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REVIEW ARTICLES

Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review†

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Editor's key points

- This is a review of the impact of increasing blood flow to predefined goals on postoperative outcome.
- For every 100 patients exposed to the intervention one can expect 13 to avoid having complications.
- Also, patients remain in hospital ~1 day less.
- The intervention should be individualized as it cannot be assumed that it will reduce mortality.

Summary. This systematic review and meta-analysis summarizes the clinical effects of increasing perioperative blood flow using fluids with or without inotropes/vasoactive drugs to explicit defined goals in adults. We included randomized controlled trials of adult patients (aged 16 years or older) undergoing surgery. We included 31 studies of 5292 participants. There was no difference in mortality at the longest follow-up: 282/2615 (10.8%) died in the control group and 238/2677 (8.9%) in the treatment group, RR of 0.89 (95% CI: 0.76–1.05; P=0.18). However, the results were sensitive to analytical methods and withdrawal of studies with methodological limitations. The intervention reduced the rate of three morbidities (renal failure, respiratory failure, and wound infections) but not the rates of arrhythmia, myocardial infarction, congestive cardiac failure, venous thrombosis, and other types of infections. The number of patients with complications was also reduced by the intervention. Hospital length of stay was reduced in the treatment group by 1.16 days. There was no difference in critical care length of stay.

The primary analysis of this review showed no difference between groups but this result was sensitive to the method of analysis, withdrawal of studies with methodological limitations, and was dominated by a single large study. Patients receiving this intervention stayed in hospital 1 day less with fewer complications. It is unlikely that the intervention causes harm. The balance of current evidence does not support widespread implementation of this approach to reduce mortality but does suggest that complications and duration of hospital stay are reduced.

Keywords: fluid therapy; perioperative care; surgery

It has been known for many years that patients undergoing surgery are more likely to have serious complications or die if they have limited physiological reserve.[1 2] *Post hoc* analysis of patients undergoing major surgery revealed that survivors had a higher cardiac index (CI) and lower systemic vascular resistance than those who died.[3 4] Commonly monitored vital signs (heart rate, arterial blood pressure, central venous pressure, temperature, and haemoglobin concentration) were found to be poor predictors of mortality when compared with the flow-related variables cardiac output (CO) and total body oxygen delivery (DO_2).[5 6] In particular, survivors of major surgical procedures were found to have higher values for CO or DO_2. More recently, studies have shown mixed results for the impact of oxygen transport on postoperative morbidity and mortality.[7–9] New therapeutic options and monitoring techniques that became available in the 1970s, particularly the introduction of the pulmonary artery flow-directed catheter (PAC),[10 11] opened up the possibility of measuring and then manipulating an individual's cardiovascular system. It was hypothesized that targeting goals for CO and DO_2 in all patients to the values manifested by the survivors of surgery would improve outcome.[12]

†This review is an abridged version of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews* 2012, Issue 11, DOI: 10.1002/14651858.CD004082 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

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An important principle of this intervention is that the perioperative manipulation to augment CO and DO_2 would lead to an improved tissue perfusion and oxygenation. This physiological improvement would lead to better survival and fewer postoperative complications in patients undergoing major surgery.

It is almost 30 years since the initial uncontrolled data were presented suggesting that perioperative manipulation of flow-related cardiovascular variables might improve outcomes in higher risk surgical patients.[13] As then, a number of randomized trials have been undertaken in patients in the perioperative period which have investigated this issue. However, these trials differ in:

- the case mix of the patients recruited (different operation severities, comorbidities and, therefore, expected mortalities);
- the techniques used to measure CO (pulmonary artery catheter thermodilution, Doppler velocimetry);
- the specific goals targeted [CO, DO_2, maximum stroke volume (SV)];
- the techniques used to achieve the goals (fluids, fluids plus inotropes/vasoactive drugs); and
- the management of the control arm.

In addition, some of the studies were not blinded and many had small sample sizes leading to limited statistical power. Despite this, a number of non-systematic reviews have attempted to combine studies in order to draw general conclusions from the studies.[14–18] However, these reviews have identified varying numbers of trials and have not been undertaken systematically, using scientifically rigorous techniques for literature searching or for abstraction and analyses of data. Three previous systematic reviews have addressed this question[19–21] and reported improved outcomes. They do not include recently published studies and did not focus exclusively on perioperative data. Among recent systematic reviews and meta-analyses, one study included patients with trauma and sepsis[22] while other studies analysed renal function[23] and gastrointestinal complications[24] as primary outcomes.

The time is now ripe for a systematic review of the literature to address the important question: does perioperative administration of fluids, with or without vasoactive drugs, targeted to increase global blood flow in adults undergoing surgery reduce mortality, morbidity and resource utilization? To describe the effects of perioperative (24 h before surgery and up to 6 h after surgery) administration of fluids, with or without vasoactive drugs, that were targeted to increase global blood flow (relative to control) as defined by explicit measured goals on outcomes after surgery (mortality, morbidity, resource utilization, and health status).

Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2012, Issue 1), MEDLINE via OvidSP (1966 to March 2012), and EMBASE via OvidSP (1982 to March 2012). For searching in MEDLINE, we combined our topic-specific key words with the Cochrane highly sensitive search strategy for identifying randomized controlled trials (RCTs).[11] We modified this filter for use in EMBASE. We used specific keywords to identify potential studies (Appendix).

We searched the proceedings of the following major, relevant European and North American conferences from the year 2011 backwards for any eligible studies:

- American College of Surgeons (2011–1996).
- American Society of Anesthesiologists (2011–1995).
- American Thoracic Society (2011–1997*) (*=not available for searching before 1997).
- Association of Surgeons of Great Britain and Ireland (2011–1996).
- European Society of Anaesthesiologists (2011–1995).
- European Society of Intensive Care Medicine (2011–1983).
- International Anesthesia Research Society (2011–1994).
- Society of Critical Care Medicine (2011–1986).

We included RCTs, with or without blinding, that were available as full published papers. We applied no language restrictions. We included adults (aged 16 years or older) undergoing surgery in an operating theatre. Perioperative administration (initiated within 24 h before surgery and lasting up to 6 h after surgery) of fluids, with or without inotropes/vasoactive drugs, to increase blood flow (relative to control) against explicit measured goals: cardiac output (CO), CI, DO_2 or oxygen delivery index (DO_2I), oxygen consumption or oxygen consumption index ($V_{O_2}I$), SV or stroke volume index, mixed venous oxygen saturation (Sv_{O_2}), oxygen extraction ratio (O_2ER), and lactate.

Two independent authors identified titles and abstracts of potentially eligible studies. We resolved any disagreement by discussion. We obtained the full texts of potentially eligible studies. We abstracted the study characteristics including: study design; patient population; interventions; and outcomes. Two authors independently extracted data. We achieved consensus by resolving any disparity in data collection by discussion. In the absence of appropriate published data, we made at least three attempts to contact authors of eligible studies to obtain any required data. Some studies were conducted by the authors of this review. They were not involved in study selection, data extraction or risk of bias assessment. We performed the risk of bias assessment according to the Cochrane risk of bias tool.[25]

We included studies with different treatment groups, interventions and outcomes. Consequently, we performed subgroup analyses of these differences. Many studies reported the number of complications, arrhythmias and infections as total numbers, leaving unclear what the denominators were for these episodes. We have not analysed variables for which the denominator was unknown. We contacted the authors of the studies for further information and the analysis was performed with the best available information when there was no response.

