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Hypertonic salt solution for peri-operative fluid management

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Dates

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What's new

Date	Event	Description
8 April 2016	New citation: conclusions not changed	A new author has been added to the review team (Brad Shrum). We added three new studies which did not change the conclusions of the review. We updated the methods for the review.
8 April 2016	Updated	In this update, we searched CENTRAL, Pubmed, EMBASE, LILACS, and CINAHL, and reviewed the results up to April 08, 2016. We identified and screened 42 additional studies. We excluded 39 of those studies, added no studies to the 'Awaiting classification' section, or to 'Ongoing studies'. We include three new studies (Lavu 2014; Leverve 2008; Shao 2013).

History

Date	Event	Description

Abstract

Background

Fluid excess may place people undergoing surgery at risk for various complications. Hypertonic salt solution (HS) maintains intravascular volume with less intravenous fluid than isotonic salt (IS) solutions, but may increase serum sodium. This review was published in 2010 and updated in 2016.

Objectives

To determine the benefits and harms of HS versus IS solutions administered for fluid resuscitation to people undergoing surgery.

Search methods

In this updated review we have searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 4, 2016); MEDLINE (January 1966 to April 2016); EMBASE (January 1980 to April 2016); LILACS (January 1982 to April 2016) and CINAHL (January 1982 to April 2016) without language restrictions. We conducted the original search on April 30th, 2007, and reran it on April 8th, 2016.

Selection criteria

We have included randomized clinical trials (RCTs) comparing HS to IS in people undergoing surgery, irrespective of blinding, language, and publication status.

Data collection and analysis

Two independent review authors read studies that met our selection criteria. We collected study information and data using a data collection sheet with predefined parameters. We have assessed the impact of HS administration on mortality, organ failure, fluid balance, serum sodium, serum osmolarity, diuresis and physiologic measures of cardiovascular function. We have pooled the data using the mean difference (MD) for continuous outcomes. We evaluated heterogeneity between studies by I^2 percentage. We consider studies with an I^2 of 0% to 30% to have no or little heterogeneity, 30% to 60% as having moderate heterogeneity, and more than 60% as having high heterogeneity. In studies with low heterogeneity we have used a fixed-effect model, and a random-effects model for studies with moderate to high heterogeneity.

Main results

We have included 18 studies with 1087 participants of whom 545 received HS compared to 542 who received IS. All participants were over 18 years of age and all trials excluded high-risk patients (ASA IV). All trials assessed haematological parameters peri-operatively and up to three days post-operatively.

There were three (< 1%) deaths reported in the IS group and four (< 1%) in the HS group, as assessed at 90 days in one study. There were no reports of serious adverse events. Most participants were in a positive fluid balance postoperatively (4.4 L IS and 2.5 L HS), with the excess significantly less in HS participants (MD -1.92 L, 95% confidence interval (CI) -2.61 to -1.22 L; P < 0.00001). IS participants received a mean volume of 2.4 L and HS participants received 1.49 L, significantly less fluid than IS-treated participants (MD -0.91 L, 95% CI -1.24 to -0.59 L; P < 0.00001). The maximum average serum sodium ranged between 138.5 and 159 in HS groups compared to between 136 and 143 meq/L in the IS groups. The maximum serum sodium was significantly higher in HS participants (MD 7.73, 95% CI 5.84 to 9.62; P < 0.00001), although the level remained within normal limits (136 to 146 meq/L).

A high degree of heterogeneity appeared to be related to considerable differences in the dose of HS between studies. The quality of the evidence for the outcomes reported ranged from high to very low. The risk of bias for many of the studies could not be determined for performance and detection bias, criteria that we assess as likely to impact the study outcomes.

Authors' conclusions

HS reduces the volume of intravenous fluid required to maintain people undergoing surgery but transiently increases serum sodium. It is not known if HS affects survival and morbidity, but this should be examined in randomized controlled trials that are designed and powered to test these outcomes.

Plain language summary

Increased salt in solution to maintain fluid during surgery

Review question

Are solutions containing more salt than is normally used safe during surgery?

Background

People usually require fluids during surgery. Sometimes large volumes of fluid are given in order to maintain adequate blood volume, but these volumes may leave people with too much fluid. The fluids normally used during surgery have a salt balance similar to that found in blood, and are called isotonic. Hypertonic salt solutions (HS) have a higher sodium concentration than isotonic salt solutions (IS). HS might benefit people undergoing surgery by reducing the total volume of fluid required.

Search date

The evidence is up to date to April 8th, 2016.

Study characteristics

We included 18 trials that compared HS to IS in people undergoing surgery. The trials included 1087 participants. Five hundred and forty-five (545) participants received HS and 542 received IS during their operations. The participants were randomly assigned to their groups. The studies took place in 11 countries. Study participants were over the age of 18. All studies excluded people with serious health risks from participating. All studies monitored fluid levels during the operation and up to three days after.

Key results

There were seven deaths in total, three (less than 1%) from the IS group and four (less than 1%) from the HS group. The risk of death was very low in these studies. The studies did not report the occurrence of serious adverse events.

Thirteen studies reported the amount of fluid given. The IS group received a mean of 2.4 L and the HS group received 0.91 L less (1.49 L). The highest amount of sodium in the blood over the course of the study was reported by 16 studies. The IS group had a median of 139 meq/L and the HS group was 7.73 meq/L higher. The normal acceptable range is 136 to 146 meq/L.

Quality of the evidence

For deaths and adverse events the trials lacked sufficient size and duration to adequately assess differences. We assessed the quality of evidence for deaths to be very low, and future studies are likely to change the result reported here.

The reporting of the highest amount of sodium is of moderate quality. The measuring of blood sodium during an operation is a common measurement that is unlikely to be misrepresented.

Background

Description of the condition

Low-volume resuscitation with hypertonic crystalloid solutions has been investigated for over 20 years (Shackford 1983). More recently, alterations in cellular immune function with hypertonic salt solution (HS) administration have been demonstrated in experimental and clinical studies (Kølsen-Petersen 2004; Rizoli 2006). Several randomized controlled trials (RCTs) of HS resuscitation in critically ill participants have been performed. A systematic review of HS compared to isotonic salt solution (IS) in resuscitation following burns or trauma was unable to reach a conclusion regarding benefit or harm in the presence of wide confidence intervals (Bunn 2004). Trials of HS alone, or in combination with colloids, have also been performed in the trauma population. A meta-analysis comparing 250 mL of HS (with or without dextran) with administration of 250 mL of isotonic crystalloid for the treatment of hypotension either in the field or at admission to the emergency department in 1233 trauma patients failed to demonstrate that HS with dextran confers a survival benefit (Wade 1997).

Description of the intervention

Standard peri-operative care includes IS administration to counter conditions which may cause transient intraoperative hypovolaemia including: fluid deprivation during preoperative fasting; vasodilatation due to epidural or general anaesthesia; third space sequestration of intravascular fluid; insensible fluid loss and intraoperative fluid or blood loss. These conditions are often reversed at the end of an operation. In fact, IS has been shown to increase the weight of people undergoing elective major surgery by an average of three to six kilograms (kg) (Grocott 2005). While most people tolerate the additional fluid well, postoperative improvement or reversal of the conditions outlined above may place those with compromised cardiovascular or renal function at increased risk for development of pulmonary oedema. People without cardiovascular or renal risk factors may also be adversely affected by peri-operative fluid gain. A recent RCT demonstrated that peri-operative fluid restriction resulted in fewer major or minor postoperative complications compared to traditional care in 172 adult participants undergoing elective colorectal surgery (Brandstrup 2003). Another study demonstrated that fluid overload delayed return of gastrointestinal function (Lobo 2002). Conversely, failure to maintain intravascular volume during surgery may place people at risk for cardiac or cerebral ischaemia. Indeed, supplemental peri-operative fluid administration has been shown to improve tissue oxygenation (Arkiliç 2003).

How the intervention might work

HS has the potential to reduce the total volume of fluid administered during operative procedures by allowing people to draw fluid from the interstitium (and other body compartments) to counter peri-operative hypotensive effects, and thereby provide Intravascular support without excess fluid administration. In situations where large volume resuscitation may be harmful, such as in brain trauma, a role for HS is emerging (Ogden 2005). Notwithstanding, several risks have been associated with HS, including potential hypernatraemia, metabolic acidosis and vasodilatation.

Why it is important to do this review

Several RCTs of prophylactic HS administration in the peri-operative period have been published. In contrast to other trials where HS has been combined with colloid solutions to treat hypotension, these RCTs may provide a clinical picture of the effect of HS on peri-operative fluid management.

Objectives

To determine the benefits and harms of HS versus IS solutions administered for fluid resuscitation to people undergoing

surgery.

Methods

Criteria for considering studies for this review

Types of studies

We included RCTs comparing the administration of HS versus IS solution during non-emergency operative procedures, regardless of language or publication status. RCTs are the gold standard for comparing the effect of one treatment versus another.

Types of participants

We included all participants undergoing any surgical procedures.

Types of interventions

We have included peri-operative administration of either HS or IS solutions. We permitted concomitant measures so long as they applied to both arms of the study. We excluded studies that compared HS and a colloidal solution to IS alone. Additionally, we excluded studies that compared HS and IS solutions administered by inhalation or absorption from the nasal mucosa and involving non-surgical patient populations (burns, trauma and head injury).

Types of outcome measures

Primary outcomes

1. Mortality

Defined as any deaths occurring during the study period. Where all participants are included in the results for other outcomes we have extrapolated that as indicating no deaths.

2. Serious adverse events

We collected other adverse outcomes as defined by each trial, or if any of the following occurred: any organ failure, any requirement for dialysis (renal failure) or prolonged ventilation (pulmonary failure); use of medical therapy for either pulmonary oedema or circulatory support (cardiac failure) or for confusion (cerebral failure).

