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Review Article

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Efficacy and safety of intraoperative controlled hypotension: a systematic review and meta-analysis of randomised trials

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Abstract

Background: Intraoperative controlled hypotension improves surgical field visibility by reducing blood loss (efficacy) but poses potential risks linked to organ hypoperfusion (safety). The use of controlled hypotension persists despite increasing evidence of associations between intraoperative inadvertent hypotension and adverse outcomes. Therefore, we tested the hypothesis that the focus and results of intraoperative controlled hypertension research differ across anaesthesia and surgery investigators because of differing priorities.

Methods: We systematically reviewed randomised trials comparing controlled hypotension with usual care with trials categorised by investigators' affiliation.

Results: We identified 48 eligible trials, of which 37 were conducted by anaesthesia investigators and 11 by surgery investigators. For the primary outcome, 54% of the anaesthesia-led trials focused on safety, whereas all (100%) surgery-led trials focused on efficacy (P=0.004). Compared with usual care, mean arterial pressure in controlled hypotension was 23% (95% confidence interval [CI] 17–29%) lower in anaesthesia trials and 30% (95% CI 14–37%) lower in surgery trials; estimated blood loss was 44% (95% CI 30–55%) less in anaesthesia trials and 38% (95% CI 30–49%) less in surgery trials. Overall, blood loss was reduced by 43% (95% CI 32–53%), and trial sequential analysis supported an efficacy conclusion. Mean arterial pressure and estimated blood loss reductions were associated (R^2=0.41, P=0.002). All trials were underpowered for safety outcomes, and none adequately evaluated myocardial or renal injury.

Conclusions: Anaesthesia researchers prioritised safety outcomes, whereas surgery researchers emphasised efficacy in controlled hypotension trials. Controlled hypotension significantly reduces blood loss. In contrast, safety outcomes were poorly studied. Given increasing observational evidence linking inadvertent hypotension to myocardial and renal injury, the safety of controlled hypotension remains to be addressed.

Systematic review protocol: PROSPERO (CRD42023450397).

Keywords: anaesthesia; controlled hypotension; efficacy; randomised trial; safety; surgery

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Editor's key points

- The safety of intraoperative controlled hypotension remains inadequately studied, particularly with respect to myocardial and renal injury. In this systematic review, the authors highlight the disparity in research focus, with anaesthesiologists emphasising safety and surgeons emphasising efficacy.
- Future research should comprehensively evaluate the safety of controlled hypotension, focusing on potential organ injuries. Adequately powered trials are needed to assess outcomes effectively.

Intraoperative controlled hypotension is defined as a deliberate reduction of blood pressure and is predominantly used in an effort to minimise intraoperative blood loss and optimise surgical field conditions.[1] Several systematic reviews with meta-analyses report that intraoperative controlled hypotension reduces blood loss and improves surgical field conditions.[2–7] However, most previous systematic reviews focused on efficacy rather than safety outcomes, were limited to specific surgical patient populations, and did not explore differing focus related to researchers' speciality affiliations. Many observational analyses report that intraoperative inadvertent hypotension at levels used for controlled hypotension is associated with myocardial and renal injury.[8–11] In contrast, randomised trial evidence is mostly neutral but with substantial limitations.[12] Although intraoperative controlled and inadvertent hypotension differ in many aspects, both can compromise organ perfusion and result in tissue injury. Nonetheless, the use of intraoperative controlled hypotension remains popular despite observational evidence linking intraoperative inadvertent hypotension to organ injury.[4,5,13]

There are substantial differences between intraoperative controlled hypotension and inadvertent hypotension (Table 1). Controlled hypotension is generally used in younger and healthier patients whereas inadvertent hypotension is most common in patients who are older, comorbidity-bound, or severely ill.[14] Controlled hypotension is generally used for low-risk surgeries, such as orthognathic,[5] cosmetic, functional endoscopic sinus surgery,[6] and orthopaedic surgeries,[4,7] whereas inadvertent hypotension is more likely to occur in moderate-to-high-risk surgeries.

For instance, a large-scale study analysed 22,109 adults who had American Society of Anesthesiologists (ASA) physical status 3 and 4, and reported that 88% of patients experienced at least one episode of hypotension, defined as mean arterial pressure less than 65 mm Hg for 1 min.[14] The mechanisms underlying controlled and inadvertent hypotension also differ. Controlled hypotension is typically induced by vasodilatory drugs or deepening anaesthesia, whereas inadvertent hypotension has a variety of potential causes, such as hypovolaemia, massive bleeding, myocardial failure, pulmonary hypertension, and vasodilation. The complications most associated with inadvertent hypotension are myocardial and renal injury.[8] However, it remains unclear whether controlled hypotension would cause similar or different profiles of adverse outcomes, as discussed in a recent systematic review.[4] Therefore, understanding the safety of intraoperative controlled hypotension is paramount to inform clinical decision-making.

We were particularly interested in understanding whether different backgrounds of researchers are associated with different priorities and results in intraoperative controlled hypotension research. Our study, which was registered as the Anaesthesiologist versus Surgeon-dependent Results of Intraoperative Controlled Hypotension (AS-RICH) systematic review, tested the hypothesis that anaesthesia investigators emphasise organ hypoperfusion and injury, whereas surgeons prioritise blood loss and operative conditions. Consequently, this study has two primary objectives. First, we compared the primary outcomes for anaesthesia-led and surgery-led controlled hypotension trials. Second, we used meta-analytic methods to evaluate the overall efficacy and safety of controlled hypotension.

Methods

Our study approach diverges from conventional systematic reviews in aiming not only to synthesise available evidence, but also to discern disparities in approach across investigator specialities. We, therefore, categorised investigators' affiliations for eligible trials as primarily anaesthesia or surgery and then compared key trial attributes between the groups. Our study was registered in PROSPERO (CRD42023450397) on August 14, 2023. This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary File 1).[15] Patients and the public were not directly involved in our research design, implementation, reporting, or dissemination.

Trial selection

We considered trials that met the following criteria for inclusion: (1) involved adult or paediatric surgical patients; (2) randomised patients to intraoperative controlled hypotension *vs* usual care; and (3) reported efficacy, safety, or both outcomes. We excluded trials that were conducted in non-surgical patients, compared various methods for controlled hypotension (e.g. remifentanil *vs* dexmedetomidine), or were conducted in pregnant women.

Information sources and search strategy

We systematically searched the following databases without time restrictions: Ovid MEDLINE, EMBASE, and Web of Science. The first search was conducted on July 8, 2023, followed by an updated search on November 21, 2023. We developed the systematic search strategy based on the study aim and examples of eligible publications (Supplementary File 2). We also screened the reference lists of eligible articles for additional records. In addition, we conducted keyword searches in the PubMed and Google Scholar databases to identify any additional relevant records.

Trial selection process

Records retrieved from the systematic literature search were imported into EndNote (Clarivate, London, UK) for record management. The 'Find Duplicates' feature in EndNote was used to remove duplicate records, followed by a manual review to eliminate any remaining duplicates. Retracted articles were also excluded. Research personnel were divided into two teams, each of which independently screened the remaining

Table 1 Differences between intraoperative controlled hypotension and inadvertent hypotension. *Refer to the results of this systematic review. †Refer to the data presented in Supplementary Table S4.

