Albumin Versus Crystalloid for Pump Priming in Cardiac Surgery: Meta-Analysis of Controlled Trials

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Objectives: **To determine the effects of pump priming fluid choice on platelets, fluid balance, and clinical outcomes.**

Design: **Meta-analysis of controlled clinical trials. Primary endpoints were platelet counts, colloid oncotic pressure, on-bypass fluid balance, postoperative weight gain, and colloid usage.**

Setting: **Cardiac surgery with cardiopulmonary bypass.**

Patients: **Adult and pediatric patients undergoing cardiac surgery, including coronary artery bypass grafting, valve procedures, and correction of congenital cardiac anomalies.**

Interventions: **Extracorporeal circuit priming with either albumin or crystalloid.**

Measurements and Results: **The meta-analysis included 21 controlled trials with 1,346 total patients. Albumin prime significantly reduced the on-bypass drop in platelet counts. The pooled weighted mean difference in platelet count drop with albumin versus crystalloid prime was -23.8×10^9/L (confidence interval [CI], -42.8 to -4.7×10^9/L). The colloid oncotic pressure decline was also smaller when albumin rather than crystalloid was used for priming, with a pooled weighted mean difference of −3.6 mm Hg (CI, −4.8 to −2.3 mmHg) during bypass and −2.0 mmHg (CI, −2.9 to −1.1 mmHg) after surgery. Albumin prime correspondingly reduced on-bypass positive fluid balance (−584 mL; CI, −819 to −348 mL) and postoperative weight gain (−1.0 kg; CI, −0.6 to −1.3 kg) compared with crystalloid. Postoperative colloid usage was lower with albumin than crystalloid prime (−612 mL; CI, −983 to −241 mL).**

Conclusions: **Albumin prime better preserves platelet counts than crystalloid. Albumin also favorably influences colloid oncotic pressure, on-bypass positive fluid balance, postoperative weight gain, and colloid usage. The clinical significance of these observations merits further investigation.**

KEY WORDS: cardiopulmonary bypass, extracorporeal circulation, hemodynamics, on-pump, platelets

SINCE THE early 1970s, albumin has been commonly added as a constituent of the extracorporeal circuit priming fluid during cardiac surgery. Two chief considerations have prompted the use of albumin for this purpose. First, albumin can coat the fluid pathway surface, thereby diminishing contact between the blood and nonbiological materials that could result in protein denaturation, platelet activation and consumption, release of inflammatory mediators, and initiation of the complement cascade.[1-3] Second, albumin in the prime can attenuate the on-bypass fall in colloid oncotic pressure (COP) that might lead to myocardial, pulmonary, intestinal, and cerebral edema.[4,5]

Effects on platelet number and function are a central concern in choice of priming fluid because of the risks of platelet-related thrombotic and hemorrhagic complications associated with cardiopulmonary bypass (CPB). Intraoperatively, platelet activation by thrombogenic surfaces of the extracorporeal circuit can contribute to oxygenator thrombosis manifested by high transoxygenator pressure gradients and sharply reduced platelet counts.[6] Inclusion of albumin in the prime is the only measure shown to be effective in avoiding oxygenator thrombosis, which is the leading cause of emergency oxygenator replacement.[7] Postoperatively, platelet depletion and dysfunction may promote nonsurgical bleeding. In a study of patients undergoing surgery with CPB, total chest tube drainage was shown to be significantly associated with decreases in both platelet count and aggregability.[8]

Avoidance of fluid shifts because of decreasing COP may be of value in maintaining adequate respiratory function. Inclusion of albumin in the prime has been shown to reduce extravascular lung water accumulation and pulmonary shunt fraction.[9,10] Notwithstanding these advantages of albumin, crystalloid has been increasingly substituted as the prime to reduce fluid acquisition costs. This practice has been based partly on inconsistencies in the data documenting the benefits of albumin in the prime and partly on the lack of unequivocal evidence that albumin prime improves outcomes. For instance, the lack of a significant albumin prime effect on respiratory function and time to extubation has been reported.[11]

Because most reported trials comparing albumin with crystalloid prime have involved small numbers of patients, it is difficult to judge whether inconsistent findings indicate that differences in priming fluid effects are small or simply that the trials lacked statistical power. For example, in most trials, the artificial colloid hydroxyethyl starch was not found to exert a significant effect on bleeding after cardiac surgery; whereas, when all the trials were combined in a recent meta-analysis, a consistent and significant increase in postoperative bleeding was apparent in patients receiving hydroxyethyl starch either for pump priming or volume expansion.[12] Thus far, the evidence from trials comparing albumin with crystalloid as the priming fluid has not been systematically reviewed. The authors therefore conducted a meta-analysis of such trials to test the hypothesis that albumin prime better maintains platelet counts and COP and lessens on-bypass and postoperative fluid imbalance. The study also assessed whether choice of priming fluid significantly affects postoperative colloid usage, time to extubation, homologous blood transfused, and length of stay.

