared different FFP dosing regimens. The available data did not allow any quantitative evaluation (Table 2).

Blood Loss

A total of 8 studies reported blood loss. One study reported blood loss within the first 6 postoperative hours, with a mean reduction of 1.2 mL/kg (95% CI −0.7 to 3.2).[17] The remaining 7 studies reported blood loss within the first 24 postoperative hours, with a mean reduction of 1.3 mL/kg (95% CI -3.7 to 1.0; p = 0.06) in the FFP groups compared with control and heterogeneity being moderate (I^2 = 50%, p = 0.06).[6,15,16,23,28,29]

Transfusion

Eight studies reported blood-product transfusion requirements. Due to heterogeneous reporting in mL/kg, mL, or numbers of patients transfused, a quantitative analysis was not feasible. One study demonstrated significantly less cryoprecipitate being transfused in the FFP group.[21] Another study reported significantly more FFP transfusions in the control group, while there were no differences in the transfusion of platelets and autologous salvaged blood.[15] However, most of the studies (n = 6) reported no difference in the total amount of allogeneic blood products transfused among the groups (Supplement 2).[15-17,23,28,29]

Laboratory Results

Eight studies reported laboratory and/or point-of-care parameters. Seven of the studies reported that fibrinogen levels or functional fibrinogen, as measured by rotational thromboelastometry or thromboelastography, were significantly higher in the FFP groups immediately after heparin reversal. Mean fibrinogen levels ranged from 0.58-to-1.71 g/L in the control groups and from 1.0-to-1.85 g/L in the intervention groups. Fibrin thromboelastometry (FIBTEM) maximum clot firmness (MCF) values ranged from 4-to-7.2 mm in the control groups, and from 7-to-9.9 mm in the intervention groups.[15,17,21,23,28,29] At 24 hours in the intensive care unit (ICU), fibrinogen levels and functional fibrinogen values were comparable and, equally, no differences in platelet count, prothrombin time, and activated partial thromboplastin time (aPTT) were detected.[15,21]

Bianchi et al. compared early FFP use in addition to the prime with late FFP administration after separation from CPB. The FIBTEM MCF values were significantly higher in the early FFP arm after heparin reversal and at arrival to the ICU but not at subsequent points. Fibrinogen values did not differ between study arms at arrival to the ICU; however, they were significantly higher in the early FFP arm at 24 and 48 postoperative hours. No significant between-group differences were observed regarding aPTT, international normalized ratio, and platelet count.[16]

Further Outcomes

Four studies reported ventilation time, ICU stay, and postoperative hospital stay with no significant between-group differences.[16,23,28,29] Three studies reported mortality and did not record differences between groups.[16,17,23]

Dosing and Efficacy Outcomes: Albumin Intervention Groups

Dosing

Dosing regimens and their reporting were heterogeneous, which limited any dose comparison.

One study compared 2 different albumin dose ranges by targeting a higher versus lower COP, and demonstrated that a higher COP target during bypass resulted in significantly shorter ventilation times, higher platelet counts at 24

Table 2
CPB Priming Protocols[15-33]