Factor	Controlled hypotension	Inadvertent hypotension
Patients	Younger,* healthy, most ASA physical status 1 or 2,* low risk	Likely older, likely with comorbidities, likely acutely ill, higher risk
Surgery	Low risk (e.g. head and neck, dental, cosmetic, and orthopaedic),* short duration*	High risk (major, noncardiac, trauma, vascular, and cardiac),[11] † likely long duration
Intention	Intentional and controlled	Unintentional and inadvertent
Purpose	To improve surgical conditions and outcomes by minimising blood loss	Unplanned, requiring interventions to mitigate risk and stabilise the patient
Mechanisms	Drug-induced (vasodilatory)	Hypovolaemic, massive bleeding, vasodilatory, cardiogenic, pulmonary hypertension, distributive, drug-related, and so on
Mean arterial pressure	Approximately 60–65 mm Hg*	Comparable; definitions varied among different studies[11] †
Efficacy	Effective in reducing intraoperative blood loss*	Not applicable
Safety	Inadequately studied, potential risks not fully investigated	Association with adverse outcomes per cohort or observational studies (not randomised trials)[8,11] †
Monitoring	Intensely monitored and adjusted	Often unrecognised initially; may require urgent corrective measures
Reversibility	Reversible as it is drug-induced and closely monitored	Can be challenging to reverse, especially if underlying causes are severe
Contraindications	Patients prone to ischaemic injury (hypertension, cerebrovascular abnormality disease, coronary artery disease, etc.)	Not applicable, unwarranted condition
Generalisability	Likely applicable to selected patients	Not applicable, unwarranted condition
Clinical management	Proactive approach with predefined protocols	Reactive approach, often requiring complex multidisciplinary management

records. Discrepancies between the teams were resolved through discussions with senior investigators.

Data collection process

The two research teams worked independently and in parallel to collect data from the eligible trials. We used a pre-designed Excel™ (Microsoft, Redmond, WA, USA) form for data collection and management. Each trial was assigned to a dedicated row, and each variable was allocated to a distinct column. The variables for which the data were sought were pre-defined to align with the objectives of this systematic review. Data obtained by the two teams were then compared side by side and merged. Between-team discrepancies were resolved by discussion.

Data items

We collected the following information from the eligible trials: (1) year of publication; (2) journal impact factor; (3) geographic region of trial origination; (4) researchers' affiliation; (5) type of primary outcome; (6) number of patients randomised; (7) patient age; (8) type of surgery; (9) type of anaesthesia; (10) method of inducing intraoperative controlled hypotension; (11) blood pressures in each group; (12) estimated blood loss; (13) details and results of efficacy-related outcomes; (14) details and results of safety-related outcomes; and (15) risk of bias.

Trial categorisation per researchers' affiliations

One of our aims was to determine whether there were differences between intraoperative controlled hypotension research conducted by anaesthesia *vs* surgery researchers. We thus grouped trials based on researchers' affiliations. We used the following rules: (1) the trial was considered as being conducted by anaesthesia researchers if both the first and corresponding authors were affiliated with an anaesthesia department; (2) the trial was considered as being conducted by surgery researchers if both the first and corresponding authors were affiliated with a surgery department; (3) if the first and corresponding authors were affiliated with both anaesthesia and surgery departments, we categorised the trial based on the predominant affiliation of other authors, defined as the affiliation with which $\geq$80% of authors were affiliated; and (4) if the authors did not fall into the above-mentioned classifications, the affiliation was classified as 'other'.

Outcome categorisation

We categorised outcomes as efficacy-related and safety-related. We defined efficacy-related outcomes as estimated blood loss, transfusion requirements, quality of surgical field, and surgical duration. We defined safety-related outcomes as organ complications, mortality, and duration of hospitalisation. Organ complications included cerebral hypoxia, cerebral hypoperfusion or ischaemia, neurological injury, cognitive impairment, elevated cardiac enzymes, electrocardiographic

changes, myocardial ischaemia, pulmonary injury, acute kidney injury, elevated hepatic enzymes, gastrointestinal hypoperfusion or ischaemia, postoperative nausea and vomiting, and coagulopathy.

Trial risk of bias assessment

The research team was split into two groups to evaluate the risk of bias independently and simultaneously in individual trials using the revised Cochrane tool.[16] This tool assessed the risk of bias stemming from various processes, including randomisation, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Discrepancies between the teams were resolved by consensus.

Statistical analysis

We compared trials with anaesthesia and surgery affiliations on type of primary outcome, year of publication, journal impact factor, region of trial origination, the number of patients randomised, patient age, type of surgery, method of controlled hypotension, actual blood pressure, estimated blood loss reduction, and risk of bias. Continuous variables were presented as medians and interquartile ranges (IQRs) and were compared between groups using the Wilcoxon rank sum test. Categorical variables were expressed as counts and percentages and were compared across groups using Pearson χ^2 or Fisher's exact test as appropriate. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated when appropriate.

We performed meta-analyses to investigate the actual mean arterial pressure (MAP) in controlled hypotension and usual care groups, the percentage reductions in MAP and estimated blood loss, and any other efficacy- or safety-related metrics whenever the same metric was reported by three or more than three trials. Percentage reductions (MAP, estimated blood loss, and surgical duration) were defined as the difference in measurements between controlled hypotension and usual care groups divided by the measurement in the usual care group (calculated from mean values reported by the original trials), which was then multiplied by 100%. Analyses were stratified by the investigators' primary affiliations to anaesthesia or surgery. We used fixed-effects models when the total number of trials was less than five where the between-trial variance cannot be estimated[17] and otherwise used random-effects models using the R package 'meta' (R Foundation for Statistical Computing, Vienna, Austria).[18] The I^2 statistic was calculated to estimate heterogeneity across the included trials.

We used a two-sided trial sequential monitoring boundary in our trial sequential analysis. We calculated the required information size using α=0.05 and β=0.20, along with an empirical mean difference. The software used for these analyses was Trial Sequential Analysis version 0.9.5.10 beta, provided by the Copenhagen Trial Unit, Centre for Clinical Intervention Research (www.ctu.dk/tsa). Funnel plots and Egger's test were used to analyse the potential publication bias for direct comparisons based on three or more studies.[19]

We also used a scatterplot to visualise the association between the percentage reductions in MAP and estimated blood loss, with the percentage reductions calculated using the method described above. Linear regression models were fitted to quantify those associations.

Statistical significance was defined by two-tailed *P*-values less than 0.05 for all tests without correction for multiple analyses. All statistical analyses were performed using R version 4.3.1.

Certainty of evidence

The certainty of the evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework, which appraises the quality of a body of evidence based on the risk of bias, imprecision, inconsistency, indirectness, and publication bias for the targeted outcome. The certainty of the evidence was graded as very low, low, moderate, and high (https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/).