Secondary outcomes

3. Fluid balance over the study period

We used authors' definitions where provided. For studies not clearly specifying the study period, we defined it to include the immediate preoperative (induction of anaesthesia), intraoperative and postoperative periods (up to 24 hours after surgery). Studies can report the fluid balance by reporting the difference in fluid given minus fluid excreted or by the change in weight of the participant. For studies that only reported weight change, we applied a conversion factor, wherein 1 kg = 1 L (litre), to calculate fluid balance. Fluid balance is expressed in litres.

4. Total volume of intravenous fluid delivered

A report of the volume of resuscitating fluid given to the participant intravenously during the peri-operative and recovery period as reported by the studies. Fluid delivered is expressed in litres.

5. Peri-operative diuresis

A measure of the urine output from the participant during the operative period. Diuresis is reported as litres.

6. Maximum serum sodium concentration

As measured from the participant's blood during the study and reported as milliequivalents per litre (meq/L).

7. Final serum sodium concentration

As measured in the participant's blood at the end of follow-up, and reported as milliequivalents per litre (meq/L).

8. Duration of endotracheal intubation after operation

As reported by each study and converted to hours (h).

9. Duration of stay in intensive care after operation

As reported by each study and converted to hours (h).

10. Duration of stay in hospital after operation

As reported by each study and converted to days (d).

11. Other outcomes

We collected data regarding serum osmolarity, expressed as milliosmoles per kilogram of water (mOsm/kg H2O) and peri-operative haemodynamic parameters: pulmonary artery wedge pressure, measured by mm of mercury (mm Hg); and cardiac index (CI), derived from cardiac output (CO = Heart rate/stroke volume/1000) and body surface area (BSA), CI = CO/BSA; it is a measure of the volume of blood passing through one square meter each minute (L/min/M²).

Search methods for identification of studies

Electronic searches

For this updated review we have searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 4, 2016); MEDLINE (January 1966 to April 2016); EMBASE (January 1980 to April 2016); LILACS (January 1982 to April 2016) and CINAHL (January 1982 to April 2016). We limited the publication types to clinical trials, controlled clinical trials, RCTs, multicentre studies and meta-analyses, without language restrictions.

We originally used the search strategy described in the appendices (Appendix 1 MEDLINE; Appendix 2 EMBASE; Appendix 3 CINAHL; Appendix 4 LILACS; Appendix 5 CENTRAL) to search until August 2009. We have updated the search terms since the original search (see Appendix 6). In addition, we searched trial registries including clinicaltrials.gov/, www.controlled-trials.com/ and www.ifpma.org/clinicaltrials.html for ongoing trials. We sought letter or email contact with principal investigators to inform them of the meta-analysis and to ask for additional information.

The search was last run on April 8th, 2016.

Searching other resources

We handsearched the bibliographies of retrieved articles and the abstracts of conference proceedings published in *Anaesthesia and Intensive Care*; *Anaesthesia and Analgesia; British Journal of Surgery; Critical Care Medicine*; *Journal of Vascular Surgery and Trauma; Injury;* and *Infection and Critical Care* for the years 2000 to 2006.

Data collection and analysis

Selection of studies

Vivian McAlister (VM) with Brad Shrum (BS) scanned titles and abstracts identified by the initial search to exclude overlapped and irrelevant studies. Three authors (Tammy Znajda (TZ), Karen Burns (KB) and BS) identified trials that met our inclusion criteria. Brian Church (BC) resolved differences in data recorded and we resolved all differences of opinion through discussion.

Data extraction and management

At least two of the review authors abstracted data independently from the studies, using standardized forms developed for this review. We wrote to primary study authors for information regarding missing data or data that were not clearly stated. We resolved differences of opinion through discussion. We abstracted data pertaining to the included participants, interventions applied and outcomes reported for each trial. Where translation was needed we sought the help of native speakers of the language who had scientific training. The translator collected relevant information on the data collection forms provided.

We abstracted the following details from each of the included studies:

1. Participants (inclusion and exclusion criteria; mean age; proportion of men; aetiology of disease; weight before and after surgery; serum electrolytes before, during and after surgery);
2. Interventions (type of surgery; concentration and volume of hypertonic saline given; total volume of fluid administered and concomitant therapy);
3. Trials (setting; methodological quality; publication status; duration of follow-up and all outcomes).

Assessment of risk of bias in included studies

We based our assessment of 'Risk of bias' on the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The assessments were based on the allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases (Lundh 2012; Wood 2008).

Allocation sequence generation

Low risk of bias: sequence generation was achieved using computer random-number generation or a random-number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.

Uncertain risk of bias: the method of sequence generation was not specified.

High risk of bias: the sequence generation method was not random.

Allocation concealment

Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomization unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially-numbered, opaque, and sealed envelopes).

Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.

High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

Low risk of bias: blinding was performed adequately. Additionally, we defined lack of blinding (detection and performance bias) as not likely to affect the assessment of the outcome mortality.

Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to introduce bias in the results.

High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of

blinding (all other outcomes than mortality and non-subjective laboratory measures).

Incomplete outcome data

Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.

Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to introduce bias in the results

High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

Low risk of bias: the trial reported clinically relevant outcomes, which we defined as mortality, hepatic encephalopathy, and serious adverse events. If we had access to the original trial protocol, the outcomes should be those specified in that protocol. If we obtained the protocol from a trial registry such as www.clinicaltrials.gov, we only used the information if the investigators registered the trial before inclusion of the first participant.

Unclear risk of bias: not all predefined criteria were reported fully, or it was unclear whether data on these outcomes were recorded or not.

High risk of bias: one or more predefined outcomes were not reported.

Other bias

Low risk of bias: the trial appeared to be free of other bias domains, including: medicinal dosing problems or follow-up (as defined below).

Uncertain risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.

High risk of bias: there were other factors in the trial that could put it at risk of bias, such as the administration of inappropriate treatments being given to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups being compared).

Evidence Quality

The control of bias in the included trials was part of the overall assessment of the quality of the body of evidence, which we classified as ‘High’, ‘Moderate’, ‘Low’, or ‘Very Low’. We based the assessment on the specific evidence grading system developed by the GRADE collaboration (GRADE 2004).

Measures of treatment effect

We performed the analyses in Review Manager 5 (RevMan 2014). We used the result value and number of participants in all intervention arms to calculate the mean difference (MD) for continuous outcomes, with 95% confidence intervals (CIs).

Unit of analysis issues

If the standard error of the mean was recorded in a study, we converted it to standard deviation following the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 7.7.3.2. Briefly, SD = SE x Sqrt(n).

Dealing with missing data

We used the last observed response carried forward (LOCF) for participants with missing data.

Assessment of heterogeneity

We assessed heterogeneity visually through the use of funnel plots and further assessed it using the I^2 value. We explored sources of heterogeneity through sensitivity, subgroup, and meta-regression analyses. The analyses included the extracted participant, intervention, and trial characteristics listed above as explanatory variables.

Assessment of reporting biases

We used funnel plot asymmetry to detect reporting biases where there were more than nine studies, to avoid false detections (Sterne 2001a; Sterne 2001b). Where funnel plots appeared to have asymmetry, we deployed the test by Matthias Egger (Egger 1997) as described by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate. We considered reporting biases to be evident where $P < 0.05$.

Data synthesis

We combined data in fixed-effect meta-analysis if the group I^2 was less than 30%. Where I^2 was 30% or greater, we used random-effects meta-analyses. We conducted intention-to-treat (ITT) analyses including all participants irrespective of compliance or follow-up. In studies that had more than two treatment arms, we incorporated only two arms of the trial into the meta-analysis: the arm using IS and the treatment arm evaluating HS solution. If there were two HS arms, we selected the one most different in concentration from IS for analysis. Where meta-analysis was not possible due to a lack of events we used the Clopper-Pearson method to estimate treatment group CIs (Clopper 1934).

Summary of findings table

We summarize the compiled data for this meta-analysis in the Summary of findings table 1. Each outcome is shown with its anticipated incidence per 1000 people for each treatment group. The MD is shown with 95% CIs for

continuous outcomes. The overall quality of the evidence for each outcome has been determined using the Guideline Development Tool from the GRADE working group criteria and that of Cochrane (GRADE 2004; Higgins 2011). We rated the quality of the evidence as high, moderate, low, or very low, and have shown it visually and textually. Where studies have been downgraded from high quality, we have used footnotes to indicate the reason. Notes are included for each outcome to briefly describe it, and if appropriate the method of measurement.

Subgroup analysis and investigation of heterogeneity

When appropriate after consideration of statistical and clinical heterogeneity, we performed subgroup analyses based on the following a priori criteria:

1. Type of surgery
2. Dose of HS: trials were stratified into three comparisons according to the dose of HS, calculated as the volume of 3% HS required to give the same amount of sodium: 7 mL/kg or less (comparison 01); 7.1 to 10 mL/kg (comparison 02); > 10 mL/kg (comparison 03). We specified these dose stratifications before the review was conducted on the basis of an anticipated range of HS doses
3. Volume of crystalloid given to the control group: trials were stratified into three comparisons according to the total volume of fluid transfusion received by IS participants: < 2 L (comparison 01); 2 L to 5 L (comparison 02); > 5 L (comparison 03). We specified these volume stratifications in advance of the review on the basis of an anticipated range of peri-operative fluid administration

We interpreted a lack of overlap between two CIs in the subgroup analyses as representing a statistically significant difference.

Sensitivity analysis

Where the data permitted we performed a sensitivity analysis using the following *a priori* criteria. We removed studies that were deemed to have a moderate or higher risk of bias based on the aforementioned criteria (see Assessment of reporting biases). Where potential for bias was uncertain the review authors considered the potential impact of each domain on the results. For the purposes of sensitivity analysis, unknown sequence randomization or allocation concealment did not increase the risk of bias in a study, but unknown or high risk in any other domains did increased the risk of bias.