Study	Year	Total No	Treatment Group	Prime Volume (mL) (Treatment)	Dosing (Treatment)	Control Group	Prime Volume (mL) (Control)	Dosing (Control)	Comment
Akca	2015	20	HES 130/0.4 n = 10	NG	330.0 ± 122.93 mL* HES 130/0.4 6%	Ringer's lactate n = 10	NG	320 ± 161.93 mL*	
Bianchi	2017	73	FFP "early" n = 36	280 (280-360)	Volume was obtained difference between circuit priming volume and the calculated amount of RBC to maintain Hct.	FFP "late" n = 37	280 (280-360)	Volume of albumin 5% was obtained as the difference between circuit priming volume and the calculated amount of RBC to maintain Hct.	Post CPB during ultrafiltration: Early FFP-group: Half of the volume was replaced with albumin 5% (15 ml/kg). Late FFP: Half of the volume was replaced with FFP (15 mL/kg); additional 15 mL/kg FFP during hemostasis before transfer to the ICU.
Dieu	2020	59	FFP n = 30	NG	15 mL/kg	PlasmaLyte n = 29	NG	15 mL/kg	
Fu	2016	60	0.9% NaCl + RAP n = 26	600	Preop: active supplementation with crystalloid or colloid solution	Bank blood components n = 33	600	RBC calculated according to target Hct + 100 mL plasma + 10 g albumin 25%	
Golab	2011	70	Albumin COP > 18 mmHg* n = 34	300	CPB prime: albumin volume calculated to achieve 5% albumin concentration During CPB: additional albumin to preserve COP >18 mmHg	Albumin COP > 15 mmHg* n = 35	300	CPB prime: 0.5 g/kg albumin During CPB: additional albumin to preserve COP >15 mmHg	Treatment/control were added to a prime of individual amounts of RBCs, FFP, and gelofusine.
Gruenwald	2008	64	RFWB n = 31	400	Added to achieve a Hct of 22% to 24%	Bank blood components n = 33	400	added to achieve a Hct of 22% to 24%; Before X-clamp removal: 1 unit FFP	Treatment/control were added to a prime of PlasmaLyte and 75 mL albumin 25%.
Hanart	2009	119	HES 130/0.4 n = 60	350-850 weight-dependent	50 (45-50) mL/kg† HES 130/0.4 6% for intraoperative fluid replacement including CPB prime	Albumin n = 59	350-850 weight-dependent	50 (37-50) mL/kg albumin 4%† for intraoperative fluid replacement including CPB prime	Treatment/control were added to a prime of RBC and additional Ringer's lactate if needed.
Lee	2013	A: 54 B: 67	FFP A: n = 26 B: n = 34	NG weight-dependent	A: 150 (150, 150) mL† B: 300 (150, 300) mL†	Albumin A: n = 28 B: n = 33	NG weight-dependent	A: 50-100 mL albumin 20% B: 50-100 mL albumin 20%	Treatment/control were added to a prime of RBC and PlasmaLyte to eliminate volume differences to achieve the calculated prime volume.
McCall	2004	20	FFP n = 10	646 ± 103*	252 ± 46 mL* FFP 40 ± 29 mL* albumin 25%	Albumin n = 10	636 ± 93*	100 ± 9 mL* albumin 25%	Treatment/control added to a prime of PlasmaLyte, RBC, and albumin (target COP 16 mmHg).

(*continued on next page*)

Table 2 (*continued*)