Results

Our literature search on November 21, 2023, yielded 3329 records. After eliminating 602 duplicates and eight retracted reports, we screened 2719 reports and identified 48 eligible records through the systematic literature search. Although we identified 10 additional records through screening relevant articles' reference lists and a Google Scholar search, none met the eligibility criteria. Consequently, our final analysis included 48 reports (Supplementary Fig. S1).[20–67]

Trial characteristics

Among the 48 trials, 13 (27%) were published before 2000. The median 5-yr average impact factor of the journals in which the eligible 48 trials were published was 2.1 (IQR 0.9–4.2). The regional distribution of publications was China (*n*=8, 17%), Europe (*n*=8, 17%), the USA and Canada (*n*=7, 15%), the Middle East (*n*=11, 23%), and other regions including Taiwan, Japan, India, and Australia (*n*=14, 29%). Most trials focused on patients having head and neck procedures (*n*=28, 58%), with further details of the type of surgery presented in Supplementary Table S1. All but one trial was conducted in surgical patients given general anaesthesia.

The median number of patients included in eligible trials was 49 (IQR 32–60). Forty-six trials reported patient average age; of these trials, 25 (54%) were conducted in patients with an average age between 18 and 40 yr, 15 (33%) trials in patients with an average age greater than 40 yr, and six (13%) trials in patients with an average age <18 yr. Fifteen trials involving 604 patients reported details of ASA physical status, with 392 (65%) categorised as ASA 1, 201 (33%) as ASA 2, and 11 (2%) as ASA 3.

Among 48 eligible trials, 38 (79%) had a high overall risk of bias, nine (19%) had some concerns, and only one (2%) was considered to have a low overall risk of bias. The characteristics of individual trials are presented in Supplementary Table S1, and the risks of bias of individual trials are presented in Supplementary Table S2.

Researchers' affiliations and type of primary outcomes

All the trials were affiliated with either anaesthesia or surgery departments, with 37 (77%) categorised as anaesthesia-affiliated and 11 (23%) as surgery-affiliated. Twenty-eight (58%) trials designated an efficacy measure as the primary outcome, whereas the remaining 20 (42%) trials used a safety measure as the primary outcome.

Comparison between trials with anaesthesia vs surgery affiliations

Of the 37 trials with an anaesthesia affiliation, 17 (46%) defined an efficacy-related outcome measure as the primary outcome, whereas 20 (54%) used a safety-related outcome measure. In contrast, all 11 (100%) trials with a surgery affiliation defined a primary efficacy-related outcome (P=0.004, Supplementary Table S3). The median age was 35.5 (IQR 31.5–44.8) yr in anaesthesia-led trials and 26.2 (IQR 21.2–34.9) years in surgery-led trials (P=0.08). The overall risk of bias was high in both anaesthesia (81%) and surgery (73%) trials. Other trial characteristics were also generally similar (Supplementary Table S3).

Intraoperative blood pressure in controlled hypotension vs usual care groups

Hypotension was induced with nitrates in 17 (35%) trials, alpha-2 agonists in nine (19%) trials, beta-blockers in eight (17%) trials, deep anaesthesia in six (13%) trials, and various other methods in eight (17%) trials.

Twenty-nine trials reported the actual MAP in the controlled hypotension group, with 11 (38%) trials reporting MAP <60 mm Hg, 14 (48%) trials reporting a range between 60 and 70 mm Hg, and four (14%) trials reporting values higher than 70 mm Hg. Twenty-five trials reported the actual MAP in the usual care group, with none reporting MAP below 60 mm Hg, three (12%) trials reporting a range between 60 and 70 mm Hg, and 22 (88%) trials reporting values higher than 70 mm Hg.

In patients assigned to controlled hypotension, the pooled MAP was 62 (95% CI 59–66) mm Hg based on the data from 20 trials with anaesthesia affiliation and 59 (95% CI 54–70) mm Hg based on the data from seven trials with surgery affiliation. Overall, the MAP was 61 (95% CI 59–66) mm Hg in controlled hypotension groups based on the data from 27 trials (Fig. 1a).

In patients assigned to usual care, the pooled MAP was 80 (95% CI 78–86) mm Hg based on the data from 18 trials with anaesthesia affiliation and 85 (95% CI 70–99) mm Hg based on the data from seven trials with surgery affiliation. Overall, the MAP was 81 (95% CI 78–88) mm Hg in usual care groups based on the data from 25 trials (Fig. 1b).

Mean arterial pressure, estimated blood loss, and surgical duration reductions

The percentage reduction of MAP was 23% (95% CI 17–29%) based on the data from 18 trials with anaesthesia affiliation and 30% (95% CI 14–37%) based on the data from seven trials with surgery affiliation. The MAP reductions were similar between anaesthesia-led and surgery-led trials. Overall, the MAP reduction was 25% (95% CI 19–30%) based on the data from 25 trials (Fig. 2a).

The percentage reduction of estimated blood loss was 44% (95% CI 30–55%) based on the data from 25 trials with anaesthesia affiliation and 38% (95% CI 30–49%) based on the data from nine trials with surgery affiliation. There was no difference in reported efficacy for anaesthesia-led and surgery-led trials. Overall, the estimated blood loss reduction was 43% (95% CI 32–53%) based on the data from 34 trials (Fig. 2b).

The percentage reductions in MAP and estimated blood loss were significantly associated based on the data from trials with anaesthesia affiliation (R^2=0.29, P=0.03), from trials with surgery affiliation (R^2=0.80, P=0.01), and overall (R^2=0.41, P=0.002; Fig. 3).

Thirty-four trials reported surgical duration. The mean surgical duration reduction was 7.8% (SD 11.6%) in 26 trials with anaesthesia affiliation and 7.3% (6.7%) in eight trials with surgery affiliation (P=0.89). Overall, the median surgical duration was 101 (IQR 75–149) min in controlled hypotension groups and 115 (IQR 81–162) min in usual care groups (P=0.33).

Safety outcomes

Thirty-three trials reported safety-related outcomes (Table 2).[20–22,24–26,31–34,36–42,44–46,49,54,56–63,65–67] Of them, 31 had an anaesthesia affiliation, and two had a surgery affiliation.[40,56] These trials investigated various safety-related outcome measures using various metrics. Ten trials investigated neurocognitive outcomes, including postoperative sedation,[20,44] electrical stapedial reflex threshold,[22] S100B protein,[34] unspecified neurological complications,[34] psychomotor functions,[36] cerebral blood flow,[59] internal jugular vein oxygen saturation,[59] cerebral tissue oxygen saturation,[62,63,67] and postoperative cognition.[54,58,62,63] Four trials investigated cardiovascular outcomes, including ST depression,[45,49] creatine kinase-myocardial band,[45] troponin,[45] and myocardial oxygen demand (rate-pressure product).[32,61] Five trials investigated hepatic outcomes based on liver injury markers and function tests.[46,56,57,60,61] Two investigated renal outcomes based on creatinine clearance.[32,57] Three trials investigated gastrointestinal outcomes, including perfusion[37] and postoperative nausea and vomiting.[39,42] Seven trials investigated acute anaemia.[21,25,26,31,33,65,67] Three trials investigated coagulopathy.[26,31,65] Three trials investigated arterial blood gas.[24,32,49] Three trials investigated the length of hospital stay.[38,40,45] Four trials investigated postoperative pain control.[20,41,42,66] One trial investigated wound infection.[40] Three trials investigated postoperative shivering.[39,42,66] One trial investigated the time to extubation.[44] We could not synthesise safety data using meta-analysis because of the heterogeneity of outcomes and the inadequacy of trials that could be pooled.