We assessed inconsistencies and variability in the outcomes among the studies by the I^2 statistic. Variations of $>40\%$ in the

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outcomes may not be explained by sampling variation. We assumed substantial heterogeneity when the I^2 statistic exceeded 40%.[25] We assessed graphical evidence of reporting biases using contour enhanced funnel plots with a subsequent Harbord or Egger's test.[26 27] We performed statistical analysis using Review Manager 5.1.[28] We applied the intention-to-treat method for all analyses. We used both fixed-effect and random-effects models for the primary outcome analysis and the fixed-effect model for the secondary outcomes. We used relative risks (RRs) and 95% confidence intervals (95% CI) for dichotomous outcomes and mean difference [standard deviation (SD) of the mean or 95% CI] for continuous variables.

Because of the heterogeneous nature of the selected studies, we conducted subgroup analyses in the following areas:

(1) The urgency of surgery (elective or emergency).
(2) The type of surgery (general, vascular, cardiac, other).
(3) The timing of the intervention (perioperative, intraoperative, and postoperative).
(4) The type of intervention (fluids, fluids with vasoactive agents).
(5) The intervention goals (CO, SV, and oxygen indices).

We analysed mortality, both over the longest follow-up and hospital or 28-day mortality, with fixed-effect and random-effects models. In addition, we excluded studies with fewer than 100 participants. The intervention in the protocol group varied. The control group in some studies had explicit blood flow goals to standardize care. Further, some studies did not fully control for co-interventions, for instance admission to critical care. We performed sensitivity analysis excluding these studies.

We assessed mortality (at longest available follow-up) as the primary outcome. Mortality (all reported time frames), morbidity measures such as rates of overall complications [rates of renal impairment, arrhythmia, respiratory failure or acute respiratory distress syndrome (ARDS), infection, myocardial infarction, congestive heart failure or pulmonary oedema, and venous thrombosis] and length of intensive care unit stay, length of hospital stay as secondary outcomes.

Results

The initial electronic search identified 18 951 potential studies (Fig. 1). After removal of duplicated studies, the search yielded 10 462 studies. We identified 66 potentially eligible studies after screening of the abstracts. Of those 66 studies, 35

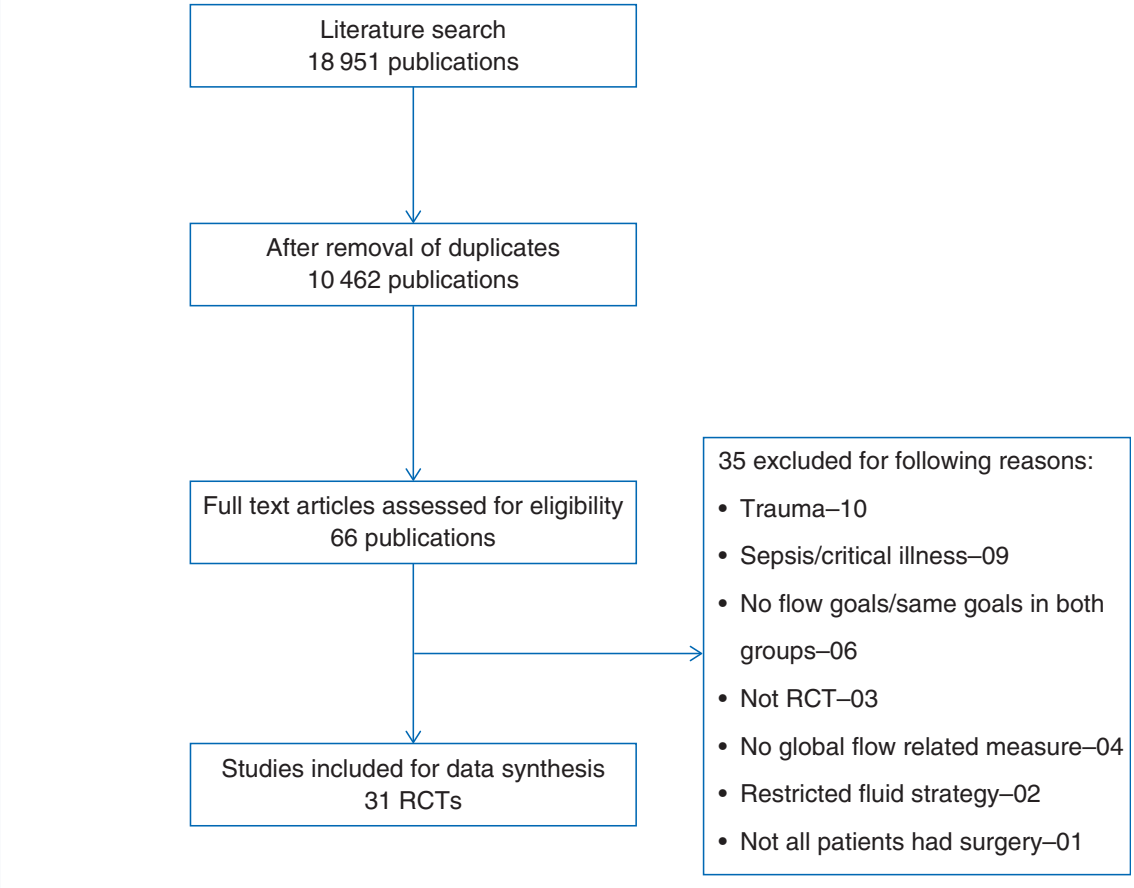

Fig 1 Flow diagram of study selection.

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potentially eligible studies did not meet the study inclusion criteria for several reasons. The remaining 31 fully published studies (5292 participants) met the inclusion criteria.[29–59] These studies were conducted in Europe (20), the USA (seven), India (one), Brazil (one), Japan (one), and Canada (one). Most studies (24 studies) recruited participants having elective surgery. The studies were published between 1988 and 2011. The study characteristics of the included studies are summarized in Table 1. We excluded 35 studies that had not met our inclusion criteria.