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Table 1. Characteristics of Included Trials

Trial	n*	Setting	Prime		Major Findings
			Composition	Albumin (%)†	
Öhqvist et al, 1981[4]	14	Aortic valve replacement	2,000 mL Ringerdex® *v* 200 mL 20% albumin + 1,800 mL Ringerdex®	2	COP and arterial oxygen tension higher in albumin prime group after bypass
Öhqvist et al, 1981[5]	16	Aortic valve replacement	2,000 mL Ringerdex® *v* 400 mL 20% albumin + 1,600 mL Ringerdex®	4	Smaller COP decline during bypass in albumin than crystalloid prime group and earlier post bypass return to baseline
Sade et al, 1985[9]	57	CABG, valve procedures and CABG/ valve procedures	2,500 mL RL *v* 800 mL/m^2 5% albumin added to RL to make total volume of 2,500 mL	3	Intraoperative COP higher in albumin than RL prime group and postoperative pulmonary shunt fraction and weight gain lower
Kamada et al, 1988[15]	38	Coronary bypass operation	1,000 mL Isolyte® S + 500 mL 20% mannitol with no albumin *v* with 100 mL 25% albumin *v* with 200 mL 25% albumin	1.6 3.1	Proportions of crenated erythrocytes respectively greater by 18 and 10 fold during and after bypass with crystalloid prime as compared with 3.1% albumin prime
Karliczek et al, 1989[16]	—‡	Routine coronary artery surgery	RL *v* 5% albumin in RL	—‡	Albumin prime attenuated on-bypass hypotension
Marelli et al, 1989[17]	100	Aortocoronary bypass, valve and other reparative intracardiac procedures	1,600 mL RL *v* 200 mL 25% albumin + 1,400 mL RL	3.1	Intraoperative crystalloid requirement greater in RL prime group and postoperative CVP and PAWP lower; urine output greater in RL group at 6-12 h postoperatively; 21% of albumin patients received diuretic at 24 h *v* 4% of RL group
McGrath et al, 1989[18]	49	Elective myocardial revascular-ization	2,000 mL RL *v* 500 mL 5% albumin + 1,500 mL RL	1.25	In crystalloid prime group, 4.5-fold greater postoperative colloid requirement and 58% larger post-operative weight gain
Bonser et al, 1990[19]	24	Elective coronary artery operations	2,000 mL Hartmann's solution *v* 400 mL 4.5% albumin + 1,600 mL Hartmann's solution	0.9	No between-group differences in complement factors B and C3 or split products Ba and C3d
Hoeft et al, 1991[10]	20	CABG	1,400 mL RL + 500 mL 5% glucose + 100 mL bicarbonate *v* 400 mL 20% albumin + 1,000 mL RL + 500 mL 5% glucose + 100 mL bicarbonate	4	Intra- and postoperative COP and COP-PAWP gradient greater in albumin prime group; EVLW in RL group increased by over 60% *v* baseline level but minimal EVLW increase in albumin group; no difference in alveolar-arterial oxygen gradient
Boldt et al, 1992[1]	36	CABG	2,250 mL RL *v* 250 mL 5% albumin + 1,000 mL RL + 1,000 mL 5% dextrose *v* 400 mL 20% albumin + 1,850 mL RL	0.6 3.6	Lower on-bypass positive fluid balance in albumin prime group; in 0.6% albumin group maximum platelet aggregation greater than in other groups
London et al, 1992[20]	60	CABG and valve procedures	2,000 mL RL *v* 300 mL 25% albumin + 1,700 mL RL	3.8	Intraoperative COP higher and volume requirement lower in albumin prime group
Zabala et al, 1993[21]	60	Open heart surgery using CPB	1,250 mL Isolyte® E + 20 mL/kg 20% mannitol *v* 200 mL 20% albumin + 1,000 mL Isolyte® E + 20 mL/kg 20% mannitol	3.3	Intra- and postoperative COP maintained closer to baseline level in albumin prime group; blood lactate concentration higher in crystalloid group during surgery and after transfer to ICU
Abbott et al, 1994[22]	19	Elective, first-time CABG	2,000 mL sodium lactate, 15 mmol KCl, 20 g mannitol, 8000 IU heparin, 1.5 g cefuroxime *v* 2000 mL 4.6% albumin as plasma protein solution, 15 mmol KCl, 20 g mannitol, 8,000 IU heparin, 1.5 g cefuroxime, 50 mmol sodium bicarbonate	4.6	2 fold rise in on-bypass intraocular pressure contemporaneous with 50% fall in COP among crystalloid but not albumin recipients

Table 1. Characteristics of Included Trials (Cont'd)