Among reported outcome measures, intraoperative controlled hypotension demonstrated superiority over usual care in postoperative pain control,[20,66] postoperative wound discharge,[39] nausea and vomiting,[39,66] shivering,[39,66] wound infection,[40] dehiscence,[40] and necrosis.[40] However, intraoperative controlled hypotension was found to be inferior to usual care in several aspects, including arterial blood gas partial pressures,[24] liver protection,[46,60] time to extubation,[44] spontaneous platelet aggregation,[26] S100B protein plasma concentrations,[34] unspecified neurological complications,[34] and cerebral tissue oxygen saturation.[62]

No trials examined the incidence of myocardial injury after noncardiac surgery (MINS), defined as myocardial infarction meeting the universal definition or prognostically significant troponin elevation thought to be caused by myocardial ischaemia.[68,69] This complication is associated with intraoperative inadvertent hypotension and has long-term consequences.[68,70,71] Although one trial (N=102) reported measuring troponin, the report did not disclose specific troponin concentrations or the fraction of patients who crossed MINS thresholds. Instead, it simply reported that troponin levels in both the controlled hypotension and usual care groups remained normal. Furthermore, none of the trials was remotely powered for this relatively sparse complication.[45]

No trials specifically reported the incidence of postoperative acute kidney injury defined by an increase in

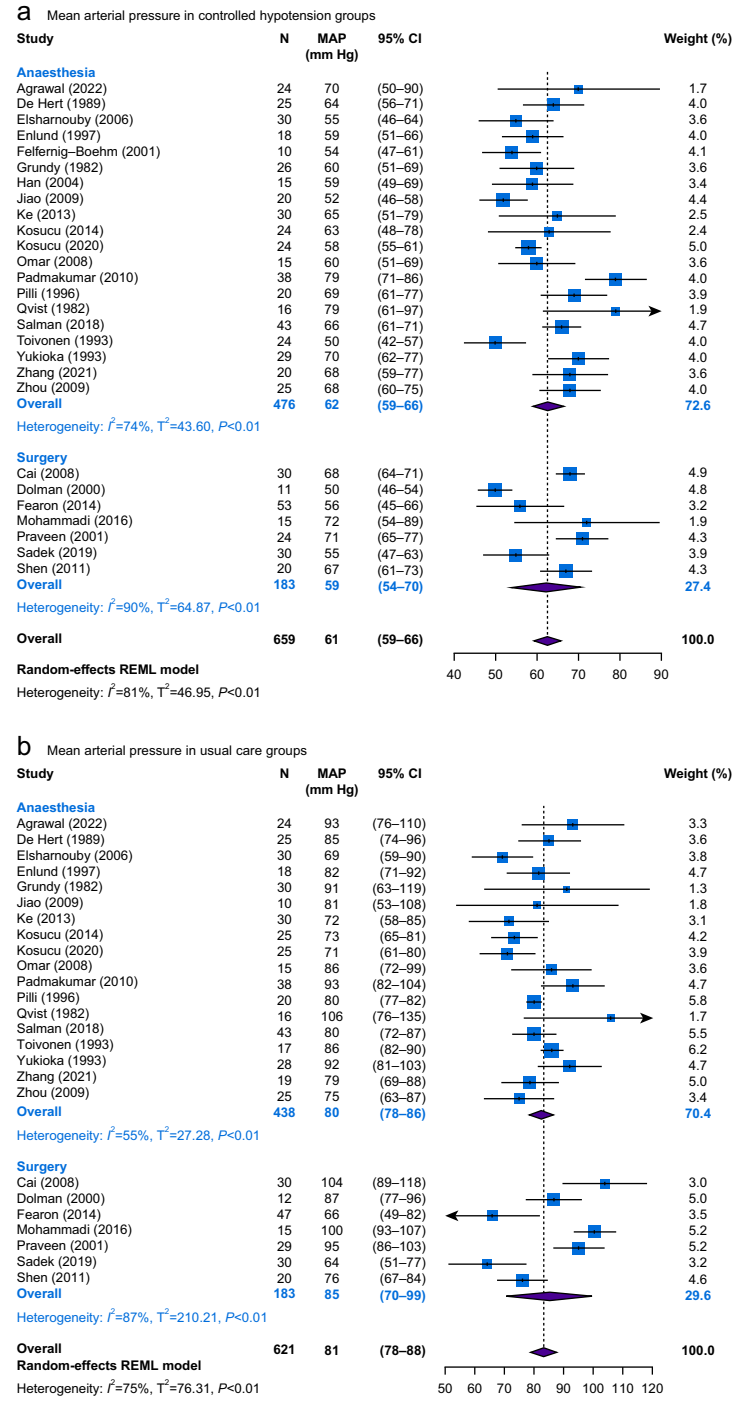

Fig 1. Mean arterial pressure in (a) controlled hypotension and (b) usual care groups. MAP was based on the group mean values from different studies. The analysis was stratified per anaesthesia *vs* surgery researchers. For studies that did not report 95% CI, 95% CI (in italics) was estimated based on the mean standard errors across studies. CI, confidence interval; MAP, mean arterial pressure.

creatinine levels, a complication that is associated with intraoperative inadvertent hypotension with long-term consequences.[70,72,73] However, two trials reported findings related to creatinine clearance.[32,57] One reported that on postoperative days 7–8, patients subjected to nitroprusside-induced hypotension exhibited a creatinine clearance of 73 ml min^{-1}, whereas those receiving usual care showed a clearance of 101 ml min^{-1}.[57] The other trial documented a creatinine clearance of 56 ml min^{-1} during prostaglandin E1-induced hypotension, contrasting with a 66 ml min^{-1}