Results

Description of studies

Results of the search

From 284 reports identified by the search strategy, 25 reports met the criteria for further assessment (Figure 1). Of these 25 references, we excluded seven studies after detailed review because they were not randomized (Auler 1987; Shao 2005), did not compare to an IS group (Li 2014; Li 2015), or did not report our desired primary or secondary outcomes (Auler 1992; Yang Z 2014; Yousefshahi F 2013) (see Characteristics of excluded studies). We found no recently completed studies in registries of clinical trials including clinicaltrials.gov/; www.controlled-trials.com/; and www.ifpma.org/clinicaltrials.html.

Included studies

Eighteen studies with 1087 participants were included (Baraka 1994; Bruegger 2005; Cross 1989; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kølsen-Petersen 2004; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Veroli 1992; Wang 1997; Younes 1988) (see Characteristics of included studies). The included trials were performed in a wide variety of surgical situations: aortic surgery (four trials) (Bruegger 2005; Shackford 1983; Shackford 1987; Younes 1988); lower limb surgery (three trials) (Ishikawa 1996; Jarvela 2000; Veroli 1992); transurethral prostate resection (three trials) (Baraka 1994; Kato 1996; Kimura 1994); coronary artery bypass grafting (three trials) (Cross 1989; Jarvela 2001; Leverve 2008); hysterectomy (one trial) (Kølsen-Petersen 2004); hernia repair (one trial) (Wang 1997); general surgery (one trial) (Durasnel 1999); pancreaticoduodenectomy (one trial) (Lavu 2014); and neurological surgery (one trial) (Shao 2013). Anaesthetic techniques included: general anaesthesia (ten trials) (Bruegger 2005; Cross 1989; Jarvela 2001; Kato 1996; Kølsen-Petersen 2004; Lavu 2014; Shackford 1983; Shackford 1987; Shao 2013; Younes 1988) and spinal anaesthesia (seven trials) (Baraka 1994; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Kimura 1994; Veroli 1992; Wang 1997).

Studies were performed in 11 countries, which include Brazil, China, Denmark, Finland, France, Germany, Indonesia, Japan, Lebanon, Niger, and USA. Four publications were written in languages other than English, including Japanese (two trials) (Ishikawa 1996; Kimura 1994); French (one trial) (Durasnel 1999); Portuguese (one trial) (Younes 1988). The majority of included studies had small sample sizes, enrolling between 20 and 72 participants. The largest study enrolled 259 participants (Lavu 2014). The interval between the first and last study was approximately 30 years (1983 to 2014). Only one of the studies was designed to determine differences in short-term mortality (Lavu 2014), with the remaining studies focusing on fluid and haemodynamic measurement during the peri-operative period. Follow-up extended into the postoperative period in 10 trials (Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Kato 1996; Kølsen-Petersen 2004; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987), with durations ranging from the stay in the recovery unit to 90 days postoperative, while the other trials confined their observations to the period of anaesthesia. Two studies reported results with standard error which we converted to standard deviation by multiplication with the square root of the number in the group (Shackford 1983; Shackford 1987).

Two authors of included studies whom we contacted for further information responded. Dr. Lavu kindly provided mean and standard deviation values that were not available in the publication (Lavu 2014), and Dr. Jarvela provided additional methodological details regarding random sequence generation and allocation concealment for two studies (Jarvela 2000; Jarvela 2001). Dr. Shao was contacted regarding methodology but did not respond (Shao 2013).

Excluded studies

Seven studies were found but ultimately excluded from analysis; two due to a lack of randomization (Auler 1987; Shao 2005), two because there was no isotonic saline control group (Li 2014; Li 2015), and three due to an absence of primary or secondary outcomes (Auler 1992; Yang Z 2014; Yousefshahi F 2013). Dr. Yousefshahi was contacted for further information but did not respond (Yousefshahi F 2013).

Risk of bias in included studies

The overall risk of bias in the included studies is undetermined due to a large number of studies (72%) not fully reporting methodology (Characteristics of included studies). The domains with the largest potential for bias are for performance and detection bias. For performance and detection bias, eight studies did not provide sufficient information to determine the potential for bias (Baraka 1994; Bruegger 2005; Durasnel 1999; Jarvela 2000; Kimura 1994; Leverve 2008; Wang 1997; Younes 1988) and five studies did not protect their studies from performance or detection bias (Ishikawa 1996; Jarvela 2001; Shackford 1983; Shackford 1987; Shao 2013). Despite there being limited or unknown protection from performance bias it is unlikely that participants were informed of the fluid given to them for resuscitation. However, care givers and outcome assessors were either not blinded or insufficient information was given to determine the risk of bias, although this is unlikely to impact the majority of our measured outcomes, including mortality (Analysis 1.1), serious adverse events (Analysis 1.2), peak and final serum sodium (Analysis 1.6, Analysis 1.7), and maximum intraoperative serum osmolarity (Analysis 1.8), pulmonary artery wedge pressure (Analysis 1.9), and cardiac index (Analysis 1.10). Performance and detection bias could impact the results of fluid measurements, leaving the outcomes of fluid balance (Analysis 1.3), total volume of crystalloid administered (Analysis 1.4), and diuresis during study period (Analysis 1.5), at a greater risk of this source of bias and overall bias (Figure 2; Figure 3).

Allocation (selection bias)

Four trials described adequate random sequence generation (Cross 1989; Jarvela 2001; Kølsen-Petersen 2004; Lavu 2014), using a table of random numbers or computer-generated random numbers. The remaining 14 studies alluded to randomization but did not describe the method used (Baraka 1994; Bruegger 2005; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Kato 1996; Kimura 1994; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Veroli 1992; Wang 1997; Younes 1988).

Adequate allocation concealment was reported in six trials, four in the publication (Cross 1989; Kølsen-Petersen 2004; Lavu 2014; Shao 2013) and two through correspondence with the author (Jarvela 2000; Jarvela 2001).

From our assessment, four trials had a low risk of selection bias (Cross 1989; Jarvela 2001; Kølsen-Petersen 2004; Lavu 2014) (Characteristics of included studies).

Blinding (performance bias and detection bias)

Five studies reported adequate concealment of treatment from participants, personnel, and outcome assessors (Cross 1989; Kato 1996; Kølsen-Petersen 2004; Lavu 2014; Veroli 1992); we have rated them as having a low risk of performance and detection bias (Characteristics of included studies).

Incomplete outcome data (attrition bias)

We assessed 16 trials at a low risk of attrition bias (Baraka 1994; Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kølsen-Petersen 2004; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Veroli 1992; Wang 1997; Younes 1988). Each of the 16 studies provided clear information about all participants including those with missing outcome data (Characteristics of included studies).

Of the 1121 enrolled participants, 1087 completed the protocol. Four participants in the HS group failed to complete the study, one because of consent withdrawal (Kølsen-Petersen 2004); one for an anaphylactic reaction to another medication (Kølsen-Petersen 2004); one because of operative complication which met *a priori* exclusion criteria (Lavu 2014); and one without a reason specified (Durasnel 1999). Seven participants in the IS group failed to complete the protocol, four because of operative complications which met a priori exclusion criteria (Lavu 2014), one because of an urgent return to the operating room for control of haemorrhage (Kølsen-Petersen 2004); one because of a transfer to another hospital (Kølsen-Petersen 2004) and one without a reason specified (Durasnel 1999). Twenty-three participants failed to complete the protocol and were withdrawn from the studies without further information (Ishikawa 1996; Leverve 2008). One participant was withdrawn from Ishikawa 1996, while the other study had 22 people removed from the analysis due to major protocol violation or incomplete data collection, although they were still included in the safety profile (Leverve 2008).

Selective reporting (reporting bias)

Seventeen of the studies reported all of the clinically relevant outcomes that were appropriate for their trial design (Baraka 1994; Cross 1989; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kølsen-Petersen 2004; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Veroli 1992; Wang 1997; Younes 1988) (Figure 2; Figure 3). However, only one of the studies explicitly reported mortality (Lavu 2014). The remaining studies

imply there were no deaths through their other outcome data and we have assessed them to be at an unclear risk of reporting bias (Figure 3). Additionally, the study by Bruegger 2005 reported a disproportionately low number of female participants and we have assessed this as an unclear risk of bias because it was not explained.

Other potential sources of bias

Baseline parameters were reported in each study and appeared to be similar in both study groups in all trials. We found no evidence for other sources of bias in any of the studies (Characteristics of included studies).

Effects of interventions

Primary outcomes

1. Mortality

One trial reported occurrences of deaths (Lavu 2014), four in the HS group and three in the IS group. From all of the studies there were 545 participants in the HS group and 542 in the IS group. Because only one study reported events an analysis to compare treatment groups could not be performed. Assessment of the HS group using the Clopper-Person estimation shows that the upper bound for occurrences of events using a 95% CI is 0.019 (19/1000). Due to the paucity of events, neither a sensitivity nor subgroup analysis was feasible. We determine the quality of the evidence is very low (Summary of findings table 1).

2. Serious adverse events

There were no reports of serious adverse events such as organ failure, myocardial infarction, cerebrovascular accident or central pontine myelinolysis reported in the trials. The outcome was not explicitly measured and we have extrapolated the data. There were 1087 participants, 542 in the IS group and 545 in the HS group. Although an analysis comparing the treatment groups cannot be performed, assessment of the HS group utilizing the Clopper-Pearson estimation shows that the upper bound for occurrences of events using a 95% CI is 0.007 (7/1000). We have graded the quality of the evidence for this outcome as very low (Summary of findings table 1).