Study	Year	Total No	Treatment Group	Prime Volume (mL) (Treatment)	Dosing (Treatment)	Control Group	Prime Volume (mL) (Control)	Dosing (Control)	Comment
Miao N	2014	60	HES 130/0.4 n = 30	450	250 mL HES 130/0.4 6%	Albumin 3.3% n = 30	450	50 mL albumin 20%	Treatment/control added to a prime of Multiple Electrolytes Injection to ensure a total volume of 450 ml.
Miao X	2014	91	FFP n = 46	NG	10-20 mL/kg	Gelofusin n = 45	NG	20 mL/kg	Treatment/control were added to a prime of 100-200 mL Plasmalyte, with/without RBC.
Miao X	2015	75	FFP A: n = 37	NG	1-2 units	Gelofusin n = 38	NG	10-20 mL/kg	Treatment/control were added to a prime of 100-200 mL Plasmalyte, with/without RBC.
Mou	2004	200	Fresh whole blood n = 96	NG	½ unit for circuit priming ½ unit during rewarming	Bank blood components n = 104	NG	½ unit RBC + ½ FFP for circuit priming ½ unit RBC during rewarming	Treatment/control added to a prime of 25% albumin (10% of the total priming volume).
Oliver	2003	56	FFP n = 28	800-1,200 weight-dependent	1 unit	Albumin n = 28	800-1,200 weight-dependent	200 mL albumin 5%	Treatment/control added to a prime of PlasmaLyte
Patel	2016	105	A: albumin n = 35 B: HES 130/0.4 n = 35	350-550 weight-dependent	A: 10 mL/kg albumin B: 20 mL/kg HES 130/0.4 6%	C: Ringer's lactate n = 35	350-550 weight-dependent	NG	
Riegger	2002	86	Albumin 5% n = 44	99.7 ± 27.4 ml/kg*	Crystalloid solution with 25% albumin added to make 5 g/100 mL of albumin	Crystalloid fluid n = 42	95.8 ± 24.8 mL/kg*		
Van der Linden	2013	55	HES 130/0.4 n = 31	400-800 weight-dependent	Up to 50 mL/kg HES 130/0.4 6% for Intraoperative volume replacement including CPB prime	Albumin n = 30	400-800 weight-dependent	Up to 50 mL/kg albumin 5% for Intraoperative volume replacement including CPB prime	
Yu	2008	151	Albumin 5% n = 68	280-390	48.2 ± 11.5 mL/kg*	Albumin 3% n = 83	280-390	50.8 ± 12.1 mL/kg*	
Zhou	2020	65	Succinylated gelatin 4% + albumin n = 32	210-240	10 mL/kg gelatin 25-50 mL (5-10g) albumin	Succinylated gelatin 4% n = 33	210-240	20 mL/kg gelatin	

NOTE. Studies included in the meta-analysis are marked in yellow.

Abbreviations: COP, colloid osmotic pressure; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hct, hematocrit; HES, hydroxyethyl starch; ICU, intensive care unit; IQR, interquartile range; NG, not given; RBC, red blood cells; RAP, retrograde autologous blood; RFWB, reconstituted fresh whole blood.

* Mean ± SD.

† Median (IQR).