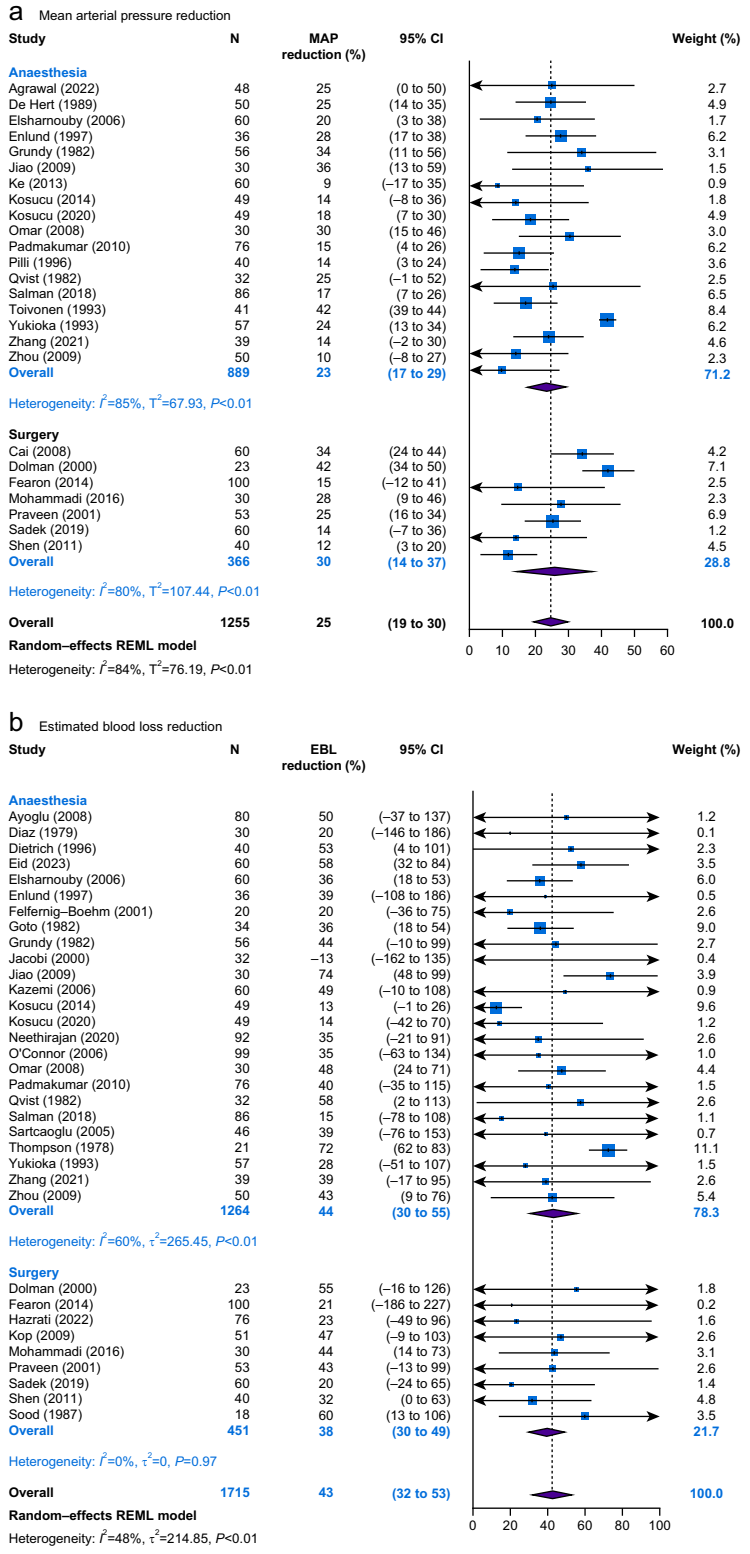

Fig 2. Percentage reductions in (a) mean arterial pressure and (b) estimated blood loss. The MAP and EBL reductions might or might not come from the same studies. The analysis was stratified per anaesthesia *vs* surgery researchers. The percentage reduction was defined as the difference between the mean measurements in controlled hypotension and usual care groups divided by the mean measurement in the usual care group, which was then multiplied by 100%. For studies that did not report 95% CI, 95% CI (in italics) was estimated based on the mean standard errors across studies. CI, confidence interval; EBL, estimated blood loss; MAP, mean arterial pressure.

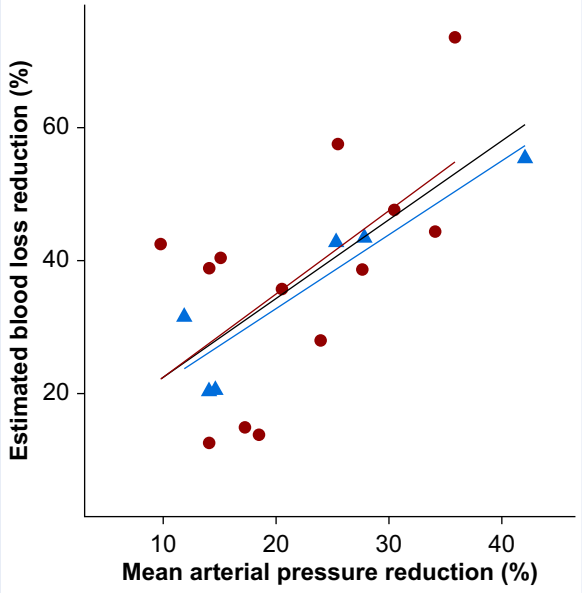

Fig 3. Associations between percentage reductions in mean arterial pressure and estimated blood loss. The percentage reduction was defined as the difference between the mean measurements in controlled hypotension and usual care groups divided by the mean measurement in the usual care group, which was then multiplied by 100%. The association was significant in studies with anaesthesia affiliation (adjusted R^2=0.29, P=0.03; red closed circles and line), in studies with surgery affiliation (adjusted R^2=0.80, P=0.01; blue triangles and line), and in all studies (adjusted R^2=0.41, P=0.002; black line).

clearance 15–45 min after induced hypotension.[32] Both trials suggested that hypotension reduced creatinine clearance, although neither claimed statistical significance.

No trials investigated the incidence of postoperative delirium, a complication possibly associated with intraoperative hypotension.[74] However, several trials focused on other cerebral outcomes.[34,59,62,63,67] One reported that cerebral blood flow velocity measured using transcranial Doppler was 57 cm s^{-1} in the controlled hypotension group, compared with 71 cm s^{-1} in the usual care group. This trial also indicated that internal jugular vein oxygen saturation was 71% in the controlled hypotension group *vs* 75% in the usual care group.[59] Another trial supported these findings showing that cerebral tissue oxygen saturation, measured using near-infrared spectroscopy, was 71% in the controlled hypotension group compared with 75% in the usual care group.[62] However, neither trial reported statistically significant differences in cerebral tissue oxygen saturation between controlled hypotension and usual blood pressure management,[59,62] as corroborated by the other reports.[63,67] One trial observed a significant increase in S100B levels in cerebrospinal fluid in the controlled hypotension group compared with the usual care group among patients having intracranial aneurysm clipping.[34] Only one trial presented results of mini-mental state examinations, which did not differ significantly.[62]

Certainty of evidence

The certainty of the body of efficacy evidence was deemed low for several reasons. First, imprecision did not appear to be a concern, as the required information size was reached for trials with estimated blood loss reported (Fig. 4 and Supplementary Fig. S2). Second, 38 out of 48 (79%) trials were assessed as having an overall high risk of bias and nine (19%) trials as having some concerns (Supplementary Table S2 and Fig. S3). Third, inconsistency in estimated blood loss reduction, indicated by an overall I^2 of 55%, could be a concern (Fig. 2b). However, the estimated blood loss reduction was characterised by a tight 95% CI (32–54%), and the strong association between MAP and estimated blood loss reductions suggests a dose–response relationship (Fig. 3). Therefore, the data overall appear consistent. Fourth, indirectness was not a factor, as the trials directly investigated the outcomes of interest. Finally, both the Funnel plot (Supplementary Fig. S4) and Egger's test (P<0.001) suggested some publication bias.

Regarding safety, the certainty of the evidence was graded as very low for various reasons. Among 33 trials that reported safety-related outcome measures, 27 (82%) were categorised as having an overall high risk of bias and five (15%) as having some concerns. Imprecision was noted as each safety-related outcome was supported by only one or two small trials.[75] Inconsistency could not be evaluated through typical statistical criteria owing to the inability to evaluate heterogeneity (I^2). However, disagreements among various trials, as shown in Table 2, led to a downgrade for inconsistency. Moreover, most trials did not directly investigate the most important safety outcomes, myocardial and renal injury, resulting in a downgrade as a result of indirectness. Publication bias was impossible to evaluate because the number of trials that could be pooled was insufficient for all outcomes.