Secondary outcomes

3. Fluid balance

Peri-operative fluid balance was calculated in eight trials with 737 participants (51.1% HS, 48.9% IS) (Bruegger 2005; Cross 1989; Jarvela 2001;Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013). Overall, the fluid balance was positive in both groups (Summary of findings table 1), the mean volume for the IS group being 4.4 L and 1.9 L lower for the HS group (MD -1.92, 95% CI -2.61 to -1.22; I^2 = 91%; P < 0.00001; Analysis 1.3). We rate the quality of this evidence as low (Summary of findings table 1).

We conducted a sensitivity analysis using only studies deemed to have a low risk of bias (Cross 1989; Lavu 2014). The fluid balance was again found to be statistically significantly lower for the HS group (MD -1.47, 95% CI -2.84 to -0.09; participants = 279; P = 0.04; I^2 = 60%; Analysis 2.1).

Subgroup analysis suggested no significant effect of the type of surgery (Analysis 3.1), dose of HS given (Analysis 3.2), or the total volume of fluid transfused (Analysis 3.3). There were too few studies to adequately investigate the high levels of heterogeneity.

4. Total volume of crystalloid administered

The volume of intravenous fluid administered to participants was reported in 13 trials with 871 participants (51.3% HS, 48.7% IS) (Bruegger 2005; Cross 1989; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Younes 1988). IS participants received a mean volume of 2.4 L (Summary of findings table 1). Participants in the HS group received 1.49 L, considerably less fluid intravenously than those in the IS group (MD -0.91, 95% CI -1.24 to -0.59; I^2 = 99%; P < 0.00001; Analysis 1.4). We rate the quality of the evidence for this outcome as moderate (Summary of findings table 1).

We conducted a sensitivity analysis to include only studies deemed to be at low risk of bias (Cross 1989; Kato 1996; Lavu 2014). We found that the amount of fluid used in the HS group was still statistically significantly less than in the IS group (MD -1.08, 95% CI -1.92 to -0.24; I^2 = 75%; P = 0.01; Analysis 2.2).

A subgroup analysis according to type of surgery (Analysis 3.4) and the dose of HS (Analysis 3.5) did not reveal differences between the subgroups. The high degree of heterogeneity for this outcome was not explained by subgroup analysis according to type of surgery (Analysis 3.4) or the dose of HS (Analysis 3.5). Funnel plot analysis showed this outcome to cluster symmetrically (Figure 4), except for three outliers from studies that used considerably more HS than other trials (Lavu 2014; Shackford 1983; Shackford 1987). However, exclusion of these three trials from the analysis did not eliminate heterogeneity.

5. Diuresis during study period

Urine output during the trial was reported in nine trials including 777 participants (51.1% HS, 48.9% IS) (Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Lavu 2014; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013). There was no difference in peri-operative urine output (L) between the two groups (MD 0.11, 95% CI -0.09 to 0.31; I^2 = 69%; P = 0.28; Analysis 1.5). We rate the quality of the evidence to be low for risk of bias (downgraded one level because the majority of the studies have not confirmed blinding of outcome assessors, and bias could seriously impact this result) and imprecision (downgraded one level: the volume of crystalloid solution delivered has a large range between studies).

A sensitivity analysis limited to studies with a low risk of bias (Cross 1989; Lavu 2014) did not change the findings of the outcome (MD 1.25, 95% CI -1.17 to 3.67; studies = 2; I^2 = 33%; Analysis 2.3).

Stratification by type of surgery (Analysis 3.6), dose of HS (Analysis 3.7), or the total volume of crystalloid use in the IS group (Analysis 3.8) did not alter the outcome or the degree of heterogeneity.

6. Peak serum sodium

The maximum serum sodium was measured in all but two trials (Durasnel 1999; Lavu 2014), and included 780 participants (50.6% HS, 49.4% IS) from 16 trials. Maximum serum sodium was higher in the HS group than the IS group, 147.4 versus 139.1 meq/L (MD 7.73, 95% CI 5.84 to 9.62; I^2 = 97%; P < 0.00001; Analysis 1.6). The maximum average serum sodium ranged between 138.5 and 159 in HS groups compared to between 136 and 143 meq/L in the IS groups. We rate the quality of the evidence as moderate for this outcome (Summary of findings table 1).

Sensitivity analysis restricted to studies with a low risk of bias did not change the outcome or the heterogeneity of the studies (Analysis 2.4).

Subgroup analysis by type of surgery (Analysis 3.9), the dose of crystalloid administered (Analysis 3.10), or by volume of HS (Analysis 3.11) did not alter the outcome or the heterogeneity between trials. Funnel plot analysis which showed peak serum sodium of each study clusters symmetrically around a positive MD. There is substantial overlap of MD from each study, regardless of the dose of HS given (Figure 5).

7. Final serum sodium

Twelve studies with 640 participants (51.4% HS, 48.6% IS) reported final serum sodium (Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Kato 1996; Kølsen-Petersen 2004; Leverve 2008; Shackford 1983; Shackford 1987; Shao 2013; Wang 1997; Younes 1988). By the end of the study period the serum sodium mean difference between the groups was considerably reduced from those reported at peak (MD 3.45, 95% CI 2.46 to 4.44; I^2 = 88%, P < 0.00001; Analysis 1.7) and the range for final average serum sodium was within normal limits: 136 to 146 meq/L and 136 to 140 meq/L in the HS and IS groups respectively. We assess the quality of this evidence as moderate (Summary of findings table 1).

A sensitivity analysis restricted to studies with a low risk of bias did not change the outcome or heterogeneity (Analysis 2.5).

Neither the result nor heterogeneity were altered in subgroup analysis by surgery type (Analysis 3.12), dose of HS (Analysis 3.13) or volume of crystalloid (Analysis 3.14).

8 - 10. Duration of endotracheal intubation, intensive care stay and hospital stay

None of the trials reported the duration of mechanical ventilation and the length of stay in hospital. Only one trial (Cross 1989) reported the length of stay in intensive care, with mean stays (standard deviation) of 2.3 (0.2) versus 2.4 (0.6) days in the HS and IS groups respectively (P = 0.63).

11. Other outcomes of interest

Ten trials with 369 participants (50.9% HS, 49.1% IS) (Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kølsen-Petersen 2004; Shackford 1983; Shackford 1987; Shao 2013; Younes 1988) reported maximum serum osmolarity (Analysis 1.8). We found that there was a statistically significant increase in serum osmolarity with HS, increased 5.3% from the median level of 289 mOsm/kg H20 in the IS group (MD 15.29 mOsm/kg H2O higher with HS, 95% CI 12.27 to 18.31; I^2 = 86%, P < 0.00001). We assess the quality of the evidence to be moderate. We downgraded the study quality because of a high degree of heterogeneity that probably derives from the wide range of crystalloid fluid given across the studies. Future high-quality studies are likely to change this result.

Intraoperative pulmonary artery wedge pressure (Analysis 1.9) was reported in three studies with 150 participants (50.7% HS, 49.3% IS) (Jarvela 2001; Shackford 1983; Shackford 1987). There was no difference between the treatment groups (MD 0.16, 95% CI -1.69 to 2.02; I^2 = 0%; P = 0.86).

Maximum intraoperative cardiac index was reported in six studies with 418 participants (51.7% HS, 48.3% IS) (Cross 1989; Jarvela 2000; Jarvela 2001; Leverve 2008; Shackford 1983; Shackford 1987). We found that the maximum intraoperative cardiac index was elevated 11.7% in the HS group over the median level of 2.9 L/min/m^2 in the IS group (MD 0.34, 95% CI 0.19 to 0.49; I^2 = 40%; P = 0.0001; Analysis 1.10). We rate the quality of these data to be high (Summary of findings table 1).

Although only one of the trials (Lavu 2014) specifically reported adverse events, they have not met our criteria to be considered *serious* adverse events. Adverse events were reported over a 90-day follow-up period and the study found no difference between the HS and IS groups.

Discussion

Summary of main results

It was not possible to determine differences with respect to mortality or major morbidity between the treatment arms of this meta-analysis. A preliminary survey carried out before designing the meta-analysis suggested that trials of peri-operative HS were usually designed to measure fluid volumes, haemodynamics and biochemistry rather than measure important clinical outcomes. Despite this, we chose mortality as the primary outcome for this review and we collected serious adverse event data because of their clinical importance.

Peri-operative diuresis was similar in the HS and IS participants, suggesting that adequate intravascular volumes

were maintained throughout surgery despite the fact that HS participants received significantly less intravenous fluid than IS participants (Summary of findings table 1). All of the participant groups completed surgery with a positive fluid balance (Summary of findings table 1). In some trials, the positive fluid balance was almost 10 L by the end of surgery. Pulmonary oedema was not recorded in the trials but it is reasonable to be concerned that excess fluid of this magnitude would result in pulmonary oedema in a population at risk of this complication. Use of HS significantly reduced the positive fluid balance experienced by all participants undergoing surgery. HS increased serum sodium and osmolarity (Summary of findings table 1). The doses of HS varied considerably between trials, but even in those who received very high doses of HS no adverse events related to hypernatraemia were encountered. Serum sodium returned to normal limits by the end of the study.

Overall completeness and applicability of evidence

Meta-analysis of the outcomes measured by the trials provides a reasonably complete picture of the immediate impact of HS on peri-operative fluid management. HS significantly reduces the positive fluid balance experienced by people undergoing surgery while maintaining a stable haemodynamic state. This observation was independent of the type of surgery or whether peri-operative fluid protocol was restricted or unrestricted by volume. HS conserved fluid at lower doses as much as at higher doses. However the trials were not designed to look at the impact of the interventions on mortality or longer-term morbidity.