Trial	n*	Setting	Prime		Major Findings
			Composition	Albumin (%)†	
Jenkins and Curtis, 1995[11]	51	Elective cardiac surgery requiring CPB	2800 mL RL + 10000 units heparin *v* 300 mL 25% albumin + 2800 mL RL + 10000 units heparin	2.4	On-bypass positive fluid balance greater in RL than albumin prime group; no significant difference in respiratory parameters or time of extubation
Scott et al, 1995[23]	64	Nonurgent first-time CABG	2,000 mL Plasma-Lyte® *v* 1,000 mL 4.6% albumin as plasma protein solution + 1,000 mL Plasma-Lyte®	2.3	Greater postoperative positive fluid balance and colloid requirement in crystalloid prime group: lower intra- and postoperative urine output and greater postoperative furosemide requirement in albumin group
Buhre et al, 1997[24]	26	Mitral valve replacement in patients with 3rd or 4th degree mitral valve insufficiency	1,400 mL RL + 500 mL 5% glucose + 100 mL bicarbonate *v* 400 mL 20% albumin + 1,000 mL RL + 500 mL 5% glucose + 100 mL bicarbonate	4	No significant difference in hemodynamic function, EVLW or time of extubation; marked fall in stroke volume index at 1 h postoperatively in crystalloid but not albumin prime group
Aukerman et al, 1998[25]	76	Correction of congenital heart anomaly in pediatric patients	8.4% Normosol® R, 25 mEq/L $NaHCO_3$, 100 U/kg heparin, 0.25-0.5 g/kg 25% mannitol + antibiotic without *v* with albumin added to final concentration of 4%§	4	Less postoperative weight gain in albumin prime group
Palanzo et al, 1999[3]	40	Non-emergency first-time open-heart surgery	2,200 mL Isolyte® S, 10 mEq sodium bicarbonate and 5000 U porcine sodium heparin without *v* with 100 mL 25% albumin	1.1	Intraoperative plateletdrop in crystalloid but not albumin prime group
Canver and Nichols, 2000[26]	428	Isolated primary CABG	2,200 mL Isolyte® S *v* 50 mL 25% albumin + 2150 mL Isolyte® S	0.6	No between-group differences in blood product usage, length of stay or mortality
Zarro et al, 2001[27]	53	Non-emergency myocardial revascular-ization in consecutive patients	2,200 mL Isolyte® S *v* 250 mL 5% albumin + 2000 mL Isolyte® S	0.6	38% less postoperative weight gain in albumin prime group, but difference not statistically significant
Myers et al, 2002[28]	115	CPB	1,800 mL Normosol® R + 60 mL heparin (5000 units) *v* 250 mL 5% albumin + 1,550 mL Normosol® R + 60 mL heparin (5000 units)	0.7	Higher COP, lower volume requirement and smaller platelet count drop during bypass in albumin prime group

Abbreviations: CABG, coronary artery bypass graft; COP, colloid oncotic pressure; CPB, cardiopulmonary bypass; CVP, central venous pressure; EVLW, extravascular lung water; ICU, intensive care unit; PAWP, pulmonary arterial wedge pressure; RL, Ringer's lactate.

Products: Ringerdex®, Pharmacia, Uppsala, Sweden; Isolyte® S, McGaw, Inc, Irvine, CA; Isolyte® E, Baxter, S.A., Valencia, Spain; Plasma-Lyte®, Baxter Healthcare Proprietary Ltd, Old Toongabbie, NSW, Australia; Normosol® R, Abbott Laboratories, North Chicago, IL.

*Total patients receiving albumin or crystalloid prime in study.

†Final prime albumin concentration in patients receiving albumin prime.

‡Not reported.

§Packed red blood cells added to prime for all patients weighing less than 5 kg and also for those greater than 5 kg if patient's calculated resultant hematocrit after hemodilution would be less than 18%-20%.

METHODS

Controlled trials were included if they compared albumin with crystalloid as the pump priming fluid in cardiac surgery with CPB. Both randomized and nonrandomized controlled trials were eligible for inclusion. The primary endpoints of interest were platelet counts, COP, fluid balance, and colloid usage. Time to extubation, homologous blood transfused, and length of stay were also assessed as secondary endpoints. Availability of data for all endpoints was not a trial inclusion criterion, and the meta-analysis comparing albumin and crystalloid with respect to a particular endpoint (eg, COP) was based on the subset of included trials with data for that endpoint.

Between-trial heterogeneity was anticipated, and 3 potential effect size modifiers were identified a priori that might explain such heterogeneity: prime albumin concentration, the use of randomization, and year of publication. Analyses were planned to assess the influence of these variables. Prime albumin concentration was selected to assess

Table 2. Operative and Postoperative Patient Data

Parameter	n*	Pooled Group Mean (CI)		p
		Albumin	Crystalloid	
Operative				
Ischemia time (min)	13	67.3 (56.6-78.0)	64.3 (55.4-73.1)	0.40
Bypass time (min)	14	105.2 (86.7-123.7)	103.9 (90.7-117.1)	0.80
Postoperative				
Time to extubation (h)	8	18.6 (15.2-22.0)	17.5 (13.9-21.2)	0.82
Homologous blood transfused (mL)†	5	812 (408-1,215)	817 (414-1,220)	0.88
Blood Loss (mL)†	10	817 (587-1,048)	881 (693-1,069)	0.17
Intensive care unit stay (d)‡	4	3.6 (1.7-5.5)	2.8 (1.6-4.1)	0.70
Hospital stay (d)‡	3	9.5 (5.8-13.2)	9.8 (4.9-14.6)	0.98

*Number of trials with data.