All included studies had randomly allocated participants. Using the Cochrane risk of bias tool we assessed the methods

Table 1 Characteristics of included studies. CI, cardiac index; DO_2, oxygen delivery; DO_2I, oxygen delivery index; FTc, corrected flow time; O_2ER, oxygen extraction ratio; SV, stroke volume; SVV, stroke volume variation; SVI, stroke volume index; Sv_{O_2}, mixed venous oxygen saturation; $V_{O_2}I$, oxygen consumption index

Study	Number of patients	Mode of surgery	Type of surgery	Timing	Fluids with or without inotropes	Goals
Bender and colleagues[29]	104	Elective	Vascular	Pre	Fluids and inotropes	CI
Berlauk and colleagues[30]	89	Elective	Vascular	Pre	Fluids and inotropes	CI
Bonazzi and colleagues[31]	100	Elective	Vascular	Pre	Fluids and inotropes	CI, DO_2I
Boyd and colleagues[32]	107	Elective, emergency	General, vascular	Pre, post	Fluids and inotropes	DO_2I
Cecconi and colleagues[33]	40	Elective	orthopaedic	Intra	Fluids and inotropes	SV
Challand and colleagues[34]	179	Elective	Gastrointestinal	Intra	Fluids	SV
Conway and colleagues[35]	57	Elective	General	Intra	Fluids	SV, FTc
Donati and colleagues[36]	135	Elective	Major abdominal surgery	Intra	Fluids and inotropes	O_2ER
Gan and colleagues[37]	100	Elective	General	Intra	Fluids	SV, FTc
Jerez and colleagues[38]	390	Elective	Cardiac	Post	Fluids and inotropes	Sv_{O_2}, CI
Jhanji and colleagues[39]	135	Elective	Gastrointestinal surgery	Post	Fluids and inotropes	SV
Kapoor and colleagues[40]	30	Elective	Cardiac	Post	Fluids and inotropes	CI, SVV
Lobo and colleagues[41]	37	Elective	General, vascular	Pre	Fluids and inotropes	DO_2I
Mayer and colleagues[42]	60	Elective	Major abdominal surgery	Intra	Fluids and inotropes	CI, SV
Mckendry and colleagues[43]	174	Elective, emergency	Cardiac	Post	Fluids and inotropes	SVI
Mythen and colleagues[44]	60	Elective	Cardiac	Intra	Fluids	SV
Noblett and colleagues[45]	103	Elective	General	Intra	Fluids	SV, FTc
Pearse and colleagues[46]	122	Elective, emergency	Vascular, general, urology	Post	Fluids and inotropes	DO_2I
Pillai and colleagues[47]	66	Elective	Urology	Intra	Fluids	SV, FTc
Pölönen and colleagues[48]	393	Elective	Cardiac	Post	Fluids and inotropes	Sv_{O_2}, lactate
Sandham and colleagues[49]	1994	Elective, emergency	General, vascular, thoracic, hip fracture	Pre	Fluids and inotropes	DO_2I, CI
Senagore and colleagues[50]	64	Elective	Laparoscopic colectomy	Intra	Fluids	SV
Shoemaker and colleagues[51]	58	Elective, emergency	General, vascular	Pre	Fluids and inotropes	CI, DO_2I, VO_2I
Sinclair and colleagues[52]	40	Emergency	Hip fracture	Intra	Fluids	SV, FTc
Ueno and colleagues[53]	34	Elective	Liver	Post	Fluids and inotropes	CI, DO_2I, VO_2I
Valentine and colleagues[54]	120	Elective	Vascular	Pre	Fluids and inotropes	CI
Van der Linden and colleagues[55]	57	Elective	Vascular	Intra	Fluids and inotropes	CI
Venn and colleagues[56]	59	Emergency	Hip fracture	Intra	Fluids	SV, FTc
Wakeling and colleagues[57]	134	Elective	General	Intra	Fluids	SV
Wilson and colleagues[58]	138	Elective	General, vascular	Pre	Fluids and inotropes	DO_2I
Ziegler and colleagues[59]	72	Elective	Vascular	Pre	Fluids and inotropes	Sv_{O_2}

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of randomization as adequate in 17 studies (55%) and methods of allocation concealment as adequate for 20 studies (65%). We assessed blinding of personnel or participants as adequate in only 12 studies (39%), reflecting the nature of the intervention. We assessed blinding of outcome assessment as adequate in eight studies (26%). Attrition bias was detected in one study[49] where a large number of participants were lost to the follow-up, which may have introduced attrition bias. In one study,[42] the second author has been found to have fabricated results in some clinical studies. We recognized this as a potential high risk. Exclusion of participants after randomization was noted in seven studies which may have induced selection bias (Fig. 2). To test the effect of publication bias, we performed Harbord and colleagues' test for the primary outcome, which showed a significant small-studies effect with a regression bias −0.72 (95% CI: −0.08 to −1.39) (Fig. 2).[27]

Data synthesis

Mortality

Long-term mortality

Thirty studies[29–59] reported mortality data and further information was obtained from authors for one study.[47] A number of different definitions were used and some papers reported more than one definition. Using data from the longest reported follow-up, the overall mortality was 238/2677 (8.9%) in the intervention group and 282/2615 (10.8%) in the control group, RR of 0.89 (95% CI: 0.76–1.05; P=0.18) (Fig. 3). The results were sensitive to analytical methods, becoming statistically significant with two methods: the inverse variance random-effects model, RR of 0.72 (95% CI: 0.55–0.95; P=0.02); and the Mantel–Haenszel random-effects model, RR of 0.72 (95% CI: 0.55–0.95; P=0.02) (Tables 2 and 3).