To date, we have only found one trial where mortality and adverse events were explicitly measured over a period that extended beyond the original hospital stay (Lavu 2014). Mortality at 90 days did not differ between treatment groups of participants undergoing pancreaticoduodenectomy, but there is no evidence to suggest that this result would remain true at different centres or for different procedures. Until there are more, high-power studies examining mortality in different surgical procedures at multiple centres, we cannot say with certainty that there is no effect of HS on mortality. This same study also measured postoperative complications (non-serious adverse events). Although the result was not statistically significant, there were over 10% more postoperative complications in the IS group. Future trials will be necessary to test this finding.

This review showed that people receiving HS had a transient increase in serum sodium (Summary of findings table 1). Hypernatraemia has the potential to harm but this was not seen in the included studies. In hyponatraemic people, the risk of central pontine myelinolysis is thought to be related to underlying conditions more than the rate of electrolyte repletion, but increases in serum sodium of more than 10 meq/L per day should be avoided if possible (Kumar 2006). It is not known if people with normal serum sodium are at a similar risk of hyperosmotically induced demyelination. No episodes of central pontine myelinolysis were reported in these studies where the participants had normal serum sodium levels at baseline, and we did not find any case reports in the literature of central pontine myelinolysis in people who received HS.

Is there a potential therapeutic window for HS in people undergoing surgery, where peri-operative weight gain can be minimized without a risk of significant hypernatraemia? Hypernatraemia is transient after administration of HS. However, it would seem prudent to avoid large increases in serum sodium. This is possible, with these studies suggesting that up to 10 ml/kg of 3% HS will reduce the positive fluid balance peri-operatively by up to 1.5 L in the average adult without increasing serum sodium inappropriately. There is insufficient evidence to determine if such a reduction in peri-operative fluid excess would improve clinically relevant outcomes but it provides the basis for an RCT.

The evidence is strong for a reduction in the volume of peri-operative fluid required to maintain homeostasis with HS. There is no direct evidence that this results in better survival or quality of life. The principal barrier to meta-analysis of some outcomes is a high degree of heterogeneity between the trials. Heterogeneity appears to be due to differences in the magnitude of the effect observed rather than differences in the effect itself. Subgroup analysis identified sources of heterogeneity in some instances. For example, there was considerable heterogeneity in peri-operative diuresis even though there was no significant difference in diuresis between the test group, HS, and the control.

Overall there is a strong need for well-controlled, high-quality studies with adequate design to measure both short- and long-term variables. The results of this systematic review and future studies could prove to be very important to patient care, particularly when low volumes of resuscitating fluid are needed. At this time the results show promise for HS as a safe choice for resuscitation during surgery where reduced volumes would be beneficial, but more evidence is needed.

Quality of the evidence

The quality of evidence across these trials ranged from high to very low. The majority of trials included in this study cover relatively few participants. The trials were conducted in several eras when other peri-operative practices may have changed. There was also a large variation in the dose of HS given between studies which may have resulted in the high heterogeneity between them. Furthermore, many of the studies did not specify the methods of allocation concealment or randomization, which again probably reflects the era in which many of the studies were reported.

For determining mortality, the trials lacked sufficient size, duration and reporting to adequately assess important differences. Furthermore, only one study (Lavu 2014) explicitly reported the outcome, and we have extrapolated the data on the basis that other outcomes were reported by each study for all included participants. We have assessed the quality of evidence for mortality to be very low, and future studies are likely to change the result reported here (Summary of findings table 1).

We rate the quality of the evidence for fluid balance and diuresis to be low (Summary of findings table 1). There is a systemic lack of blinding of personnel across these studies, leaving these outcomes prone to bias. High-quality study results are likely to change this outcome.

The reporting of peak and final serum sodium is of moderate quality (Summary of findings table 1). The level of blood sodium during surgery is a common hospital measurement that is unlikely to be biased. The difference in the number of samples

collected by the different studies impacts the quality of this outcome. Future studies are likely to change this result.

We have rated the quality of the evidence for the maximum intraoperative cardiac index as high (Summary of findings table 1). The measurement during an operation is a common hospital procedure that is unlikely to be biased. The studies that report this outcome are well controlled, and the values reported are consistent across the studies. Future studies are unlikely to change this result.

Potential biases in the review process

Having searched the largest medical research data bases, without limit by language of publication, it is highly likely that we have found all published data that met our inclusion criteria.

The review authors tried to reduce the impact of personal bias in the presentation and analysis of the results. When assessing the degree that individual bias components would impact study results, we have undoubtedly relied on our own experiences. We have assumed, in cases where the information was not available, that the reports were conducted by compassionate physicians and dedicated researchers who have performed their work honestly and to the best of their abilities. Because of this, we have left our analysis open to being impacted by fraudulent reports.

Agreements and disagreements with other studies or reviews

This is the first systematic review of HS compared to IS for peri-operative fluid management. This update confirms the findings of the first version (McAlister 2006). The findings are consistent with reviews of HS given for other indications such as fluid management in people with burns (Bunn 2004).

Authors' conclusions

Implications for practice

There was insufficient evidence from the included studies to suggest that the use of HS confers any clinical benefit or harm in terms of mortality or major morbidity compared to the use of IS. There is no reason to prefer HS for the routine management of people having surgery. The reduction in positive fluid balance when using HS may suggest HS would be an appropriate choice when fluid restriction is required in selected individuals or clinical situations.

Implications for research

HS administration to people undergoing surgery should be compared to standard practice, using RCTs of high methodological rigour in order to determine any impact on participant survival and other clinically relevant outcomes. Sample size estimation is problematic, given the very low reported incidence of mortality or significant morbidity in the control groups in these trials. The duration of any future trial should be sufficient to cover the period of peri-operative mortality or major morbidity which is usually considered to be 60 days or at least the postoperative hospital stay.

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Contributions of authors

Conceiving the review: T Znajda (TZ), K Burns (KB), V McAlister (VM) B Church (BC)
Co-ordinating the review: VM
Undertaking manual searches: TZ, K.B, VM, Eric McArthur (EM), BS
Screening search results: TZ, KB, VM, BC, EM, BS
Organizing retrieval of papers: TZ, VM, BS
Screening retrieved papers against inclusion criteria: TZ, KB, VM, EM, BS
Appraising quality of papers: TZ, KB, VM, EM, BS
Abstracting data from papers: TZ, KB, VM, BC, EM, BS
Writing to authors of papers for additional information: VM, BS
Obtaining and screening data on unpublished studies: TZ, KB, VM, BS
Data management for the review: TZ, KB, VM, EM
Entering data into Review Manager (RevMan 2014): VM, KB, EM, BS
RevMan statistical data: VM, KB, EM
Other statistical analysis not using RevMan: KB
Double entry of data: (data entered by person one: VM ; data entered by person two: KB ; data entered by person two alternates: EM, BS)

Interpretation of data: TZ, KB, VM, EM
Statistical analysis: TZ, KB, VM, EM
Writing the review: VM
Securing funding for the review: Not applicable
Performing previous work that was the foundation of the present study: TZ, KB, VM, BC
Guarantor for the review (one author) VM
Persons responsible for reading and checking review before submission: TZ, KB, VM, BC, EM, BS

Declarations of interest

Shrum, Bradly: none identified
McArthur, Eric: none identified
Burns, Karen: none identified
Chruch, Brian: none identified
Znadja, Tammy: none identified
McAlister, Vivian: none identified

Differences between protocol and review

Bradly Shrum was added as an author since the initial publication of our protocol (McAlister 2006).

Studies did not provide data regarding duration of hospitalization, duration of endotracheal intubation, length of stay in ICU. Studies did not explicitly provide data on adverse outcomes such as: any organ failure, any requirement for dialysis (renal failure) or prolonged ventilation (pulmonary failure); use of medical therapy for either pulmonary oedema or circulatory support (cardiac failure) or for confusion (cerebral failure).

In addition to the prespecified outcomes, we also collected data regarding serum osmolarity and peri-operative haemodynamic parameters including pulmonary wedge pressure and cardiac index, as they were reported in multiple studies. We analysed these outcomes by the same method as all other outcomes.

We have made minor changes to our statistical analysis to be in line with current Cochrane standards. We now use mean difference instead of standardized mean difference for continuous outcomes. We now use risk ratio instead of risk difference for dichotomous outcomes. We have also employed the random-effects model where heterogeneity was detected by an I^2 value greater than 30%.

Published notes

Characteristics of studies

Characteristics of included studies

Baraka 1994

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Lebanon Language: English Single centre Inclusion criteria: consenting adult men undergoing transurethral resection of the prostate under spinal anaesthesia Exclusion criteria: ASA IV Number eligible: not specified Number enrolled: 33 (HS 17; NS 16) Number completed study: 33 Age: not reported Gender: men only
Interventions	*Hypertonic saline group* IV solution: 3% HS Dose: 7 ml/kg Duration: before spinal anaesthesia *Isotonic salt solution group* IV solution: NS Dose: 7 ml/kg Duration: before spinal anaesthesia *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Peak serum sodium Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to two groups." Not described
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to two groups." Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Outcomes are reported for all enrolled participants We note a discrepancy between the number of participants enrolled to hypertonic saline described in the text (n = 17) and the number reported in table 1 (n = 19). It is our assessment that, given the age of this publication, the error is typographical
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Bruegger 2005

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: no Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Germany Language: English Single centre Inclusion criteria: people undergoing elective infrarenal aortic aneurysm repair Exclusion criteria: ASA IV; renal dysfunction; congestive heart failure; recent brain infarction; contra-indication to starch or dextran. Intraoperative exclusion criteria were suprarenal clamping and aortic aneurysm that extended into the iliac arteries Number eligible: Not specified Number enrolled: 28 (HS 14; NS 14) Number completed study: 28 Age: not reported Gender: men 25, women 3
Interventions	*Hypertonic saline group* IV solution: 7.5% NaCl Dose: 250 ml *Isotonic salt solution group* IV solution: NS Dose: 250 ml *Co-interventions:* dextran 70 given with HS; hydroxyethyl starch given with NS Co-interventions applied differentially between groups: No Study period: duration of surgery plus 72 hours
Outcomes	Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	Different colloids given to experimental and control groups. Study included because the effect of the different colloids is equivalent. The study was designed to test a commercially available hypertonic salt-colloid combination with an isotonic salt-colloid comparison