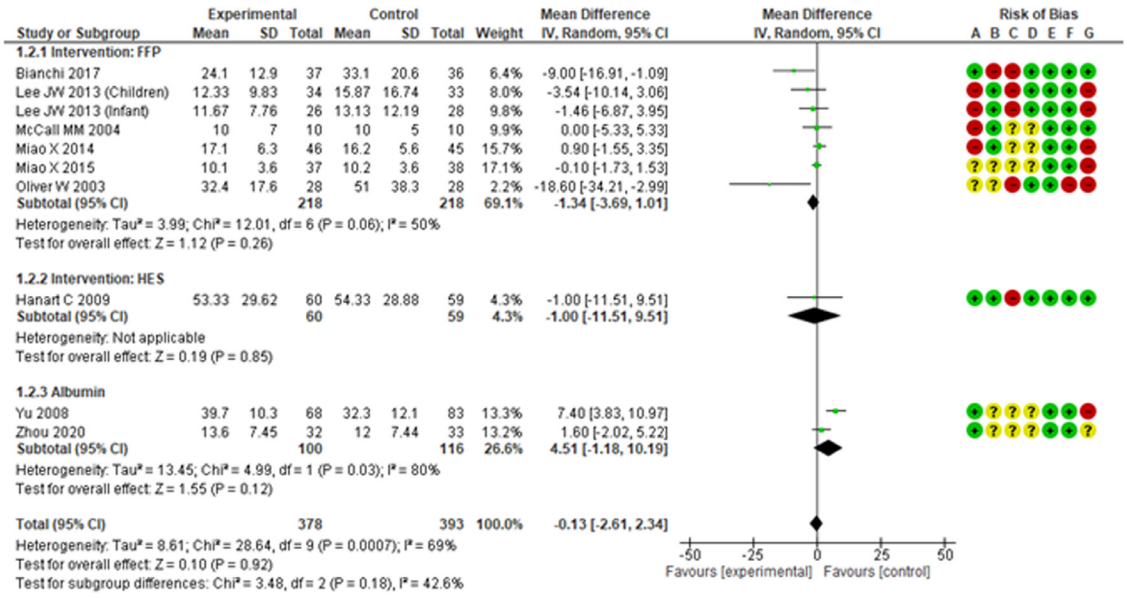

Fig 2. Risk of bias categories: (A) Random sequence generation (selection bias), (B) Allocation concealment (selection bias), (C) Blinding of participants and personnel (performance bias), (D) Blinding of outcome assessment (detection bias), (E) Incomplete outcome data (attrition bias), (F) Selective reporting (reporting bias), (G) Other bias.

postoperative hours, and lower lactate levels at the end of surgery. No differences in blood loss or transfusion requirement were reported.[19]

Another study compared high- versus low-dose albumin priming. Between the 2 groups, no statistically significant differences for blood loss, transfusion, length of ventilation, ICU stay, and hospital stay were found.[30]

Blood Loss

Only 3 studies reported blood loss. In one study, there was no difference in the proportion of children with postoperative drain loss ≥30 mL/72 hours across groups treated with albumin, HES, and crystalloid solution.[24] The remaining 2 studies reported blood loss in mL/kg/24 hours and were included in the meta-analysis. The mean reduction of blood loss was not significant (-2.07 mL/kg/24 hours [95% CI -4.49 to 0.34]) in the albumin intervention groups compared with control. Of note, while one of the studies compared gelatin plus albumin against gelatin alone, the other study compared 5% versus 3% albumin priming solutions.[26,30]

Transfusion

One study showed significantly fewer children in the albumin group required FFP within the first 72 hours compared to the HES and crystalloid fluid groups.[24] Another study reported more patients receiving red blood cells (RBCs) in the albumin group compared to control.[25] A further study reported no differences in the use of blood products and hemostatic drugs between groups.[26]

Laboratory Results

One study reported significantly higher platelet levels intra- and postoperatively in the albumin group compared to the other 2 groups.[24] Accordingly, another study reported significantly higher platelet counts 24 hours post-CPB in the albumin group targeting a higher COP.[19] A third study reported no significant differences in perioperative coagulation parameters. Only during chest closure was platelet consumption in the gelatin-only group significantly lower than in the albumin group.[26]

Further Outcomes

Two studies reported ventilation time, ICU stay, and postoperative hospital stay, with no significant between-group differences recorded.[25,26]

Dosing and Efficacy Outcomes: Artificial Colloid Intervention Groups

Dosing

Dosing regimens and their reporting were heterogeneous, which limited any dose comparison.

Blood Loss

Six studies reported blood loss, one of which reporting postoperative drainage in mL/kg per 24 hours and, therefore, was included in the meta-analysis. Mean blood loss was 1.00 mL/kg/24 hours (95% CI -11.51 to 9.51) lower in the artificial colloid group compared with control.[31]

One further study reported postoperative drainage in number of patients with <30 mL/72 hours, with no difference found between groups treated with HES compared with albumin.[24] One study reported blood loss in mL/6 hours and the remaining 3 studies in mL/24 hours, with no significant differences observed.[27,31-33]

Transfusion

Two studies reported no significant difference in the amount of transfused RBC or FFP.[27,33] A further study observed a significantly lower number of children in the HES group requiring allogeneic RBC transfusion compared with albumin, while another study reported significantly more children in the HES group requiring FFP within the first 72 hours compared with albumin.[24,31]

Laboratory Results

Three studies reported no significant differences in perioperative coagulation parameters between treatment and control groups.[27,31] A further study observed significantly lower platelet counts in patients receiving HES compared with albumin.[24]

Further Outcomes

Three studies reported ventilation time, ICU stay, and postoperative hospital stay, with no significant between-group differences.[27,31,33]