Discussion

During surgery, surgeons sometimes request intraoperative controlled hypotension to reduce bleeding and improve visibility in the surgical field. Our meta-analysis confirms that intraoperative controlled hypotension is effective, with an ~15% reduction in estimated blood loss for every 10% decrease in MAP. In contrast, despite nearly 50 randomised trials comparing intraoperative controlled hypotension with usual care, the safety of the practice remains unclear. This is concerning in light of many observational analyses documenting associations between inadvertent hypotension and myocardial and renal injury.[8,9]

There was a distinct divergence between trials with anaesthesia and surgical backgrounds. Researchers affiliated with surgery departments prioritised efficacy-related outcomes. Specifically, no trials performed by surgery investigators had safety-related primary outcomes, and more than 80% incorporated no safety-related outcomes whatsoever. In contrast, researchers affiliated with an anaesthesia department tended to prioritise safety-related outcomes, with approximately half of the anaesthesia-led trials having a safety-related primary outcome and 84% including safety outcomes.

Previous systematic reviews also suggested the efficacy of intraoperative controlled hypotension. A 2008 review found

Table 2 Safety-related outcomes reported by the original studies. This table includes both the primary and secondary outcome measures. α-GST, alpha-glutathione S-transferase; π-GST, pi-glutathione S-transferase; ΔrSO_2, change in regional cerebral oxygen saturation; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transferase; CKMB, creatine kinase-myocardial band; FENa, fractional excretion of sodium; LFT, liver function test; MMSE, mini-mental state examination; PAH, para-aminohippurate; pHi, intracellular pH; PONV, postoperative nausea and vomiting; PT, prothrombin time; PTT, partial thromboplastin time; rSO_2, regional cerebral oxygen saturation; SKT, Syndrom-Kurztest (a standardised psychomotor function test); TT, thrombin time. *Two studies[40,56] were affiliated with surgery; the remaining 31 studies were affiliated with anaesthesia.

Authors (year)*	Safety-related outcome measures	Results		Comparison or conclusions
		Controlled hypotension	Usual care	
Agrawal and colleagues (2022)[20]	Postoperative sedation, postoperative pain	Postoperative sedation: 3.08 (SD 0.65) Postoperative pain (VAS): 1.54 (1.69)	Postoperative sedation: 2.29 (0.75) Postoperative pain (VAS): 3.08 (1.17)	Inferior postoperative sedation, superior postoperative pain per authors
Ayoglu and colleagues (2008)[21]	Haemoglobin, haematocrit	Septoplasty: Haemoglobin: 12.9 (16.2) g L^{-1} Haematocrit: 37.8% (26.3%) Tympanoplasty: Haemoglobin: 12.8 (10.1) g L^{-1} Haematocrit: 36.1% (23.4%)	Septoplasty: Haemoglobin: 12.9 (11) g L^{-1} Haematocrit: 36.4% (14.5%) Tympanoplasty: Haemoglobin: 13.0 (12.3) g L^{-1} haematocrit 37.9% (22.7%)	No difference per authors
Bakhet and colleagues (2019)[22]	Electrical stapedial reflex threshold	3 (apex): 17.5 (5.3) 9 (middle): 18.2 (5.5) 20 (base): 20.2 (5.2)	3 (apex): 16.4 (4) 9 (middle): 17.9 (10.6) 20 (base): 19.5 (6.5)	No difference per authors
De Hert and colleagues (1989)[24]	Pa_{O_2}, Pa_{CO_2}	Pa_{O_2}: 155.8 (32.9) mm Hg Pa_{CO_2}: 45.2 (2.6) mmHg	Pa_{O_2}: 169.2 (30.2) mm Hg Pa_{CO_2}: 40.9 (1.9) mm Hg	Inferior per authors
Diaz and Lockhart (1979)[25]	Haemoglobin, haematocrit	Haemoglobin: 11.2 (1.4) g L^{-1} Haematocrit: 32.3% (4.1%)	Haemoglobin: 11 (1.9) g L^{-1} Haematocrit 32.1% (5.6%)	No difference per authors
Dietrich and colleagues (1996)[26]	Spontaneous platelet aggregation, haemoglobin	Spontaneous platelet aggregation: 1.3 (IQR −0.3 to 7.8) Ω h^{-1} Haemoglobin: 13.7 g dl^{-1}	Spontaneous platelet aggregation: 2.4 (IQR 0.0–7.0) Ω h^{-1} Haemoglobin: 13.5 g dl^{-1}	Inferior spontaneous platelet aggregation per authors; no difference in haemoglobin
Eid and colleagues (2023)[65]	Haemoglobin, PT, aPTT, platelet count, fibrinogen, D-dimer, antithrombin	Haemoglobin: 12.22 (0.95) g L^{-1} PT: 13.06 (0.44) s aPTT: 36.15 (2.09) s Platelet count: 249.50×10^9 (44.22×10^9) L^{-1} Fibrinogen: 270.33 (38.95) mg dl^{-1} D-dimer: 1.46 (0.45) μg ml^{-1} Antithrombin: 98.63% (5.01%)	Haemoglobin: 10.97 (0.99) g L^{-1} PT: 14.52 (0.56) s aPTT: 40.87 (2.76) s Platelet count: 206.00×10^9 (38.52×10^9) L^{-1} Fibrinogen: 242.50 (30.08) mg dl^{-1} D-dimer: 2.35 ± 0.71 μg ml^{-1} Antithrombin: 86.83% (5.61%)	Superior per authors
Felfernig-Boehm and colleagues (2001)[31]	Haemoglobin, platelet count, PT, TT, PTT, fibrinogen, antithrombin, D-dimer	Haemoglobin: 10.7 g L^{-1} Platelet count: 215×10^9 L^{-1} PT: 84.4% TT: 14.1 s PTT: 36.2 s Fibrinogen: 222 mg dl^{-1} Antithrombin: 90.7% D-dimer: 3.02 μg ml^{-1}	Haemoglobin: 10.1 g L^{-1} Platelet count: 182×10^9 L^{-1} PT: 71.2 % TT: 15.9 s PTT: 41.2 s Fibrinogen: 170 mg dl^{-1} Antithrombin: 78.4% D-dimer: 3.21 μg ml^{-1}	No comparison and no comments by the authors
Goto and colleagues (1982)[32]	Rate pressure product, Pa_{O_2}, Pa_{CO_2}PAH clearance, creatinine clearance,FENa	Rate-pressure product: 6865 (364) Pa_{O_2}: 113 (10) mm Hg Pa_{CO_2}: 36 (2) mm HgPAH clearance: 320 (52) ml min^{-1}Creatinine clearance: 56 (4) ml min^{-1}FENa: 1.35% (0.38%)	Not specified	No comparison with control group available