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Allocation concealment is not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Outcomes are reported for all enrolled patients
Selective reporting (reporting bias)	Unclear risk	Quote: "We studied 28 patients (three female)" We note the disproportionately low number of women enrolled in the study but there is insufficient evidence to prove bias There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Cross 1989

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: USA Language: English Inclusion criteria: consenting people undergoing coronary artery bypass Exclusion criteria: cardiac arrhythmia; cardiac, pulmonary, renal, hepatic failure Number eligible: not given Number enrolled: 20 (HS 11; ISS 9) Number completed study: 20 Age: not reported Gender: men 19, women 1
Interventions	*Hypertonic saline group* IV solution: HS (1.8%, 304 meq Na/L) Dose: 100 cc/hour Duration: Postoperative admission to ICU for 24 hours Subsequent maintenance: D5/0.45NaCl if serum sodium > 155 meq/L *Isotonic salt solution group* IV solution: NS Dose: 100 cc/hour Duration: admission to ICU for 24 hours Postoperative maintenance: D5/0.45NaCl if serum sodium > 155 meq/L *Co-interventions:* Co-interventions applied differentially between groups: no Study period: 24 hours from the beginning of surgery
Outcomes	LOS hospital LOS ICU Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned", "the code was not broken" The sequence generation is not described. Randomization was probably performed
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned", "the code was not broken" A code was used to conceal allocation
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Physicians and nurses directly involved in patient care did not know the identity of the solution" Likely as stated
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Physicians and nurses directly involved in patient care did not know the identity of the solution", "the code was not broken until after the end of the study" Likely as stated
Incomplete outcome data (attrition bias)	Low risk	Outcomes are reported for all participants enrolled in the study
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Durasnel 1999

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Niger Language: French Single centre Inclusion criteria: consenting adults undergoing surgery using spinal anaesthesia Exclusion criteria: systemic infection, coagulopathy, allergy to local anaesthetic, uncorrected hypovolaemia, congestive heart failure, kidney failure Number eligible: not specified Number enrolled: 50 (HS 25; ISS 25) Number completed study: 48 (1 from each group excluded, cause not given) Age: not reported Gender: men 39, women 9
Interventions	*Hypertonic saline group* IV solution: 7.5% HS Dose: 100 ml Duration: prior to anaesthesia *Isotonic salt solution group* IV solution: 0.9% NaCl Dose: 100 ml Duration: prior to anaesthesia *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Haemodynamic parameters Fluid volume transfused
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective, randomized, double-blinded study" Not described
Allocation concealment (selection bias)	Unclear risk	Quote: "prospective, randomized, double-blinded study" Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "prospective, randomized, double-blinded study" Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "prospective, randomized, double-blinded study" Not described
Incomplete outcome data (attrition bias)	High risk	50 participants were enrolled but 1 from each group was removed without explanation
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Ishikawa 1996

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: no (1 participant in RL group excluded during study) Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Japan Language: Japanese Inclusion criteria: People undergoing lower limb or pelvic surgery with epidural anaesthesia Exclusion criteria: ASA classification II, III or IV; MAP decrease by 50 mm Hg Number eligible: 24 Number enrolled: 24 Number completed study: 24 Relevant data available on: 15 (HS 8; IS 7) Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: 7.2% HS Dose: 1.8 ml/kg Duration: 20 minutes Postoperative maintenance: ISS *Isotonic salt solution group* IV solution: NS Dose: 1 - 2 ml/kg/hr Duration: study period Co-interventions: epidural anaesthesia Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Peak serum sodium Haemodynamic parameters
Funding source	Not described
Notes	Translations supplied by Dr Hideaki Tanaka and Dr Yoshihisa Morita

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Participants, investigators and outcome assessors were not blinded
Blinding of outcome assessment (detection bias)	High risk	Participants, investigators and outcome assessors were not blinded
Incomplete outcome data (attrition bias)	High risk	Reasons for enrolled participants not completing the study not reported
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Jarvela 2000

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Finland Language: English Single centre Inclusion criteria: consenting fit people having lower limb surgery under spinal anaesthesia Exclusion criteria: ASA III or IV Number eligible: not specified Number enrolled: 40 (HS 20; ISS 20) Number completed study: 40 Age: not reported Gender: men 30, women 10
Interventions	*Hypertonic saline group* IV solution: 7.5% HS Dose: 4 ml/kg Duration: 30 minute Postoperative maintenance: D5 / 0.3% NaCl at 1 ml/kg/hour *Isotonic salt solution group* IV solution: NS Dose: 4 ml/kg Duration: 30 minute Post-operative maintenance: D5/0.3% NaCl at 1 ml/kg/hour *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery and post-anaesthetic recovery period
Outcomes	Fluid volume transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized, double-blinded study" Not described
Allocation concealment (selection bias)	Low risk	Quote: "randomized, double-blinded study" Assessed following communication with the study author
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "randomized, double-blinded study" Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "randomized, double-blinded study" Not described
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Jarvela 2001

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Finland Language: English Single centre Inclusion criteria: People undergoing elective coronary artery bypass graft Exclusion criteria: not specified Number eligible: not specified Number enrolled: 72 (HS 36; ISS 36) Number completed study: 72 Age: not reported Gender: men 59, women 13
Interventions	*Hypertonic saline group* IV solution: 7.5% HS Dose: 4 ml/kg Duration: 30 minutes Postoperative maintenance: D5/0.3% NaCl at 1 ml/kg/hour *Isotonic salt solution group* IV solution: NS Dose: 4 ml/kg Duration: 30 minutes Postoperative maintenance: D5/0.3% NaCl at 1 ml/kg/hour *Co-interventions:* 4% albumin to maintain cardiac index at 2.5 L/min/m³ Co-interventions applied differentially between groups: no Study period: duration of surgery and postoperative period until next morning
Outcomes	Fluid volume transfused Weight gain Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters Extubation times
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly allocated according to a list of random digits" Random-digit table
Allocation concealment (selection bias)	Low risk	Assessed following communication with the study author
Blinding of participants and personnel (performance bias)	High risk	Quote from correspondence: "Patients, investigators and outcome assessors were not blinded". Not performed.
Blinding of outcome assessment (detection bias)	High risk	Quote from correspondence: "Patients, investigators and outcome assessors were not blinded" Not performed
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Kato 1996

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Japan Language: English Inclusion criteria: consenting people undergoing transurethral resection of the prostate Exclusion criteria: not given Number eligible: not given Number enrolled: 40 (HS 20; ISS 20) Number completed study: 40 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: 3% HS Dose: 4 ml/kg/min Duration: adjusted to maintain mean arterial pressure at 80% of preoperative value *Isotonic salt solution group* IV solution: RL Dose: 4 ml/kg/min Duration: adjusted to maintain mean arterial pressure at 80% of preoperative value Postoperative maintenance: Co-interventions: Co-interventions applied differentially between groups: no Study period: duration of surgery plus first postoperative day
Outcomes	Fluid volume transfused Peak serum sodium Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Participants, investigators and outcome assessors were blinded
Blinding of outcome assessment (detection bias)	Low risk	Participants, investigators and outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	Clinically relevant outcomes are defined and reported.There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Kimura 1994

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: unclear Study dates: not reported
Participants	Country: Japan Language: Japanese Inclusion criteria: people undergoing transurethral resection of the prostate, spinal anaesthesia Exclusion criteria: ASA III, IV; hypertension; diabetes; endocrine disease Number eligible: 14 Number enrolled: 14 (HS 7; ISS 7) Number completed study: 14 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: HS (213 meq Na / L) Dose: 8 ml/kg/hour for 1st hour; 4 ml/kg/hour for 2nd hour; 2 ml/kg/hour for 3rd hour *Isotonic salt solution group* IV solution: RL Dose: 8 ml/kg/hour for 1st hour; 4 ml/kg/hour for 2nd hour; 2 ml/kg/hour for 3rd hour *Co-interventions*: spinal anaesthesia Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Peak serum sodium Haemodynamic parameters Plasma aldosterone, ADH
Funding source	Not described
Notes	Translation provided by Dr Hideaki Tanaka and Dr Yoshihisa Morita

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Kølsen-Petersen 2004

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: December 2001 - January 2003
Participants	Country: Denmark Language: English Inclusion criteria: adult women undergoing elective hysterectomy Exclusion criteria: ASA III or IV; cardiac failure; renal failure; anaemia; diabetes mellitus; certain medications that effect the immune response Number eligible: 192 screened Number enrolled: 62 (HS 21; NS-4 21; NS-32 20) Number completed study: 58 (1 HS participant withdrew consent; 1 HS had anaphylactoid reaction to anaesthetic agent; 1 NS-4 participant transferred to another hospital; 1 NS-32 participant returned to the operating room for haemorrhage) Study data used: HS (19) and NS-4 (20). Age: 32 - 53 Gender: women only
Interventions	*Hypertonic saline group* IV solution: 7.5% NaCl Dose: 4 ml/kg Duration: over 10 minutes before hysterectomy Postoperative maintenance: not specified *Isotonic salt solution group* IV solution: NS Dose - 2 groups: 'NS-4' received 4 ml/kg; 'NS-32' received 32 ml/kg Duration: over 10 minutes before hysterectomy Postoperative maintenance: not specified Co-interventions: anaesthesia, analgesia Co-interventions applied differentially between groups: no Study period: duration of surgery plus 48 hours after closure of the wound
Outcomes	Peak serum sodium Urine output Immunological parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "prospective, randomized, double-blind study" Randomly assorted envelopes used for study arm selection
Allocation concealment (selection bias)	Low risk	Quote: "The study-group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators" Concealment is adequate
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study fluid was subsequently hidden in an opaque box and connected to the i.v. line in such a way that neither the patient nor the investigator was aware of the nature of the fluid" Participants and personnel adequately blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment is adequately blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Four patients were excluded from the final analysis. One patient (HS group) did not wish to finish the study..." Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	Clinically relevant outcomes are defined and reported.There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Lavu 2014