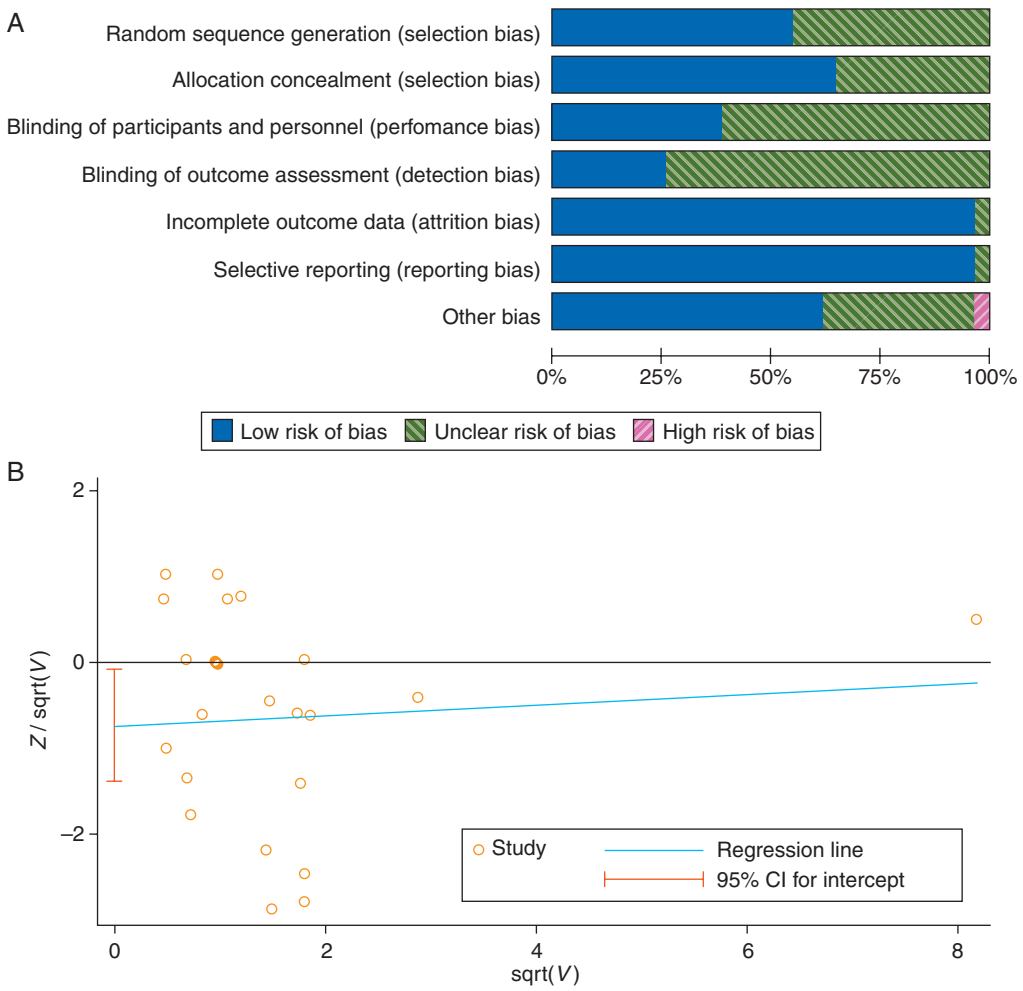

Fig 2 (A) Risk of bias graph for all included studies. (B) Galbraith plot of Harbord analysis for the primary outcome (mortality longest follow-up). Z, the efficient score; V, Fisher's information score variance. The regression slope is −0.72 (95% CI: −0.08 to −1.39).

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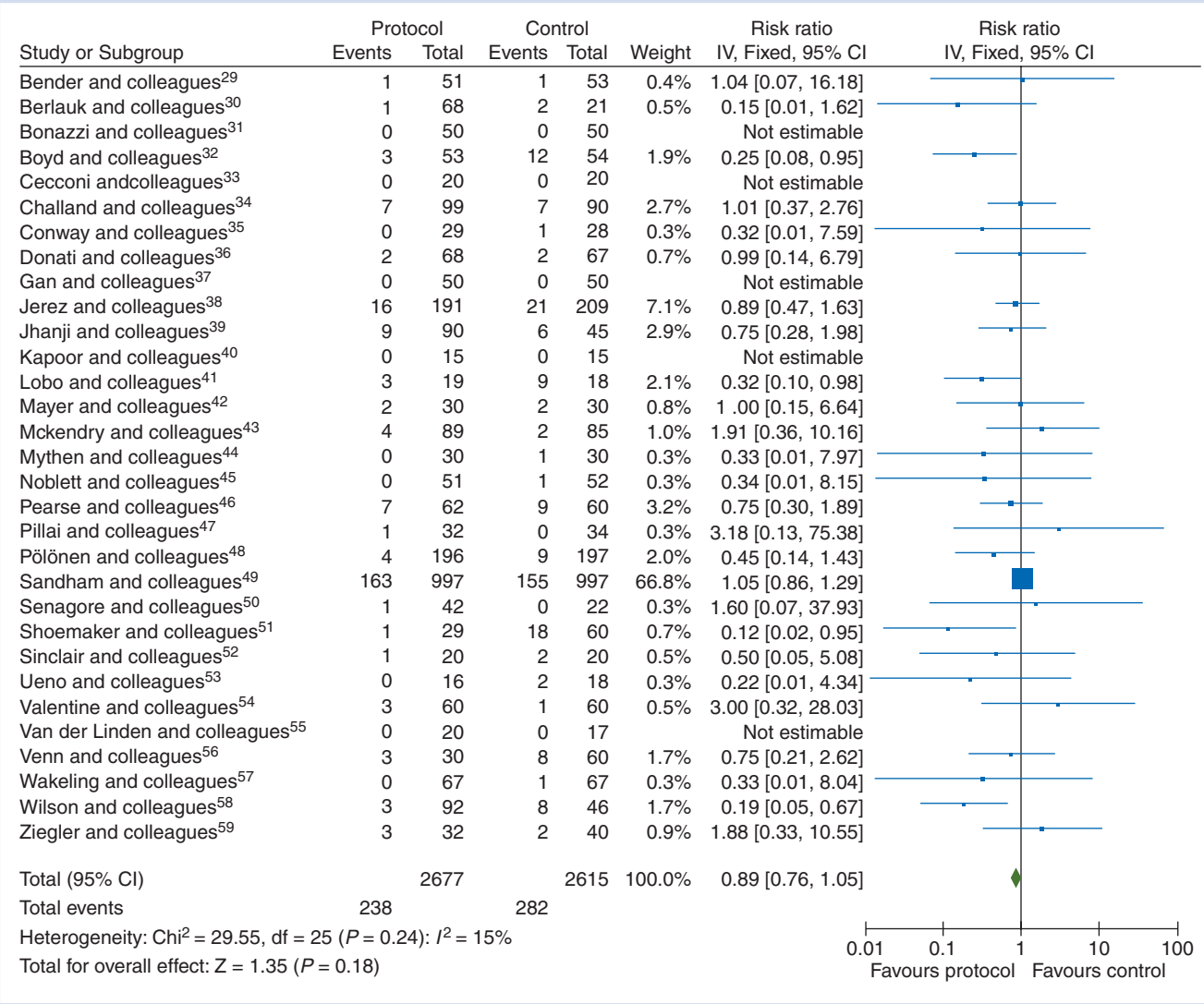

Fig 3 Forest plot of meta-analysis for primary outcome (mortality-longest follow-up).

Hospital or 28-day mortality

Hospital or 28-day mortality was reported in 30 studies[29–46 48–59] and further information was obtained from one study.[47] Pooled hospital or 28-day mortality was 146/2677 (5.4%) in the intervention group and 192/2615 (7.3%) in the control group, RR of 0.81 (95% CI: 0.65–1.00; P=0.06). The results were sensitive to analytical methods, becoming significant with three methods: the inverse variance random-effects model, RR of 0.79 (95% CI: 0.63–0.9; P=0.04), the Mantel–Haenszel fixed-effect model, RR of 0.77 (95% CI: 0.63–0.95; P=0.01), and random-effects model, RR of 0.78 (95% CI: 0.62–0.99; P=0.04) (Supplementary material Table 1).

Morbidity

We analysed seven categories of morbidity using the investigators' definitions. No two studies used the same list of morbidities after surgery. In most cases, no specific criteria were listed for morbidities. No two studies used the same criteria.

Renal impairment

We accepted the rate of renal impairment reported by study authors: we did not apply a single definition across studies. Data on renal impairment were available for 21 studies.[29–34 36 37 39–44 48 49 51 54 56–58] The intervention reduced the rate of renal impairment, RR of 0.71 (95% CI: 0.57–0.90; P=0.004).