†First 24 hours postoperatively.

‡Data from 1 study excluded because length of stay determined by Veterans Administration hospital system policy rather than patient clinical condition.[26]

dose dependency. Empirical data suggest that in some contexts the results of randomized trials may differ systematically from those of nonrandomized trials, and, therefore, in the planned analyses this possibility was investigated. Changes over time in methods and standards of care in cardiac surgery might alter effects attributable to choice of priming fluid, and thus year of publication or completion was chosen as the metric for temporal changes.

Published and unpublished trials conforming to the previously mentioned selection criteria were sought by a variety of methods. These included computer searches of bibliographic databases, the Cochrane Library, and other Internet-resident information resources; hand searching; inquiries with investigators in the field and medical directors of fluid management product suppliers; and perusal of reference lists. No language restrictions were applied. Searches were conducted between June and November 2002.

Two investigators (MMW and RJN) independently selected trials and extracted data. Disparities in selection and extraction decisions were resolved through discussion. Extracted data consisted of patient demographics; surgical procedures performed; priming fluid composition; trial design; major study findings as reported; and pre-, intra- and postoperative variables.

The primary outcome measure for the meta-analysis was the weighted mean difference in effect size between groups. Statistically significant differences are denoted by the absence of zero from the corresponding 95% confidence interval (CI). In the case of platelet counts and COP, the difference between albumin and crystalloid in change from baseline was calculated, and the variance for change from baseline was imputed from the reported standard deviations on the assumption of intragroup correlation equal to 0.5.[13] Data were combined using random effects models, which are designed to accommodate between-trial heterogeneity. The impact of the 3 selected explanatory variables was evaluated by univariate and multivariate random effects metaregression. Publication bias was assessed by Egger's test.[14]

RESULTS

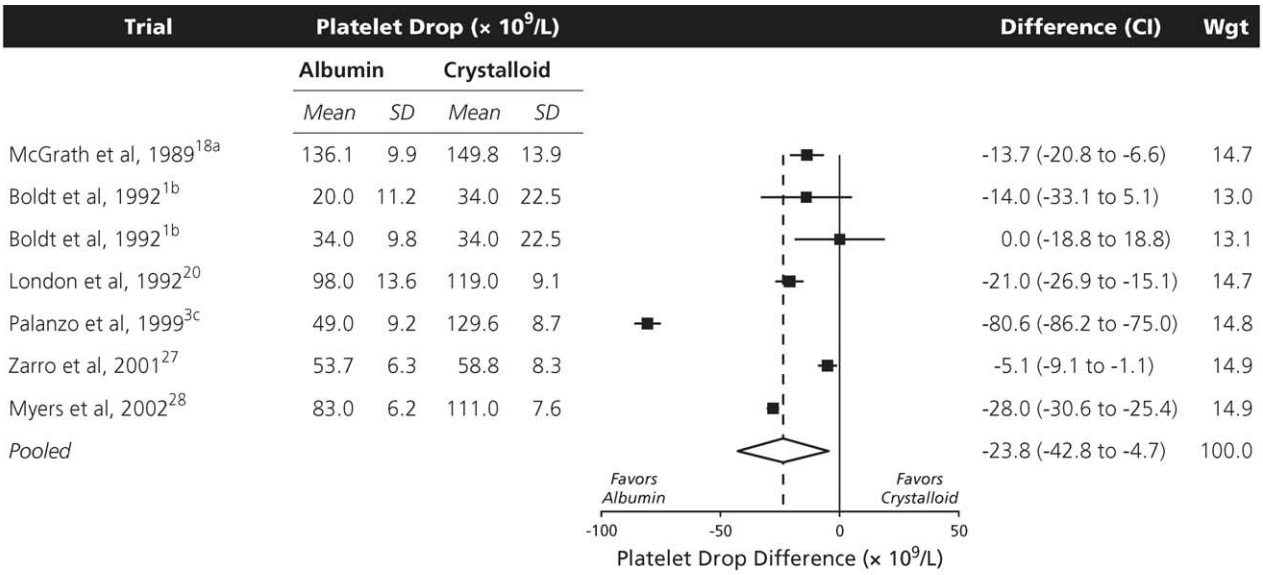
Twenty-one trials with a total of 1,346 patients were included.[1,3-5,9-11,15-28] None was unpublished. The characteristics of the trials, which were reported in the period 1981 to 2002, are summarized in Table 1. The median number of patients per trial was 50 (range, 14-428). Seventeen trials involved adults, 1 pediatric patient, and 3 of unspecified age. For the adult trials, patient age, and weight were 59.8 ± 6.2 years and 75.1 ± 5.1 kg, respectively (mean ± standard deviation). For patients receiving albumin in the prime, the median prime albumin concentration was 3% (range, 0.6%-5%). No significant between-group differences were evident in duration of ischemia or bypass (Table 2).