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: May 2011 - November 2013
Participants	Country: United States English Inclusion criteria: People undergoing pancreaticoduodenectomy Exclusion criteria: metabolic acidosis, active sepsis or bacteraemia, congestive heart failure, chronic renal insufficiency, pregnancy, sickle-cell anaemia, hyponatraemia (serum sodium <120 mmol/L), hypernatraemia (serum sodium >150 mmol/L), morbid obesity (body mass index >50), and extension of surgery to total pancreatectomy,unresectable disease or distant metastasis. Number eligible: 259 Number enrolled: 264 (LR 132, HS 132; 4 from LR became ineligible (2 unresectable, 2 total pancreatectomies), 1 from HS became ineligible (1 total pancreatectomy)) Number completed study: 259 (HS 131, LR 128) Age: 25 - 91 Gender: men 54%, women 46%
Interventions	*Lactated Ringer's group* IV solution: lactated Ringer's Dose: 15 mL/kg/hr during the operation, with blood loss replaced in a 3:1 ratio. Then at a rate of 2 mL/kg/hr. Duration: Until 8 AM POD 1. *Hypertonic saline group* IV solution: 1 mL/kg/hr of HYS (3.0% NaCl) and 9 mL/kg/hr of LR Dose: a 1 mL/kg bolus of HYS for more than 15 minutes on randomization, and then they were continued on 1 mL/kg/hr of HYS and 9 mL/kg/hr of LR for a total infused volume rate of 10 mL/kg/hr during the operation. Blood loss was replaced at a 1:1 ratio with LR. Maintained on HYS alone at a rate of 1 mL/kg/hr Duration: until 8 AM on the morning of POD 1. *Co-interventions*: None Co-interventions applied differentially between groups: NA Study period: 90 days.
Outcomes	90-day mortality Postoperative complication rate Total number of complications Intraoperative estimated blood loss Number of required fluid boluses Postoperative hospital LOS Readmission rate Peri-operative mortality
Funding source	Not described
Notes	Primary author was contacted for additional data. Author provided mean and standard deviation values for published results

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random permuted blocks with a 1:1 allocation (blocks of 6) (investigators were blinded to block size during study accrual)" Computer randomized allocation
Allocation concealment (selection bias)	Low risk	Quote: "administrator would open in sequence, a numbered, opaque envelope containing the assignment" Assignment in opaque numbered envelope and provided at the time of surgery by a third-party administrator
Blinding of participants and personnel (performance bias)	Low risk	Quote: "surgeons and anaesthesia staff blinded to the process until the assignment was revealed" Participants and personnel were blinded to allocation
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were likely unaware of treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Quote: "Five patients were excluded from the analysis after accrual due to unresectability..." Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes are identified and reported
Other bias	Low risk	No other source of bias identified

Leverve 2008

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: no (22 had to be excluded due to major protocol violation or incomplete data collection) Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Indonesia Language: English Inclusion criteria: men or women, 18–75 years, in postoperative period in ICU post-CABG surgery, either on-pump or off-pump, and requiring postoperative fluid resuscitation Exclusion criteria: people having undergone combined operations, those needing an intra-aortic balloon pump, severe arrhythmia (ventricular tachycardia, atrial flutter with rapid response, heart block), severe haemodynamic imbalance, severe bleeding and/or re-operation, liver dysfunction (SGOT and SGPT more than twice normal value) and renal failure (creatinine more than 20 mg L-1) Number eligible: 230 Number enrolled: 230 Number completed study: 208 (HL 109; RL 99) Age: 54 - 57 Gender: men 198, women 10
Interventions	*Hypertonic saline group* IV solution: HL (504.15 mmol L-1) Dose: titrated to maintain CVP between 8 and 12 mm Hg Duration: during operation Postoperative maintenance: *Isotonic salt solution group* IV solution: RL (Na = 130.5 mmol L-1) Dose: titrated to maintain PAOP between 11 and 15 mm Hg Duration: during operation Postoperative maintenance: *Co-interventions:* Co-interventions applied differentially between groups: no Study period: 12 hours post-surgery
Outcomes	Fluid volume transfused Fluid balance Peak serum sodium Urine output MAP Cardiac index
Funding source	Not described
Notes	12-hour data only available; urine output, MAP and CI determined from graphs.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Patients were randomly assigned immediately after CABG surgery" Participants were blinded. It is unknown if personnel were blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Quote: "From the 230 patients enrolled in this study, 22 had to be excluded due to major protocol violation or incomplete data collection, but they were included in the safety evaluation" Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Shackford 1983

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: USA Language: English Inclusion criteria: people undergoing aortic surgery Exclusion criteria: not specified Number eligible: 61 Number enrolled: 58 (HS 30; ISS 28) Number completed study: 58 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: HSL (250 meq Na/L) Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Postoperative maintenance: D5/0.25 NaCl *Isotonic salt solution group* IV solution: RL Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Postoperative maintenance: D5/0.25 NaCl *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of hospital stay for surgery
Outcomes	Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Participants, investigators and outcome assessors were not blinded
Blinding of outcome assessment (detection bias)	High risk	Participants, investigators and outcome assessors were not blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Shackford 1987

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Blinding of care givers: no Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: USA Language: English Inclusion criteria: People undergoing aortic aneurysm repair or aorto-bifemoral bypass Exclusion criteria: not specified Number eligible: 52 Number enrolled: 52 (HS 26; ISS 26) Number completed study: 52 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: HSL (250 meq Na/L) Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Postoperative maintenance: D5/0.25 NaCl *Isotonic salt solution group* IV solution: RL Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Postoperative maintenance: D5/0.25 NaCl *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery plus first4 postoperative days
Outcomes	Fluid volume transfused Blood transfused Fluid loss Fluid balance Weight change Peak serum sodium Urine output
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Participants, investigators and outcome assessors were not blinded
Blinding of outcome assessment (detection bias)	High risk	Participants, investigators and outcome assessors were not blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Shao 2013

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Blinding of care givers: not defined Additional features to blind fluid administered: not defined Control of co-interventions: yes Completeness of follow-up: complete Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: China Language: English Inclusion criteria: ASA I - II patients scheduled for elective neurosurgical procedures Exclusion criteria: The exclusion criteria were age, less than18 years or greater than 80 years; clinical signs of significantly increased ICP such as severe headache, blurred vision and/or papilledema; history of cardiac, pulmonary and renal dysfunction; fluid or electrolyte disturbances; preoperative coagulation disorders; and preoperative treatment with diuretics and/or osmotic agents Number eligible: 40 Number enrolled: 40 Number completed study: 40 (HS-HES 20; HES 20) Age: 27 - 53 Gender: men 21, women 19
Interventions	*Hypertonic saline group* IV solution: 250 mL of a 7.2% HS - 6% HES Dose: 250 mL Duration: intraoperative infusion *Isotonic salt solution group* IV solution: 6% HES Dose: 1000 mL Duration: intraoperative infusion *Co-interventions:* Ringer's lactated solution to maintain CVP at 8 - 12 mm Hg and the MAP at greater than 65 mm Hg. 250 mL 20% mannitol Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Volume of Ringer’s solution Volume of PRBC infused Intraoperative total urine output Blood loss Operative duration Intraoperative bleeding severity score Dural tension score Fluid balance Haemodynamic parameters Laboratory parameters
Funding source	Not described
Notes	Author was contacted for further information but did not respond

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Operative team made aware of treatment at time of operation
Blinding of participants and personnel (performance bias)	High risk	Quote: "after the induction of anaesthesia, the patients were randomly assigned" Participants are blinded to treatment. Personnel are not blinded to treatment
Blinding of outcome assessment (detection bias)	High risk	Not described Outcome assessors are probably not blinded
Incomplete outcome data (attrition bias)	Low risk	No incomplete data identified
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	None identified

Veroli 1992

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: France Language: English Inclusion criteria: consenting people having lower limb surgery with lumbar extradural anaesthesia Exclusion criteria: not specified Number eligible: not specified Number enrolled: 30 (HS 10; RL 10; NS 10) Number completed study: 30 Age: 26 - 65 Gender: men 15, women 15
Interventions	*Hypertonic saline group* IV solution: HS 5% Dose: 2.3 ml.kg Duration: preoperative bolus *Isotonic salt solution group* IV solution: RL or NS Dose: 15 ml RL/kg or 13 ml NS/kg Duration: preoperative bolus *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Fluid volume transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective double-blinded study" Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Quote: "patients were transferred to the operating theatre and were cared for by a physician (P.V.) blinded to the fluid preload administered previously" Participants and personnel blinded to treatment
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were blinded to treatment
Incomplete outcome data (attrition bias)	Low risk	Outcomes reported for all participants enrolled. Reasons for missing outcomes are reported and balanced across groups
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Wang 1997

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Blinding of care givers: unclear Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: China Language: English Single centre Inclusion criteria: consenting fit people having herniorrhaphy under spinal anaesthesia Exclusion criteria: ASA II, III or IV Number eligible: not specified Number enrolled: 60 (HS 30; ISS 30) Number completed study: 60 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: 3% HS Dose: 7 ml/kg Duration: bolus before surgery *Isotonic salt solution group* IV solution: 0.9% NaCl Dose: 7 ml/kg Duration: bolus before surgery *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	Hypotension Peak serum sodium Haemodynamic parameters
Funding source	Not described
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcomes detected
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Younes 1988