Arrhythmia

Arrhythmia was reported in 16 studies. However, we excluded three studies for which there were unit-of-analysis issues: two studies[29 30] reported the number of events; one of these studies[29] and one other study[54] reported for both the intraoperative and postoperative periods. One study[51] reported transient dysrhythmias ('almost always premature ventricular complexes') during insertion of pulmonary artery (PA) catheters. This was reported as a combined percentage (12%) for both control and protocol PA catheter groups. We were unable to identify the exact rate of arrhythmias for each group

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Table 2 Data synthesis for all outcomes. RR, relative risk; IV, inverse variance; MD, mean difference

Outcome	Number of studies	Number of patients	Statistical method	Effect size and I^2	*P*-value
Mortality (longest follow-up)	31	5292	RR (IV, fixed, 95% CI)	0.89 (0.76–1.05), I^2=15%	0.18
Mortality (hospital or 28 day)	31	5292	RR (IV, fixed, 95% CI)	0.81 (0.65–1.00), I^2=01%	0.055
Renal impairment	21	4307	RR (IV, fixed, 95% CI)	0.71 (0.57–0.90), I^2=20%	0.004
Arrhythmia	12	2921	RR (IV, fixed, 95% CI)	0.84 (0.67–1.06), I^2=00%	0.14
Total number of infections	9	733	RR (IV, fixed, 95% CI)	0.88 (0.69–1.12), I^2=00%	0.29
Infection types					
Chest/pneumonia	13	2945	RR (IV, fixed, 95% CI)	0.78 (0.61–1.00), I^2=00%	0.054
Sepsis	5	474	RR (IV, fixed, 95% CI)	0.68 (0.26–1.77), I^2=06%	0.43
Abdominal	6	55	RR (IV, fixed, 95% CI)	0.53 (0.23–1.22), I^2=00%	0.14
Wound	10	2802	RR (IV, fixed, 95% CI)	0.65 (0.50–0.84), I^2=22%	0.0013
Urinary tract	8	612	RR (IV, fixed, 95% CI)	0.54 (0.26–1.15), I^2=00%	0.11
Respiratory failure/ARDS	9	844	RR (IV, fixed, 95% CI)	0.51 (0.28–0.93), I^2=00%	0.027
Myocardial infarction	15	3328	RR (IV, fixed, 95% CI)	1.01 (0.71–1.45), I^2=00%	0.95
Congestive cardiac failure/ pulmonary oedema	14	3223	RR (IV, fixed, 95% CI)	1.00 (0.81–1.24), I^2=00%	0.98
Venous thrombosis	10	2740	RR (IV, fixed, 95% CI)	1.04 (0.39–2.77), I^2=12%	0.93
Number of patients with complications	17	1841	RR (IV, random, 95% CI)	0.68 (0.58–0.80), I^2=34%	<0.00001
Length of hospital stay	27	4729	MD (IV, random, 95% CI)	−1.16 (−1.89 to −0.43), I^2=87%	0.0019
Length of critical care stay	14	1873	MD (IV, random, 95% CI)	−0.45 (−0.94 to −0.03), I^2=87%	0.065

Table 3 Sensitivity analysis using analytical methods for the primary outcome (mortality for the longest follow-up). MH, Mantel–Haenszel

Analytical method	Results
Inverse variance RR fixed-effect model	0.89 (95% CI 0.76–1.05), *P*=0.18, I^2=15%
Inverse variance RR random-effects model	0.72 (95% CI 0.55–0.95), *P*=0.02, I^2=15%
Inverse variance odds ratio fixed-effects model	0.87 (95% CI 0.72–1.05), *P*=0.14, I^2=20%
Inverse variance odds ratio random-effects model	0.67 (95% CI 0.49–0.92), *P*=0.01, I^2=20%
Peto odds ratio	0.83 (95% CI 0.69–1.00), *P*=0.05, I^2=37%
MH odds ratio fixed-effect model	0.83 (95% CI 0.69–1.00), *P*=0.05, I^2=21%
MH odds ratio random-effects model	0.67 (95% CI 0.49–0.92), *P*=0.01, I^2=21%
MH RR fixed-effect model	0.85 (95% CI 0.73–1.00), *P*=0.05, I^2=16%
MH RR random-effects model	0.72 (95% CI 0.55–0.95), *P*=0.02, I^2=16%

separately and therefore excluded this study from the analysis. For the rest of the 12 studies[31 33 40–43 46 49 50 56 58 59] that we were able to analyse, there was no significant difference between groups in development of an arrhythmia, RR of 0.84 (95% CI: 0.67–1.06; *P*=0.14).

Infections

Infections were reported several ways in 20 studies.[29 32 33 37 39 41–44 46 47 49–52 54–58] The number of participants who had infections was reported in nine studies.[29 39 41 44 47 52 54 55 57] The number of participants with infections was unaffected by the intervention, RR of 0.88 (95% CI: 0.69–1.12; *P*=0.29).

The types of infection (such as pneumonia) were reported separately in 15 studies.[29 32 33 37 41 42 44 47 49 51 52 54–56 58] Nine studies[32 33 37 42 46 49 51 56 58] reported more than one infective complication per participant. It was not possible to add the total number of infections as the exact denominator was unknown. We, therefore, analysed each infection separately. There was no difference in the rates of: pneumonia; RR of 0.78 (95% CI: 0.61–1.00; *P*=0.05), sepsis; RR of 0.68 (95% CI: 0.26–1.77; *P*=0.43), abdominal infections; RR of 0.53 (95% CI: 0.23–1.22; *P*=0.14), or urinary tract infections; RR of 0.54 (95% CI: 0.26–1.15; *P*=0.11). The intervention significantly reduced the rate of wound infections, RR of 0.65 (95% CI: 0.50–0.84; *P*=0.0013). Two studies[43 50] reported on the total number of infections and we were unable to include these studies due to unit-of-analysis issues.

Respiratory failure or ARDS

Respiratory failure or ARDS was reported in nine studies.[32 36 37 42 44 46 51 53 58] One study[58] also included the number of participants with prolonged ventilation, which we were unable to

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analyse due to unit-of-analysis issues. The intervention significantly reduced the rate of respiratory failure/ARDS, RR of 0.51 (95% CI: 0.28–0.93; $P=0.027$).

Myocardial infarction

Myocardial infarction was reported in 15 studies.[29–33 40 42 43 46 49 51 54 56 58 59] There was no significant difference in myocardial infarction between groups, RR of 1.01 (95% CI: 0.71–1.45; $P=0.95$).

Congestive cardiac failure or pulmonary oedema

Congestive heart failure or pulmonary oedema was reported in 14 studies.[29–32 41 42 46 49 51 52 54 56–58] There was no significant difference in congestive cardiac failure or pulmonary oedema between groups, RR of 1.00 (95% CI: 0.81–1.24; $P=0.98$).

Venous thrombosis

Venous thrombosis was reported in 10 studies.[32 33 41 42 46 49–51 56 58] There was no difference in venous thrombosis between groups, RR of 1.04 (95% CI: 0.39–2.77; $P=0.93$).