Efficacy Outcomes: Blood Intervention Groups

Blood Loss

The use of reconstituted fresh whole blood, compared with bank blood, resulted in significantly less postoperative blood loss.[20] Another study compared fresh whole blood versus reconstituted bank blood, with no significant between-group differences.[22]

Transfusion

One study comparing fresh whole blood versus reconstituted bank blood observed no significant difference in transfused volume, while another study reported less intraoperative transfused blood volume in the retrograde autologous priming group compared to bank blood priming.[18,22]

Further Outcomes

One study reported higher inotropic scores, longer ventilation times and longer hospital stays for bank blood component therapy compared with patients receiving reconstituted fresh whole blood.[20] Another study found that patients who received reconstituted bank blood had a shorter length of ICU stay and a trend toward shorter ventilation than those receiving fresh whole blood.[22] There were no significant differences in ventilation time or length of ICU stay between those treated with retrograde autologous priming and those treated with blood bank prime.[18]

Discussion

Key Findings

The key findings of this systematic review were the following:

- A limited number of overall small studies of moderate methodologic quality were identified. Most studies had 1 or more areas of high or unclear risk of bias, the latter due to insufficient reporting.
- Most studies were identified for the addition of FFP to the CPB prime, followed by albumin and artificial colloids.
- More than half of the studies investigated certain subpopulations at higher risk for bleeding, such as exclusively neonates or children with cyanotic heart disease. However, half of the studies excluded other subpopulations at higher risk, such as children undergoing reoperations or those with longer surgery times.
- The investigated interventions were targeted to reduce hemodilution by increasing COP. As the dosing regimens and their reporting were heterogeneous and COP was not always recorded, dose comparison was limited. Two studies explicitly compared high- versus low-dose albumin primes. Although one of these studies reported no difference in outcomes between the groups, the one adjusting albumin dosing to specific COP targets observed significantly shorter ventilation times, higher platelet counts at 24 postoperative hours, and lower lactate levels at the end of surgery in the higher COP group, with no differences in blood loss or transfusion requirement. This efficacy only was noted with a targeted intraoperative COP of >18 mmHg in comparison with >15 mmHg; while in both arms of the nonefficacious study, intraoperative COP values were <15 mmHg, suggesting a possible dose-dependent effect.[19,30]
- Two of the studies investigating albumin reported significantly higher platelet levels intra- and postoperatively in the albumin group or in the albumin group targeting a higher COP, respectively.[19,24] This finding corresponded with data from adult studies indicating that albumin prime better preserves platelet counts than crystalloid priming fluid.[7]
- All studies comparing artificial colloids (HES) against albumin demonstrated equivalence between the groups regarding intraoperative fluid balance, blood loss, transfusion volumes, and renal function. None of the studies observed significant alterations of coagulation parameter or blood loss.
- In the studies investigating FFP, the amount of FFP added to the prime was variable, and none of the studies directly compared different dosing regimens. However, in all studies, the intervention resulted in significantly increased fibrinogen levels and/or functional fibrinogen as measured by rotational thromboelastometry or thromboelastography immediately after heparin reversal, although this effect was not sustained at 24 hours in the ICU. Furthermore, compared with late FFP administration after separation

from CPB, the addition of FFP to the prime resulted in significantly higher FIBTEM MCF values. This effect was observed after heparin reversal and upon arrival in the ICU, but not at subsequent points. Fibrinogen levels did not differ between study arms upon arrival in the ICU; however, they were significantly higher in the early FFP arm at 24 and 48 postoperative hours. No significant between-group differences with respect to aPTT, international normalized ratio, and platelet count were observed in any of the studies.