Continued

Table 2 Continued

Authors (year)*	Safety-related outcome measures	Results		Comparison or conclusions
		Controlled hypotension	Usual care	
Govil and colleagues (2017)[66]	Objective pain score, emergence agitation score	Objective pain score: 4.2 (0.7) Emergency agitation score: 7.1 (0.3) Emergency agitation (score >16): 1/30 Shivering: 2/30 PONV: 1/30 Dry mouth: 5/30	Objective pain score: 7.9 (0.3) Emergency agitation score: 13.4 ± 0.7 Emergency agitation (score >16): 12/30 Shivering: 6/30 PONV: 8/30 Dry mouth: 2/30	Superior recovery profile and lower incidence of postoperative complications per authors
Grundy and colleagues (1982)[33]	Haematocrit	Haematocrit: 37% (6%)	Haematocrit: 37% (2%)	No difference per authors
Han and colleagues (2004)[34]	S100B protein, nonspecified neurological complications	S100B protein: 2.5 μg L^{-1} Neurological complications: 3/15	S100B protein: 0.7 μg L^{-1} Neurological complications: 4/13	Inferior per authors
Jacobi and colleagues (2000)[36]	Psychomotor function	SKT-testing: 3.6 (2.1) points	SKT-testing: 3.2 (2.4) points	No difference per authors
Jiao and colleagues (2009)[37]	Gastrointestinal perfusion	pHi: 7.46	pHi: 7.45	No difference
Kazemi and colleagues (2006)[38]	Hospital stay length	Not specified	Not specified	No difference per authors
Ke and Pen (2013)[39]	Postoperative discharge, PONV, postoperative shivering	Postoperative discharge: 18/30 PONV: 1/30 Postoperative shivering: 2/30	Postoperative discharge: 27/30 PONV: 8/30 Postoperative shivering: 9/30	Superior per authors
Kop and colleagues (2009)[40]	Wound infection, dehiscence, hospital stay length	Wound infection: 1/23 Dehiscence: 0/23 Necrosis: 0/23 Average hospital stay length: 3 days	Wound infection: 3/28 Dehiscence: 3/28 Necrosis: 3/28 Average hospital stay length: 3 days	Superior per authors
Kosucu and colleagues (2014)[41]	Postoperative pain and agitation	Not specified	Not specified	No difference per authors
Kosucu and colleagues (2020)[42]	Postoperative pain, PONV, shivering	Not specified	Not specified	No difference per authors
Neethirajan and colleagues (2020)[44]	Postoperative sedation, time to extubation	Postoperative sedation score: 2.54 (0.50) Time to extubation: 9.04 (1.80) min	Postoperative sedation score: 2.09 (0.41) Time to extubation: 5.07 (1.79) min	Slower emergence from anaesthesia
O'Connor and colleagues (2006)[45]	ST depression, CKMB, troponin, hospital stay length	ST depression: 1/49; CKMB: 0/49; Troponin: 0/49; Hospital stay length (>5 days): 24/49	ST depression: 0/60; CKMB: 0/60; Troponin: 0/60; Hospital stay length (>5 days): 34/60	No difference
Omar and colleagues (2008)[46]	Markers of hepatic injury: α-GST, π-GST, hyaluronic acid, AST, ALT	α-GST: 3673 ng L^{-1} π-GST: 213.4 μg L^{-1} Hyaluronic acid: 27.8 ng ml^{-1} AST: 24.1 U L^{-1} ALT: 25.3 U L^{-1}	α-GST: 3309 ng L^{-1} π-GST: 187.2 μg L^{-1} Hyaluronic acid: 22.5 ng ml^{-1} AST: 22.4 U L^{-1} ALT: 25.1 U L^{-1}	Hypotension associated with transient reversible increase in liver enzymes reflecting minor impaired hepatocellular integrity per authors
Pilli and colleagues (1996)[49]	ST depression, ABG, desaturation	Not specified	Not specified	No difference per authors
Salman and colleagues (2018)[67]	Regional cerebral oxygen saturation (rSO_2), haemoglobin	rSO_2: 67.9% (7.1%) Haemoglobin: 9.1 (0.35) g L^{-1}	rSO_2: 67.4% (8.2%) Haemoglobin: 8.86 (0.69) g L^{-1}	Superior with preserved cerebral perfusion per authors
Sartcaoglu and colleagues (2005)[54]	Postoperative cognitive function	Not specified	Not specified	No difference per authors
Sood and colleagues (1987)[56]	LFTs	Not specified	Not specified	No difference per authors
Thompson and colleagues (1978)[57]	Creatinine clearance, LFTs	Creatinine clearance: 73 (7) ml min^{-1} LFTs: not specified	Creatinine clearance: 101.0 (18) ml min^{-1} LFTs: not specified	No difference per authors

Continued

Table 2 Continued

Authors (year)*	Safety-related outcome measures	Results		Comparison or conclusions
		Controlled hypotension	Usual care	
Toivonen and colleagues (1993)[58]	Postoperative psychological testing	Results of multiple variables reported	Results of multiple variables reported	No difference per authors
Xu and colleagues (2000)[59]	Cerebral blood flow, internal jugular vein oxygen saturation	Cerebral blood flow velocity: 56.7 (13.1) cm s^{-1} Saturation: 71.3% (8.3%)	Cerebral blood flow velocity: 71.1 (10.7) cm s^{-1} Saturation: 75.4% (11%)	No significant difference per authors
Yousif and colleagues (2009)[60]	Markers of hepatic injury: α-GST, π-GST, hyaluronic acid, AST, ALT	α-GST: 5873 ng L^{-1} π-GST: 159.1 μg L^{-1} Hyaluronic acid: 27.8 ng ml^{-1} AST: 27.1 U L^{-1} ALT: 29.9 U L^{-1}	α-GST: 3494 ng L^{-1} π-GST: 175.9 μg L^{-1} Hyaluronic acid: 19.9 ng ml^{-1} AST: 23.7 U L^{-1} ALT: 26.8 U L^{-1}	Minimal and transient hepatocellular injury only detected by α-GST and hyaluronic acid per authors
Yukioka and colleagues (1993)[61]	Myocardial oxygen demand (rate-pressure product), LFTs	Rate-pressure product: 9503 LFTs: not specified	Rate-pressure product: not specified LFTs: not specified	No difference per authors
Zhang and colleagues (2021)[62]	Regional cerebral oxygen saturation (rSO_2), postoperative cognition (MMSE)	rSO_2: 70.7% MMSE: 28.5	rSO_2: 75.4% MMSE: 28.7	Saturation different; MMSE no difference per authors
Zhao and colleagues (2022)[63]	Change in regional cerebral oxygen saturation (ΔrSO_2), postoperative cognition (MMSE)	ΔrSO_2: 0.61 (−0.70 to 5.36) MMSE: not specified	ΔrSO_2: −0.29 (−3.28 to 3.19) MMSE: not specified	Saturation no difference; MMSE no difference per authors

that all five randomised controlled trials, rated as high-quality and low-bias studies, indicated reduced blood loss with hypotensive anaesthesia, although two lacked statistical significance.[2] In 2019, a systematic review with meta-analysis across 29 studies involving 1398 participants reported a mean reduction of 377 ml (95% CI −428 to −325 ml; I^2=94%) in intraoperative blood loss with deliberate hypotension, but the authors rated the quality of the evidence as low.[4] Overall, prior work and our current analysis clearly indicate that controlled hypotension is effective in reducing blood loss.