Complications

More than one method was used to pool complications. The number of participants with complications was reported by 19 studies.[29–31 33–36 38 39 41 42 44–46 51–53 57 58] The number of complications per participant was reported by three studies.[32 38 51] The number of participants with individual complications or the number of individual complications was reported by 27 studies.[29–37 39–46 48–51 53–59] We did not pool data for the number of complications because of this variation and the associated unit-of-analysis issues. Further, six studies[31 32 37 40 43 47] that reported the number of participants with complications also reported the individual complications separately, therefore pooling of these would again lead to unit-of-analysis issues. Two studies reported the number of participants with complications separately for the intraoperative and postoperative periods.[29 54] We were unable to combine these outcomes due to unit-of-analysis issues. We therefore pooled 17 studies.[30 33–36 38 39 41 42 44–46 51–53 57 58] The number of participants with complications was reduced by the intervention, RR of 0.68 (95% CI: 0.58–0.80; $P<0.00001$).

Health status

No study reported on health status.

Resource use

Postoperative hospital stay

Postoperative length of hospital stay was reported in 28 studies.[29–37 39–52 54–58] This was reported as mean [standard deviation (SD)] by seven studies,[29 30 36 37 40 46 51] mean (range) by one study,[44] mean (95% CI) by two studies,[47 56] mean [standard error of mean (SEM)] by one study[54] and median [range or inter-quartile range (IQR)] by 15 studies.[31–35 39 41–43 45 48 49 52 55 57] We excluded one study[50] from this analysis, as we were unable to get further information. We obtained additional details for five studies.[39 44 45 57 58] We used a statistical equation to convert the median (range/IQR) to mean (SD).[60] We estimated the SD as IQR/1.35, $SEM \times \sqrt{(n)}$ or 95% CI/1.96. Four studies[30 39 51 56] had two groups in either of the intervention or control groups and these were numerically combined using equation 7.7a according to the *Cochrane Handbook for Systematic Reviews*.[25] The intervention significantly reduced the postoperative length of hospital stay, mean 1.16 days (95% CI: 0.43–1.89; $P=0.002$). We used the random-effects model as the $I^2=87\%$.

Postoperative intensive care stay

Postoperative length of critical care stay was reported by 14 studies.[29 30 32 38–42 44 46 48 51 54 58] This was reported as the mean (SD) by six studies,[29 30 38 40 42 51] mean (range) by one study,[44] mean (SEM) by one study[54] and median (range/IQR) by five studies.[32 39 41 46 48] We were able to obtain additional information for three studies.[39 44 58] Numerical conversion to mean (SD) was performed according to the previous paragraph. There was no difference in postoperative length of critical care stay, mean difference of 0.45 days (95% CI: −0.03–0.94; $P=0.06$). We used the random-effects model as the $I^2=87\%$.

Cost

Three studies[29 30 51] reported cost (United States dollars), none of which found a statistical difference. Three other studies[32 44 58] reported cost in separate publications from the original report (two reported in British pounds;[61 62] one reported in Euros.[63] Two of these[61 63] reported that the intervention significantly reduced cost. The third study[62] reported cost for a subgroup of patients included in the trial and these data were not analysed by treatment groups. For the cost analysis, only one study[30] reported in mean and SD and another[29] in mean and SEM. In view of the variety of currencies and statistical descriptors we did not attempt to pool these data.

Subgroup analyses for the primary outcome

Timing of intervention

The intervention was commenced in the preoperative period in nine studies,[29–32 49 51 54 58 59] in the intraoperative period in 15 studies[33–37 41 42 44 45 47 50 52 55–57] and in the postoperative period in nine studies.[32 38–41 43 46 48 53] In one study, participants were randomized to two intervention groups (a preoperative and an intraoperative group) with a shared control group.[30] In another study,[32] the intervention was initiated either before operation or after operation depending on when the participants came to the attention of the investigators (Table 4). There was no evidence that this had any effect on the chances of being recruited into the study and therefore we did not consider that this had potential to confound the randomization process. Further, one study[41] had both intraoperative and postoperative interventions. Timing of the intervention did not interact with mortality: preoperative, RR of 0.96 (95% CI: 0.79–1.17; $P=0.69$); intraoperative, RR of 0.67 (95% CI: 0.40–1.13; $P=0.13$); and postoperative, RR of 0.73 (95% CI: 0.50–1.06; $P=0.10$).

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Type of intervention

The intervention involved fluids alone in 10 studies[34 35 37 44 45 47 50 52 56 57] and fluids in combination with vasoactive drugs in 20 studies.[29–33 36 38 40 41 42 43 46 48 49 51 53–55 58 59] One study[39] had two intervention groups; one group had fluid alone and the other had fluids and dopexamine. These groups were analysed separately. There was no difference in mortality between groups according to the intervention provided: fluids alone, RR of 0.80 (95% CI: 0.46–1.39; P=0.43); fluids in combination with vasoactive drugs, RR of 0.90 (95% CI: 0.76–1.07; P=0.23).

Type of goal

Fourteen studies[29–32 40–42 46 49 51 53–55 58] used CO and oxygen transport goals; four studies[36 38 48 59] used Sv_{O_2}, oxygen extraction and lactate; and 13 studies[33–35 37 39 43–45 47 50 52 56 57] used SV goals. Mortality was not reduced for any of the three subgroups: CO and oxygen transport, RR of 0.91 (95% CI: 0.75–1.09; P=0.31); Sv_{O_2}, oxygen extraction and lactate, RR of 0.83 (95% CI: 0.50–1.38; P=0.47); SV, RR of 0.84 (95% CI: 0.51–1.41; P=0.51).

Mode of surgery

Twenty-four studies[29–31 33–42 44 45 47 48 50 53–55 57–59] recruited participants having only elective procedures; two studies[52 56] were exclusively of urgent or emergency surgery and five studies[32 43 46 49 51] had a mix of urgent or emergency and elective operations. None of the studies in this latter group were able to provide separate data to allow comparison between elective and urgent or emergency groups. Intervention significantly reduced the mortality of participants in RCTs of elective surgery, RR of 0.68 (95% CI: 0.48–0.94; P=0.02); mortality was unchanged for emergency or urgent operations, RR of 0.68 (95% CI: 0.23–2.06; P=0.50).

Type of surgery

Six studies[29–31 54 55 59] were exclusively of participants undergoing vascular surgery. Five additional studies[32 41 46 49 58] included participants undergoing vascular surgery, but in only one of these [32] were group-specific mortality data available. Five studies[38 40 43 44 48] were of patients undergoing cardiac surgery. Fifteen studies[33–37 39 42 45 47 50–53 56 57] were exclusively of patients undergoing general (primarily gastrointestinal, but included orthopaedic and urological) surgery. Five additional studies[32 41 46 49 58] included patients undergoing general surgery but in only one of these[32] group-specific mortality data was available. There was no interaction between type of surgery and the intervention; vascular, RR of 0.78 (95% CI: 0.34–1.79; P=0.56); cardiac, RR of 0.81 (95% CI: 0.48–1.35; P=0.42); and general surgery, RR of 0.66 (95% CI: 0.41–1.07; P=0.09).