Fourteen trials (67%) were randomized.[1,3-5,9-11,16,17,19,20,22-24] Some form of blinding was used in 5 of 21 trials (24%).[11,17,19,22,23] Patient selection criteria were described in the reports of 8 included trials.[3,9,11,18,20,22,23,28] Preoperative coagulopathy was the most frequent exclusion criterion and was applied in 5 of 8 of these trials (62%).

In 6 of 7 controlled trial comparisons (86%), the on-bypass drop in platelet counts was smaller in the albumin than the crystalloid prime group, and in 1 trial comparison there was no difference (Fig 1). The pooled difference in platelet drop of -23.8×10^9/L (CI, -42.8 to -4.7×10^9/L) was statistically significant. The magnitude of the difference was not significantly related to prime albumin concentration ($p = 0.60$), trial design ($p = 0.42$), or year of publication ($p = 0.40$). No evidence was found of publication bias with respect to platelet drop difference ($p = 0.97$). Postoperatively, there was no significant platelet drop difference between the albumin and crystalloid groups ($p = 0.10$).

As shown in Figure 2, the on-bypass COP drop was smaller for the albumin prime group in 9 of 9 of trials (100%), and the pooled difference (-3.6 mmHg; CI, -4.8 to -2.3 mmHg) was significant. In a multivariate model, the difference was larger at higher prime albumin concentrations ($p = 0.001$), whereas study design was without effect ($p = 0.71$). The model could explain 77% of the between-trial variance. Publication year was not a significant determinant of the difference ($p = 0.23$), nor was there evidence of publication bias with respect to this endpoint ($p = 0.36$).

A significant COP drop difference (-2.0 mmHg; CI, -2.9 to -1.1 mmHg) persisted postoperatively, although the difference was smaller than that on bypass. The postoperative COP drop was smaller among albumin recipients in 6 of 7 trials (86%). The postoperative difference was greater at increasing prime albumin concentrations ($p < 0.0005$) but was not significantly influenced by study design ($p = 0.42$) or publication year ($p = 0.96$). The concentration effect could explain 72% of the between-study variance. Publication bias in this endpoint was not detectable ($p = 0.60$).



[a]Intraoperative platelet count during the prebypass period not reported for this trial, and so preoperative count was used for platelet drop calculation.

[b]Two different prime albumin concentrations were tested in this trial.

[c]This was the only trial with platelet drop data in which patients receiving intraoperative blood or blood products were specifically excluded. With results of this trial excluded, a significant pooled difference in platelet drop of -14.6 × 10^9/L (CI, -25.2 to -4.0 × 10^9/L) persisted.

Fig 1. Difference between albumin and crystalloid prime in on-bypass platelet count drop. Data points representing differences for individual trials are scaled in proportion to meta-analytic weight.

Pooled on-bypass positive fluid balance was lower among albumin recipients in 10 of 10 controlled comparisons (100%), and the pooled difference (−584 mL; CI, −819 to −348 mL) was significant (Fig 3). The fluid balance difference increased at higher prime albumin concentrations, although this relationship was not statistically significant ($p = 0.30$). The difference did not vary significantly in relation to study design ($p = 0.47$) or year of publication ($p = 0.88$). No publication bias was apparent in this endpoint ($p = 0.23$).

Data on weight gain at 24 hours postoperatively compared with preoperative weight were reported in 4 trials of adults.[9,18,20,27] Weight gain was smaller for the albumin than the crystalloid prime group in all 4 trials with a significant pooled difference of −1.0 kg (CI, −0.6 to −1.3 kg). Significantly greater weight gain was also reported in a pediatric trial.[25]

Total fluid input, including crystalloid, colloid and blood products, throughout the intraoperative period, as well as the first 24 hours postoperatively, was reported for 3 trials of adults.[4,23,27] Total fluid input in the crystalloid group exceeded that in albumin recipients; however, the pooled difference of −829 mL (CI, −2,973 to 1,316 mL) was nonsignificant.