- Some of the FFP studies reported significant changes in blood loss or transfusion requirements. These studies investigated exclusively the youngest patients such as neonates, who represent a population at high risk for perioperative bleeding and, therefore, are most likely to benefit from any intervention aiming to reduce bleeding.[15,16,21,23,34]
- Reporting of endpoints related to perioperative bleeding was heterogeneous. Blood loss in mL/kg/24 hours was the most frequently and most homogeneously reported outcome and the only endpoint able to be evaluated in a meta-analysis. This revealed no significant reduction in 24-hour blood loss comparing the interventions groups against the control groups, although with substantial heterogeneity within the dataset. The heterogeneity possibly was attributable to the considerable variations in interventions, comparators, and dosing regimens.
- Two FFP studies and 2 albumin studies reported lower transfusion volumes compared to control groups. However, the lack of standardized transfusion protocols in most of the studies compromised the interpretation of transfusion outcomes.
- The data on safety outcomes were sparse and heterogeneous and, thus, unsuitable for a meta-analysis. None of the studies detected significant differences in the rates of thromboses, anaphylaxis, or renal impairment.

Limitations

This analysis had some considerable limitations. First, the validity of any meta-analysis is dependent on the quantity and quality of included studies, and, unfortunately, only a small number of studies of moderate quality were eligible for inclusion. The intra- and interstudy variability concerned the patients' age and surgical complexity (and, hence, their a priori risk of bleeding), as well as common practice in the involved study centers (eg, whether point-of-care testing was available). This variability affected the interpretation and generalizability of study results; however, it mirrored the heterogeneity in common clinical practice, imposing multifaceted challenges on the management of bleeding associated with CPB.

Also, the investigated interventions and dosing regimens were performed and reported heterogeneously, and COP was not always recorded. For these reasons dose comparison was limited.

The critical role of fibrinogen in CPB-related coagulopathy is well-documented and FFP an established and widely available fibrinogen source for supplementation.[35,36] However, the fibrinogen content of FFP is low in relation to the containing fluid volume and varies between 1.5 and 4.0 g/L, which possibly could have affected the consistency of study results and the longevity of its effects.[37] Reported endpoints related to perioperative bleeding were heterogeneous and their clinical meaningfulness should be questioned. For example, considering that the increases of fibrinogen and functional fibrinogen in the FFP groups were limited to the immediate post-CPB period, a specific evaluation of immediate postoperative bleeding (between the end of CPB and admission to ICU) might be more meaningful to assess the clinical effects of changes in fibrinogen level. Furthermore, the lack of standardized transfusion protocols mostly compromised the interpretation of transfusion outcomes.

Conclusion

The current Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) guideline recommends that colloids (such as albumin) should be preferred over crystalloid priming solutions for children undergoing cardiac surgery (Grade 1C). The addition of FFP to the CPB prime is recommended only in neonates (Grade 2C).[2]

The guideline describes that the particular risk of bleeding in the pediatric CPB cohort warrants age- and weight-adjusted blood management.[2] However, the overall sparse and heterogeneous available pediatric data investigating CPB priming fluids leads to extrapolation from adult data.[6] Hence, further specific pediatric research is required, and this meta-analysis and systematic review can, despite its limitations, possibly help to highlight gaps of knowledge and raise some important questions:

- What is the optimal COP during CPB, and does it depend on age and weight?
- Is a higher COP prime effective in reducing hemodilution and, thus, perioperative bleeding, and is it safe considering renal function?
- Is the composition of priming fluids guided by COP feasible and effective in reducing hemodilution on CPB?
- Does the preservation of platelets through the addition of albumin to the CPB prime translate to reduced perioperative bleeding?
- Are artificial colloids not only equivalent to albumin but safe to use in children undergoing cardiac surgery on CPB?
- Is a targeted addition of fibrinogen to the CPB prime guided by fibrinogen levels or functional fibrinogen feasible and safe, and could it lead to more long-lasting effects on perioperative bleeding?

Conflict of Interest

The authors are investigators in the FIBCON Trial, which is funded by CSL Behring 220,000 € (CSL-B advised on aspects of

trial design, no role in study conduct, data analysis, data presentation), Sponsor: Guy's & St Thomas' NHS Foundation Trust.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.11.031.

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