Sensitivity analyses

We performed sensitivity analyses of the analysis method used to generate RRs for mortality. The results were dependant upon both the analytical method and whether a random-effects model or fixed-effect model was used. There was no difference

Table 4 Subgroup analysis for the primary outcome. RR, relative risk; IV, inverse variance; CI, confidence interval

Subgroups	Number of studies	Number of patients	Statistical method	Effect size and I^2	P-value
Participant numbers					
>100	16	4428	RR (IV, fixed, 95% CI)	0.94 (0.79–1.12), I^2=21%	0.49
<100	15	864	RR (IV, fixed, 95% CI)	0.89 (0.29–0.90), I^2=00%	0.02
Timing of intervention					
Preoperative	9	2786	RR (IV, fixed, 95% CI)	0.96 (0.79–1.17), I^2=63%	0.69
Intraoperative	15	1202	RR (IV, fixed, 95% CI)	0.67 (0.40–1.13), I^2=00%	0.13
Postoperative	9	1341	RR (IV, fixed, 95% CI)	0.73 (0.50–1.06), I^2=00%	0.10
Type of intervention					
Fluids and inotropes	21	4354	RR (IV, fixed, 95% CI)	0.90 (0.76–1.07), I^2=41%	0.23
Fluids	11	983	RR (IV, fixed, 95% CI)	0.80 (0.46–1.39), I^2=00%	0.43
Goal of intervention					
CO, DO_2	14	3060	RR (IV, fixed, 95% CI)	0.91 (0.75–1.09), I^2=58%	0.31
Lactate, Sv_{O_2}, O_2ER	4	990	RR (IV, fixed, 95% CI)	0.83 (0.50–1.38), I^2=00%	0.47
SV	13	1242	RR (IV, fixed, 95% CI)	0.84 (0.51–1.41), I^2=00%	0.51
Mode of surgery					
Elective	24	2677	RR (IV, fixed, 95% CI)	0.68 (0.48–0.94), I^2=00%	0.02
Emergency	2	130	RR (IV, fixed, 95% CI)	0.68 (0.23–2.06), I^2=00%	0.50
Elective and emergency	5	2485	RR (IV, fixed, 95% CI)	0.99 (0.81–1.20), I^2=62%	0.89
Type of surgery					
Vascular	7	580	RR (IV, fixed, 95% CI)	0.78 (0.34–1.79), I^2=18%	0.56
Cardiac	5	1047	RR (IV, fixed, 95% CI)	0.81 (0.48–1.35), I^2=00%	0.42
General	16	1374	RR (IV, fixed, 95% CI)	0.66 (0.41–1.07), I^2=00%	0.09

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in mortality when small studies (fewer than 100 participants) were excluded, consistent with primary analysis. The effect of small studies was significant in the Harbord analysis, with a regression slope of −0.72 (95% CI −0.08 to −1.39). Participants were more likely to die in studies that recruited fewer than 100 participants, RR of 1.84 (95% CI 1.02–3.33; P=0.04).

In some studies, the fluid and drug management in the control group was comparable with the intervention in other studies. For instance, four studies[38 41 48 53] had fluid and inotropes administered in response to measures of blood flow (CI or DO_2I) in the control groups. One study[51] had one control group with DO_2I driven measures. We performed a sensitivity analysis excluding these studies and the control group from Shoemaker and colleagues.[51] The findings were consistent with the primary analyses (Supplementary material Table 2).

In some studies, fluid and inotrope administration were not the only systematic differences between the control and intervention groups. Five studies[29 31 49 54 58] did not control for the insertion and presence of a pulmonary artery flow catheter. Three studies[33 40 42] did not control for the presence of other flow sensors (FloTrac or Vigileo) and one study[56] did not control for the insertion or presence of an oesophageal Doppler probe. In one study,[51] one control group was not matched for the insertion and presence of a pulmonary artery flow catheter. We also performed sensitivity analyses excluding these studies for all outcome measures. With these studies excluded the intervention reduced mortality (longest follow-up), RR of 0.65 (95% CI: 0.48–0.89; P=0.007) and hospital or 28-day mortality, RR of 0.66 (95% CI: 0.47–0.92; P=0.01). The rates of renal failure and ARDS were no longer significantly different. The number of participants with complications and their length of hospital stay were not altered in this analysis, remaining significantly different between groups (Supplementary material Table 3).

This meta-analysis was dominated by one study.[49] In this study, a large number of participants were lost to the follow-up. We performed sensitivity analyses for the outcomes of mortality (longest follow-up and hospital or 28-day mortality) excluding this study and assuming the possibility that all patients who were lost to the follow-up died. The results were not sensitive to these analyses (Supplementary material Table 4).

Discussions

The key finding of this review is that the perioperative administration of fluids, with or without vasoactive drugs, targeted to increase global blood flow defined by explicit measured goals reduced postoperative complications and length of stay but did not reduce mortality, using the inverse variance method. Mortality was significantly reduced when we used random-effects models [Mantel–Haenszel and inverse variance; RR 0.72 (95% CI: 0.55–0.95; P=0.02)], but not fixed-effect models [Mantel–Haenszel; RR 0.85 (95% CI 0.73–1.00; P=0.05); inverse variance RR, 0.89 (95% CI 0.76–1.05; P=0.18); or Peto OR 0.83 (95% CI: 0.69–1.00; P=0.05)]. We calculated similar results for hospital and 28-day mortality. The analysis of studies with small number of patients (<100 participants) resulted in mortality being reduced by the intervention. When control group care was managed using a protocol that included explicit goals less than the intervention group (in contrast to 'usual care'), mortality was not reduced. When studies with intervention groups that were less well controlled for the intervention (for example pulmonary artery catheters were not matched to intervention groups) were excluded, there was a significant reduction in mortality at the longest follow-up; and hospital or 28-day mortality. It is notable that the sensitivity analyses are of limited value as they tend to reflect the inclusion or exclusion of the single largest study.[49]

The limited data indicate that for every 100 patients exposed to treatment, one can expect 13 in 100 to avoid a complication, 2/100 to avoid renal impairment, 5/100 to avoid respiratory failure, and 4/100 to avoid postoperative wound infection, with no effect on other types of morbidity (myocardial infarction, arrhythmia, congestive cardiac failure or pulmonary oedema, venous thrombosis, and the number of patients with infections). These results were unchanged after sensitivity analyses that excluded studies where the control group care was managed using a protocol that included explicit goals that were less than the intervention group (in contrast to 'usual care'). When studies using intervention groups that were less well controlled (control groups not matched to intervention groups) were excluded only the number of patients with complications was reduced.

The hospital length of stay was reduced by ~1-day, from 12.4 to 11.2 days, and was not sensitive to exclusion of studies where the control group care was managed using a protocol that included explicit goals that were less than the intervention group (in contrast to 'usual care') or studies using intervention groups that were less well controlled. There was no difference in critical care stay in the intervention group. This was sensitive to exclusion of studies using intervention groups that were less well controlled and the reduction was less than a day (from 4 to 3.3 days). There were insufficient data to conduct a meta-analysis of cost and no data available describing quality of life.