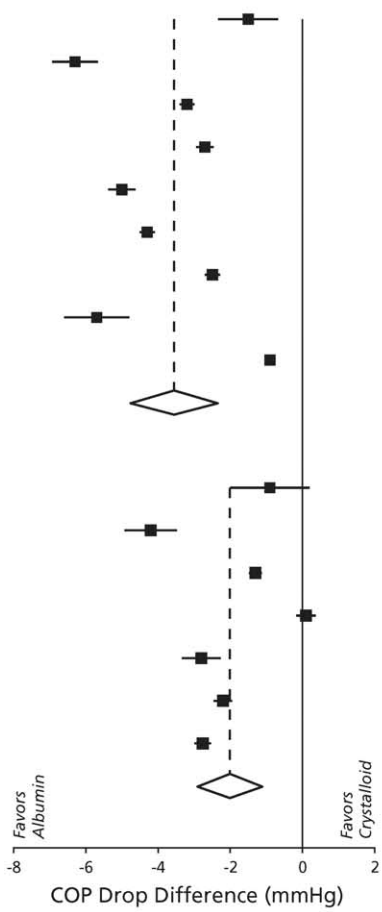
Quantitative data on postoperative diuretic usage were reported for 3 trials.[17,20,23] In these trials, diuretics were administered more frequently to albumin prime group patients, although this observation was not statistically significant (pooled odds ratio, 2.52; CI, 0.95-6.64). In contrast, average diuretic dose, which was reported in 1 of the 3 trials,[20] was lower for the albumin prime group. In 2 additional trials without quantitative data, diuretic usage was reported to be similar between the albumin and crystalloid prime groups.[9,25]

During the first 24 hours postoperatively, colloid usage was lower in the albumin than the crystalloid prime group in 6 of 6 adult trials (100%), as indicated in Figure 4. The pooled colloid usage difference (−612 mL; CI, −983 to −241 mL) was significant. The difference was augmented by higher prime albumin concentrations, although this dose effect was not statistically significant ($p = 0.20$). The difference was not affected by trial design ($p = 0.71$) or publication year ($p = 0.48$), and publication bias was not evident ($p = 0.13$). Postoperative albumin usage was also lower in 1 pediatric trial,[25] although the difference was not statistically significant.

In 4 trials of adults, data were available on combined total colloid usage for the intraoperative period, including prime colloid, and the first 24 hours after operation.[4,9,23,27] Although combined total colloid usage was higher in the albumin group, the pooled difference (98 mL; CI, −193 to 389 mL) was nonsignificant.

Postoperative crystalloid usage over the first 24 hours was lower with albumin prime in 2 of 3 trials (67%) with data.[17,18,27] However, the pooled difference (−97 mL; CI, −538 to 345 mL) was not significant. The albumin and crystalloid groups were similar in time to extubation, homologous blood transfused, and intensive care unit and hospital stay (Table 2). Albumin recipients experienced less postoperative blood loss, but the difference was not significant ($p = 0.21$).

Trial	COP Drop (mm Hg)				Difference (CI)	Wgt
	Albumin		Crystalloid			
	Mean	*SD*	*Mean*	*SD*		
On-Bypass						
Öhqvist et al, 1981[4]	9.2	0.9	10.7	0.7	-1.5 (-2.3 to -0.7)	10.7
Öhqvist et al, 1981[5]	6.1	0.7	12.4	0.6	-6.3 (-6.9 to -5.7)	11.0
Sade et al, 1985[9]	4.9	0.5	8.1	0.3	-3.2 (-3.4 to -3.0)	11.3
McGrath et al, 1989[18a]	7.1	0.4	9.8	0.5	-2.7 (-2.9 to -2.5)	11.3
Hoeft et al, 1991[10]	6.0	0.6	11.0	0.3	-5.0 (-5.4 to -4.6)	11.2
London et al, 1992[20]	6.1	0.4	10.4	0.4	-4.3 (-4.5 to -4.1)	11.3
Zabala et al, 1993[21]	8.2	0.5	10.7	0.4	-2.5 (-2.7 to -2.3)	11.3
Abbott et al, 1994[22]	3.9	0.8	9.6	1.2	-5.7 (-6.6 to -4.8)	10.6
Myers et al, 2002[28]	9.3	0.2	10.2	0.2	-0.9 (-1.0 to -0.8)	11.3
Pooled					-3.6 (-4.8 to -2.3)	100.0
Postoperative						
Öhqvist et al, 1981[4]	1.3	1.0	2.2	1.1	-0.9 (-2.0 to 0.2)	12.3
Öhqvist et al, 1981[5]	0.6	0.8	4.8	0.7	-4.2 (-4.9 to -3.5)	13.7
Sade et al, 1985[9]	3.8	0.3	5.1	0.4	-1.3 (-1.5 to -1.1)	15.0
McGrath et al, 1989[18a]	1.9	0.4	1.8	0.5	0.1 (-0.2 to 0.4)	14.9
Hoeft et al, 1991[10]	3.5	0.7	6.3	0.5	-2.8 (-3.3 to -2.3)	14.3
London et al, 1992[20]	0.3	0.4	2.5	0.6	-2.2 (-2.5 to -1.9)	14.9
Zabala et al, 1993[21]	2.3	0.5	5.1	0.4	-2.8 (-3.0 to -2.5)	14.9
Pooled					-2.0 (-2.9 to -1.1)	100.0



[a]Prebypass COP not reported, and so imputed value based on pooled data from other included trials used for COP drop calculation.