In contrast, evidence from the 33 trials reporting safety-related outcomes is marginal. Firstly, trials used diverse outcome measures and various metrics for similar outcomes. Secondly, none adequately evaluated the major complications associated with intraoperative inadvertent hypotension, namely myocardial and renal injury. Thirdly, none of the trials was remotely powered for major haemodynamic-related safety outcomes such as organ injury, which, fortunately, is relatively uncommon. Consequently, reported neutral results should be considered underpowered rather than evidence of safety. Finally, many safety (and efficacy) trials were rated as having a high potential for bias.

Safety concerns about intraoperative controlled hypotension are hardly new.[76–80] In the early 1950s, reports indicated mortality rates of approximately 0.22–0.34%, and nonfatal complications, primarily involving cerebral, coronary, and renal circulations, occurred in approximately 2.6–3.3% of patients.[81] By the early 1960s, mortality was reported as 0.10% based on a larger cohort of 9107 patients undergoing deliberate hypotension.[82] In the mid-1970s, a review article estimated that nonfatal complications occur in ~2.6% of patients and fatal complications in ~0.6%.[76] In the mid-1980s, one case series reported a cerebral morbidity rate of 0.22% and a cerebral complication-related mortality rate of 0.06% among 1802 patients.[78] Mortality in these patients was often linked to severe cerebral complications[80] or myocardial infarctions.[79]

Inadvertent hypotension, often manifesting in high-risk surgical contexts, is associated with complications including myocardial and renal injuries. Although controlled hypotension is used in select surgical contexts, potential risk remains and must be balanced against reduced blood loss and improved surgical visibility. At this point, efficacy seems clear. In contrast, safety has not been established because no existing trials are powered for sparse dichotomous serious outcomes such as myocardial and renal injury, much less overt strokes which are even less common.

As in any systematic review and meta-analysis, we were limited by the quantity and quality of the underlying trials we included. Although the number of trials was reasonable (N=48), most were small, with an average of only 49 patients per trial. Furthermore, many were at risk for bias, and there was some evidence of publication bias. All 48 (100%) trials reported efficacy outcomes, but only 33 (69%) trials reported safety outcomes—and among those, safety was the primary outcome in only 20 trials. Furthermore, various safety outcomes were evaluated, and none consistently. Thus, although there was substantial evidence for clinically meaningful efficacy, we could not make any clear conclusions about safety.

In conclusion, our systematic review demonstrates that anaesthesia and surgery investigators have different

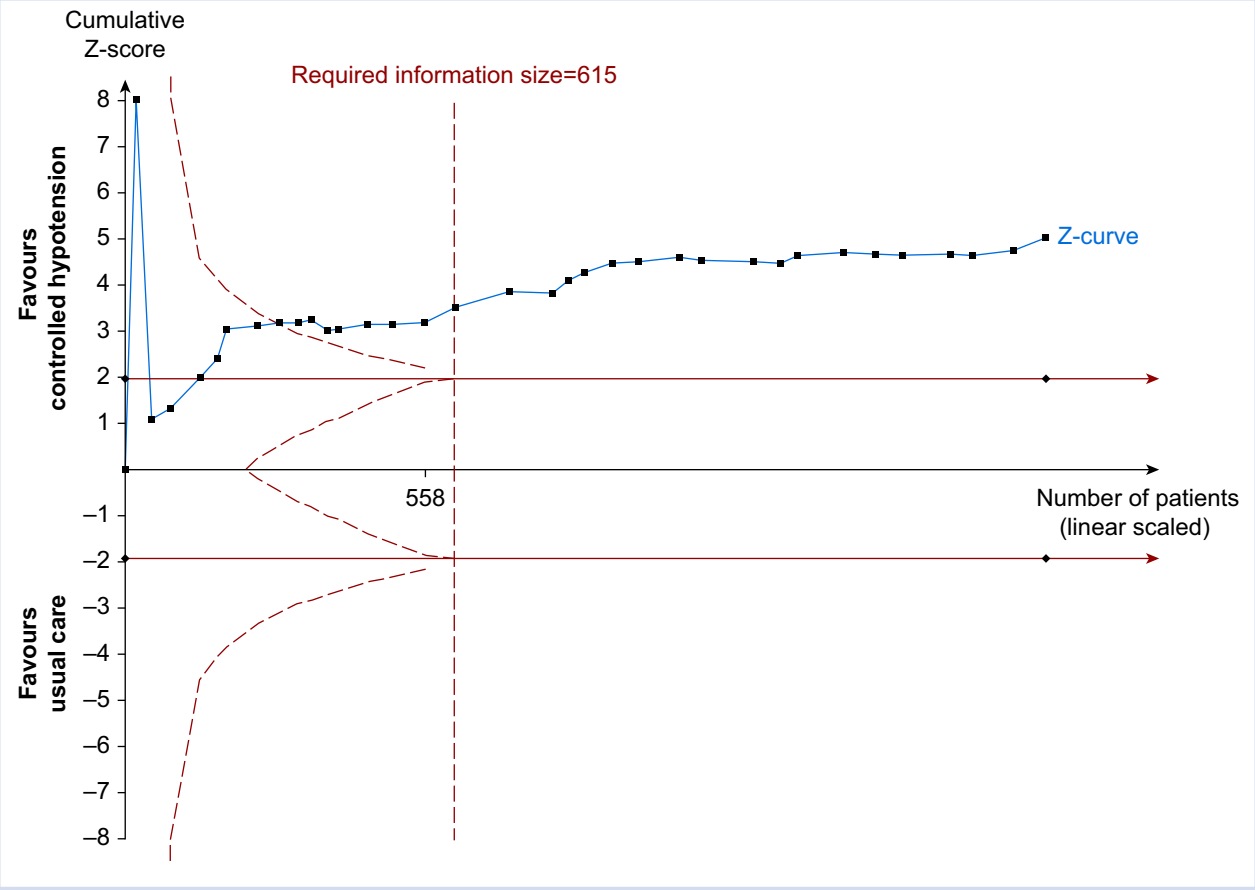

Fig 4. Trial sequential analysis based on trials reported estimated blood loss (n=34). We calculated the required sample size with α=0.05, β=0.20 (80% power), and an empirical mean difference. The cumulative Z-curve crossed both conventional and trial sequential monitoring boundaries, favouring controlled hypotension and suggesting no need for further trials.

concerns with respect to controlled hypotension, with anaesthesia investigators being more interested in safety-related outcomes, whereas surgery investigators were most interested in efficacy. As in previous meta-analyses,[4] we confirm that intraoperative controlled hypotension reduces blood loss. We additionally show that blood loss reduction is proportionate to the reduction in blood pressure. In contrast, the safety of intraoperative controlled hypotension has not been adequately studied, and available evidence does not support the practice. Given the well-documented associations between inadvertent hypotension and postoperative myocardial and renal injury, the safety of intraoperative controlled hypotension needs additional evaluation.

Authors' contributions

Concept and design: LM
Acquisition, analysis, and interpretation of data: all authors
Drafting of the manuscript: LD, LM
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: JL, DG
Administrative, technical, or material support: LD
Supervision: LM

Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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