A stratified meta-analysis to address secondary hypotheses, determined a priori, suggested that mortality was reduced in the intervention group when study participants underwent elective surgery.

The predefined analysis plan, using mortality from the longest available follow-up, increased the weight attributed to the two largest studies that both reported 1-year follow-up. Only one other study reported follow-up beyond 60 days. In this group of studies, a proportion of the operations were for cancer resection therefore introducing a possible competing cause of mortality.

Our systematic review pooled data from 31 studies with 5292 participants. Study inclusion criteria were tightly defined and the meta-analysis was rigorously conducted according to a predefined analysis plan addressing specific hypotheses. The meta-analysis combined data from a group of predominantly underpowered single centre studies. However, the included studies reflect international practice, although the majority of included studies are from major teaching

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centres. The pooled studies included adults (age >16 years) undergoing several types of surgery, including abdominal, urology, gynaecology, orthopaedic, cardiac, thoracic, and vascular. Therefore, the included studies represent the population for whom the intervention might be considered.

The quality of outcome data reporting in the included studies was variable. Mortality was reported over a variety of time frames and other outcomes were either limited or inconsistent between studies, precluding meaningful analyses in many cases. Diverse criteria and descriptions for morbidities, along with infrequent use of validated metrics, limited the precision of treatment effect estimates and the confidence that can be attached to them. Furthermore, pooling of different types of morbidity was inconsistent, limiting assessment of the overall 'morbidity load'.

Most studies tested a complex package of care (for example fluids, inotropes, monitor, goals, and critical care environment) rather than a single clearly defined intervention. Heterogeneity in the components of such a complex intervention may contribute to study heterogeneity within a systematic review. Study heterogeneity may reduce the precision of treatment effect estimates and reduce the generalizability of the results of meta-analyses.[64] By definition, it is not easy to define precisely the 'active ingredients' of a complex intervention.[65] However, hypothesis-generating subgroup analyses indicated that there were insufficient data to distinguish statistically between many of the prespecified subgroups, and highlighted the limited quantity of data in some areas for example emergency surgery.

Several possible sources of bias arose in this meta-analysis. The primary analysis was sensitive to the analytical methods used, the exclusion of larger studies, and the exclusion of studies that inadequately controlled for the intervention. Larger studies are less likely to be affected by bias[66] and the inclusion of lower quality studies can alter the interpretation of the benefit of interventions in meta-analysis.[67]

Statistical heterogeneity was generally absent (I^2<40%). Except for some analyses such as hospital length of stay, there was evidence of significant statistical heterogeneity. We used random-effects models in all cases where I^2 exceeded 40%. In all analyses of mortality, the point estimate of effect was <0.90, suggesting that the intervention was probably not harmful.

The sensitivity of our results to the methods of analysis indicates that the results of this study are far from clear-cut. Further research is essential in this area both to address the overall objective of this review and to focus on specific questions.

The studies included in this review are typical of studies in critical care research in general in that the majority of studies are underpowered and from single centres[68] and about half the studies are small (<100 participants). Future studies in this area should test an explicitly framed hypothesis, be adequately powered, methodologically rigorous, and blinded (where possible). Reporting of outcomes should be standardized (to allow comparison between studies and to facilitate the conduct of future meta-analyses) and inclusive (morbidity, health status, and resource usage).

The possibility of publication bias cannot be excluded. We found no evidence of this from contact with experts and industry but some of the identified published abstracts have yet to be published as full peer-reviewed papers. Harbord's regression test was significant at P=0.03, suggesting small study effects.[27] Language bias is possible because of the electronic databases and conferences we searched. Flaws in the original study designs are a significant potential source of bias. The meta-analysis includes 5292 participants but the unit of analysis is the study (or study subgroup) and the sample size (31 studies) is relatively small. The results of the subgroup analyses should be considered as hypothesis-generating only and are largely influenced by inclusion or exclusion of a single study.[49]

This review represents the best up-to-date summary of the literature. We framed a tightly defined question and used explicit inclusion criteria for studies and a predefined analysis plan. Our primary result does not agree with previous reviews which have been uniformly supportive of this intervention. This may be explained by the precision of the question we addressed (for example other reviews included trauma patients not having surgery) and the analytical methods used. The results of our systematic review do, however, agree with the results of the largest study in this area.[49] However, it is of concern that the Sandham study dominates the review primary analysis both in terms of number of patients (1994/5292) and weight (67%), and that the Sandham study was one of the studies where the intervention group was less well controlled (control groups not matched to intervention groups). Additionally, this study failed to achieve the intended haemodynamic goals in 80% of patients before operation and 20% during the postoperative period.[49]

Research should focus on answering these questions. Sandham and colleagues showed that a large multicentre study can be conducted in this area and several such studies are currently ongoing, in particular a large multicentre study anticipated to recruit about 700 participants (ISRCTN0 4386758). Future research will hopefully disentangle the complex package of care that forms the intervention (for example, fluids, inotropes/vasoactive agents, monitor, goals, and critical care environment) and thereby identify which components are effective in different clinical contexts.

Conclusions

Clinicians should base their decision whether to manipulate perioperative global blood flow on the magnitude of reductions in postoperative morbidities and length of hospital stay rather than upon the assumption that mortality will be reduced. For every 100 patients exposed to the intervention one can expect 13/100 to avoid having complications; 2/100 to avoid renal impairment; 5/100 to avoid respiratory failure; and 4/100 to avoid postoperative wound infection. Patients remain in hospital ~1 day less and there is no increase in harm. This intervention should be considered where the relevant resources are available and implementation will not otherwise harm the patient (for example, delay in definitive care).

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A specific limitation of this review is the large number of studies that were published >10 years and the limited amount of data that represent current practice and outcomes. A specific group that particularly merits further study, in view of the high incidence of mortality and morbidity and limited available data, is patients undergoing emergency surgery.

Future studies in this area should test an explicitly framed hypothesis, be adequately powered (and preferably multicentre), methodologically rigorous, and include blinded interventions where possible. Reporting of outcomes should be standardized (to allow comparison between studies and to facilitate the conduct of future meta-analyses) and inclusive (morbidity, health status, and resource usage).

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Appendix

Keywords used in search strategy

High-risk surgery, perioperative, preoperative, postoperative, intraoperative, aneurysm, vascular surgery, cardiac surgery, cancer surgery, trauma surgery, emergency surgery, orthopaedic surgery, optimization, optimization, goal-directed, supra-normal, vasoactive, fluids, starch, gelatin, blood product, crystalloid, colloid, fluid therapy, fluid loading, fluid administration, body fluid, oxygen delivery, lactate, acid base, oxygen consumption, base excess, base deficit, blood volume, central venous pressure, CVP, cardiac output, cardiac index, pulmonary artery flotation catheter, PAFC, right-heart catheter, Swan Ganz, Doppler, pHi, tonometry, Pc_{O_2} gap, echocardiography, stroke volume, Sv_{O_2}, mixed venous oxygen saturation, splanchnic, renal perfusion, tissue perfusion, blood flow.

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