Fig 2. Difference between albumin and crystalloid prime in COP decline from baseline during bypass and after surgery.

DISCUSSION

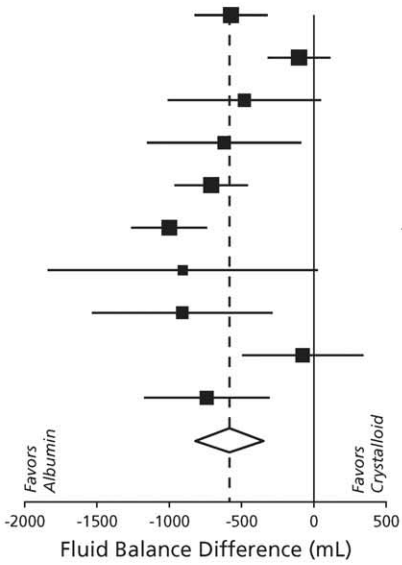
This meta-analysis shows that albumin exerts significant favorable effects during bypass on platelet count, COP, and positive fluid balance, as well as on postoperative COP, weight gain, and colloid usage in patients undergoing cardiopulmonary bypass. No significant differences were apparent in markers of hemorrhagic complications because of bypass (ie, postoperative blood loss and transfusion). Unfortunately, thrombotic complications such as stroke and neurocognitive dysfunction were not reported.

It is noteworthy that significant differences for several endpoints could be detected in this meta-analysis, even though the included studies generally involved highly selected, lower risk patient populations. It is possible that these differences would be more pronounced in routine cardiac surgical practice. CPB is often attended by potentially harmful physiologic derangements such as platelet activation, thrombosis, systemic inflammatory response syndrome, edema, organ dysfunction, thrombocytopenia, and nonsurgical hemorrhage. Perioperative fluid management could influence all of these consequences of CPB.

The optimal priming fluid in cardiac surgery is a topic of enduring and lively debate. Proponents of colloid-based prime emphasize the importance of avoiding a COP decline and concomitant edema that can compromise organ function. This meta-analysis amply shows that indeed the use of colloid prime attenuates the fall in COP. Albumin prime reduced on-bypass positive fluid balance by an average of nearly 600 mL and lowered postoperative weight gain by 1 kg.

Crystalloid advocates note the lack of clear evidence that more expensive colloidal priming fluids quantifiably im-

Trial	On-Bypass Fluid Balance (mL)				Difference (CI)	Wgt
	Albumin		Crystalloid			
	Mean	*SD*	*Mean*	*SD*		
Öhqvist et al, 1981[5]	2186	237	2759	277	-573 (-826 to -320)	12.7
Marelli et al, 1989[17]	5577	554	5679	554	-102 (-319 to 115)	13.2
Boldt et al, 1992[1a]	210	400	690	600	-480 (-1011 to 51)	8.5
Boldt et al, 1992[1a]	70	410	690	600	-620 (-1153 to -87)	8.5
London et al, 1992[20]	2230	402	2940	585	-710 (-964 to -456)	12.7
Abbott et al, 1994[22]	0	292[b]	1000	292	-1000 (-1263 to -737)	12.6
Jenkins and Curtis, 1995[11]	4969	1899	5876	1465	-907 (-1840 to 26)	4.5
Scott et al, 1995[23]	2420	881	3330	1572	-910 (-1534 to -286)	7.3
Zarro et al, 2001[27]	2814	767	2891	791	-77 (-498 to 344)	10.1
Myers et al, 2002[28]	2776	1240	3517	1133	-741 (-1175 to -307)	9.9
Pooled					-584 (-819 to -348)	100.0



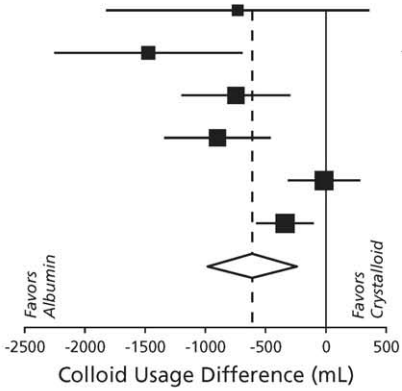
[a]Two different prime albumin concentrations were tested in this trial.

[b]Standard deviation for albumin prime group not reported and assumed to be equal to that for crystalloid group.

Fig 3. Difference between albumin and crystalloid prime in on-bypass positive fluid balance.

prove patient outcomes. This meta-analysis provides a basis for that viewpoint as well because no significant differences could be detected in time to extubation or length of stay. Nevertheless, use of crystalloid as pump prime is associated with increased postoperative colloid infusion to achieve comparable outcomes, as has been suggested by others.[20] This study documented an average increase of more than 600 mL in postoperative colloid usage in the crystalloid com-

Trial	Postoperative Colloid (mL)[a]				Difference (CI)	Wgt
	Albumin		Crystalloid			
	Mean	*SD*	*Mean*	*SD*		
Öhqvist et al, 1981[4]	695	447	1428	1405	-733 (-1825 to 359)	7.9
Sade et al, 1985[9]	1245	1702	2719	1268	-1474 (-2255 to -693)	11.8
McGrath et al, 1989[18]	215	430	962	969	-747 (-1200 to -295)	18.1
Scott et al, 1995[23]	1150	801	2050	990	-900 (-1341 to -459)	18.4
Palanzo et al, 1999[3]	200	400	215	560	-15 (-317 to 287)	21.3
Zarro et al, 2001[27]	2318	414	2658	465	-340 (-578 to -102)	22.5
Pooled					-612 (-983 to -241)	100.0



[a]Administered during first 24 h postoperatively. Colloids consisted of plasma and 5% albumin;[4] plasma and 25% albumin (data in table re-expressed in volume equivalents of 5% albumin);[9] unspecified;[18] polygeline;[23] fresh frozen plasma;[3] and fresh frozen plasma, albumin, and hydroxyethyl starch.[27]

Fig 4. Difference between albumin and crystalloid prime in colloid usage during the first 24 hours postoperatively.

pared with the albumin group. This difference would at least partly offset the higher unit acquisition cost of albumin than crystalloid for pump priming. Thus, combined total intra- and postoperative colloid usage did not differ significantly between the two study groups.

Change in platelet number is also a variable used in selecting priming fluid. In an investigation of in vitro extracorporeal membrane oxygenation circuits, albumin priming reduced the rapid fall in platelet counts and marked increase in platelet activation induced by crystalloid prime.[2] On-bypass platelet activation and consumption can potentially cause early thrombotic events as well as promoting subsequent thrombocytopenia and platelet dysfunction leading to nonsurgical bleeding.[1] Acquired transient platelet dysfunction is well recognized as a common contributor to hemorrhage in cardiac surgery patients.[1] Awareness has recently increased of intraoperative thrombotic events such as oygenator thrombosis, which has been more frequently encountered with the more widespread substitution of crystalloid for albumin prime.[6] Although typically transient and self-limiting, oxygenator thrombosis can in some cases necessitate emergency oxygenator replacement and jeopardize the outcome of the procedure.[7] Another risk related to on-bypass platelet activation would be microthrombosis in the vascular bed and consequent impaired organ perfusion. For instance, neurocognitive dysfunction after CPB is frequently encountered,[29] and intraoperative microvascular thrombosis is one proposed mechanism for the syndrome.

A consistent difference was observed in on-bypass platelet count drop between patients receiving albumin and crystalloid prime. That difference, 23.8×10^9/L, was equal to approximately 21% of the pooled mean on-bypass platelet count in the crystalloid group. The clinical significance of such a difference cannot be fully addressed by this meta-analysis because of the lack of reported data on thrombotic events and neurocognitive function in the included studies. However, a trend toward increased postoperative blood loss in patients who received crystalloid rather than albumin was found, which warrants future investigation.

Priming fluid may affect additional clinical outcomes. In 1 study, albumin prime attenuated on-bypass hypotension.[16] In another, albumin prime blunted the on-bypass and postoperative rise in blood lactic acid concentration, which was shown to be negatively correlated with COP.[21] In a third study, crystalloid but not albumin prime induced a large abrupt on-bypass rise in intraocular pressure temporally coinciding with a precipitous COP decline.[22] Elevated intraocular pressure secondary to altered COP has been implicated in the development of optic neuropathy after cardiopulmonary bypass.[30]

Although these observations on hypotension, lactic acidosis, and intraocular pressure can be attributed to the oncotic properties of albumin, other effects may be caused by nononcotic properties of albumin. These properties include antioxidant and free radical-scavenging activity; ability to modulate inflammatory processes; capacity for specifically inhibiting apoptosis in microvascular endothelial cells; and binding affinity for lipids, ions, drugs, toxic substances, and other ligands. One included study showed significantly reduced erythrocyte crenation during and after bypass with use of albumin prime.[15] Crenation with concomitant impairment of erythrocyte deformability and compromise of microcirculatory performance may result from incorporation of unbound free fatty acids into the erythrocyte membrane, and albumin prime was shown to reduce the proportion of unbound free fatty acids during and after bypass.[15] Thus, the salutary effect of albumin on erythrocyte crenation may issue from its lipid-binding properties.

Currently available evidence assembled in this systematic review suggests differences favoring albumin for extracorporeal circuit priming by several criteria. Further studies are warranted to delineate more precisely the effects of priming fluids on thrombotic and hemorrhagic complications of CPB as well as other clinical outcomes.

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