Methods	Publication type: full article Study type: RCT Baseline comparison: yes Baseline similarity: yes Blinding of care givers: unclear Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes Study dates: not reported
Participants	Country: Brazil Language: Portuguese Single centre Inclusion criteria: Adults undergoing aortic aneurysm repair or aortobifemoral bypass Exclusion criteria: not given Number eligible: not given Number enrolled: 31 (HS 18; ISS 13) Number completed study: 31 Age: not reported Gender: not reported
Interventions	*Hypertonic saline group* IV solution: 7.5% HS Dose: 4 ml/kg Duration: 15 minute bolus Postoperative maintenance: ISS to maintain CVP and MAP within 10% of starting value *Isotonic salt solution group* IV solution: 0.9% NaCl Dose: 4 ml/kg Duration: 15-minute bolus Postoperative maintenance: ISS to maintain CVP and MAP within 10% of starting value *Co-interventions:* Co-interventions applied differentially between groups: no Study period: duration of surgery
Outcomes	LOS hospital LOS ICU Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Funding source	Not described
Notes	Translation provided by Ms. Christiane Baldwin

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcomes detected
Selective reporting (reporting bias)	Unclear risk	There is no explicit reference to participant survival. Other clinically relevant outcomes that fit the trial design are reported
Other bias	Low risk	No other sources of bias identified

Footnotes

ASA: American Society Anesthesiology classification
CABG: coronary artery bypass graft
CVP: central venous pressure
D5/0.45NS: dextrose 5% in 0.45% saline
HS: hypertonic saline
HSL: hypertonic saline lactate
ICU: intensive care unit
IS: isotonic saline
ISS: isotonic salt solution
IV: intravenous
LOS: length of stay
MAP: mean arterial pressure
NS: normal saline (154 meq Na per litre)
PAOP: pulmonary artery occlusion pressure
POD: postoperative day
PRBC: packed red blood cells
RCT: randomized control trial
RL: Ringer's Lactate (130 meq Na per litre)
SGOT: serum glutamic oxaloacetic transaminase
SGPT: serum glutamate pyruvate transaminase

Characteristics of excluded studies

Auler 1987

Reason for exclusion	Consecutive participants enrolled. Study not randomized

Auler 1992

Reason for exclusion	Study of intraoperative respiratory physiology but did not measure outcomes such as weight gain, fluid balance or peak serum sodium or determine postoperative survival

Li 2014

Reason for exclusion	No comparison to IS

Li 2015

Reason for exclusion	No comparison to IS

Shao 2005

Reason for exclusion	Dr Shao kindly responded to an email query on November 30, 2006: "I performed this project non-randomly, allocated distinct groups on the basis of different diseases and operation methods, but single-blinded (for patients)"

Yang Z 2014

Reason for exclusion	No outcomes of interest reported

Yousefshahi F 2013

Reason for exclusion	No measured outcomes were relevant to this review. Authors were contacted for additional information but did not respond

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Hypertonic salt compared to isotonic salt solution for peri-operative resuscitation

Hypertonic salt compared to isotonic salt solution for peri-operative resuscitation

Patient or population: any people undergoing surgery with fluid resuscitation
Settings: people undergoing non-emergency surgery that requires fluid resuscitation in a hospital operating room in;Brazil, China,Denmark, Finland, France, Germany, Indonesia, Japan, Lebanon, Niger, USA.
Intervention: hypertonic salt solution
Comparison: isotonic salt solution

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	isotonic salt solution for peri-operative resuscitation	Hypertonic salt				
Mortality Follow-up: range 1 to 90 days	Study population -	-	-	1087 (18 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2]	Any recorded death during the study period. The risk of bias impacting this outcome is considered to be low. Only one study had incidents of mortality
Serious adverse events Follow-up: range 1 to 90 days	-	-	-	1087 (18 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2]	Other adverse outcomes are collected as defined by each trial or if any of the following occurred: any organ failure, including renal, pulmonary, cardiac, or cerebral
Fluid balance (L) Follow-up: range 1 to 3 days	The mean fluid balance (L) was 4.375	The mean fluid balance (L) in the intervention group was 1.92 lower (2.61 lower to 1.22 lower)	-	737 (8 RCTs)	⊕⊕⊖⊖ LOW [3,4]	The change in participant fluid volume at the end of fluid administration. A neutral fluid balance would be optimal
Total volume of crystalloid administered (L) Follow-up: range 1 to 3 days	The mean total volume of crystalloid administered (L) was 2.43	The mean total volume of crystalloid administered (L) in the intervention group was 0.91 lower (1.24 lower to 0.59 lower)	-	871 (13 RCTs)	⊕⊕⊕⊖ MODERATE [4]	The total volume of fluid delivered intravenously over the study period. There are no defined minimum or maximum values for fluid delivery during surgery. Less resuscitating fluid is preferred

Peak serum sodium Follow-up: range 1 to 3 days	The mean peak serum sodium (meq/L) was 139.1	The mean peak serum sodium (meq/L) in the intervention group was 7.73 higher (5.84 higher to 9.62 higher)	-	780 (16 RCTs)	⊕⊕⊕⊖ MODERATE [5]	The measurement of this variable is a common practice in operative procedures. Measured as the peak amount of sodium in the blood, given in milliequivelants per litre, over the study period. The normal acceptable range is 136 to 146 meq/L
Final serum sodium Follow-up: range 1 to 3 days	The mean final serum sodium (meq/L) was 138.3	The mean final serum sodium (meq/L) in the intervention group was 3.45 higher (2.46 higher to 4.44 higher)	-	640 (12 RCTs)	⊕⊕⊕⊖ MODERATE [5]	The measurement of this variable is common practice in operative procedures. Measured as the final amount of sodium in the blood, given in milliequivelants per litre, at the end of the study. The normal acceptable range is 136 to 146 meq/L
Maximum intraoperative cardiac index Follow-up: 1 to 3 days	The mean maximum intraoperative cardiac index (L/min/M²) was 2.9	The mean maximum intraoperative cardiac index (L/min/m²) in the intervention group was 0.34 higher (0.19 higher to 0.49 higher)	-	418 (6 RCTs)	⊕⊕⊕⊕ HIGH	The measurement of this variable is common practice in operative procedures. Measured by the volume of blood passing through one square meter each minute (L/min/M²). The normal range is 2.5 - 4.0 L/min/M²
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

Footnotes

[1]Downgraded (2 levels) for indirectness: The majority of studies have an insufficient follow-up period to adequately measure the outcome.
[2]Downgraded (1 level) for publication bias: Only one study contributes explicit evidence for the outcome.
[3]Downgraded (1 level) for risk of bias: The majority of the studies have not confirmed blinding of outcome assessors; bias could seriously impact this result.
[4]Downgraded (1 level) for imprecision: The volume of crystalloid solution delivered between studies has a large range.
[5]Downgraded (1 level) for imprecision: The duration of sample collection varies widely from study to study.

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Data and analyses

1 Hypertonic salt versus isotonic salt solution for peri-operative resuscitation

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Mortality during the study period	18	1087	Risk Ratio(M-H, Fixed, 95% CI)	Not estimable
1.2 Serious adverse events during the study period	18	1087	Risk Ratio(M-H, Fixed, 95% CI)	Not estimable

1.3 Fluid balance (L) measured at the end of the recovery period	8	737	Mean Difference(IV, Random, 95% CI)	-1.92 [-2.61, -1.22]
1.4 Total volume of crystalloid administered (L)	13	871	Mean Difference(IV, Random, 95% CI)	-0.91 [-1.24, -0.59]
1.5 Diuresis during study period (L)	9	777	Mean Difference(IV, Random, 95% CI)	0.11 [-0.09, 0.31]
1.6 Peak serum sodium (meq/L)	16	780	Mean Difference(IV, Random, 95% CI)	7.73 [5.84, 9.62]
1.7 Final serum sodium (meq/L)	12	640	Mean Difference(IV, Random, 95% CI)	3.45 [2.46, 4.44]
1.8 Maximum intraoperative serum osmolarity (mOsm/kg H2O)	10	369	Mean Difference(IV, Random, 95% CI)	15.29 [12.27, 18.31]
1.9 Maximum intraoperative pulmonary artery wedge pressure (mm Hg)	3	150	Mean Difference(IV, Fixed, 95% CI)	0.16 [-1.69, 2.02]
1.10 Maximum intraoperative cardiac index (L/min/M²)	6	418	Mean Difference(IV, Random, 95% CI)	0.34 [0.19, 0.49]

2 Sensitivity analysis - hypertonic salt versus isotonic salt solution for peri-operative resuscitation

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Fluid balance (L) measured during the study period: studies at low risk of bias	2	279	Mean Difference(IV, Random, 95% CI)	-1.47 [-2.84, -0.09]
2.2 Total volume of crystalloid administered (L): studies at low risk of bias	3	319	Mean Difference(IV, Random, 95% CI)	-1.08 [-1.92, -0.24]
2.3 Diuresis during study period (L): studies at low risk of bias	2	279	Mean Difference(IV, Random, 95% CI)	1.25 [-1.17, 3.67]
2.4 Peak serum sodium (meq/L): studies at low risk of bias	4	129	Mean Difference(IV, Random, 95% CI)	6.03 [3.96, 8.09]
2.5 Final serum sodium (meq/L): studies at low risk of bias	3	99	Mean Difference(IV, Random, 95% CI)	2.48 [0.33, 4.62]
2.6 Maximum intraoperative serum osmolarity (mOsm/kg H2O): studies at low risk of bias	2	79	Mean Difference(IV, Random, 95% CI)	15.81 [12.86, 18.77]

3 Subgroup analysis - hypertonic salt versus isotonic salt solution for peri-operative resuscitation

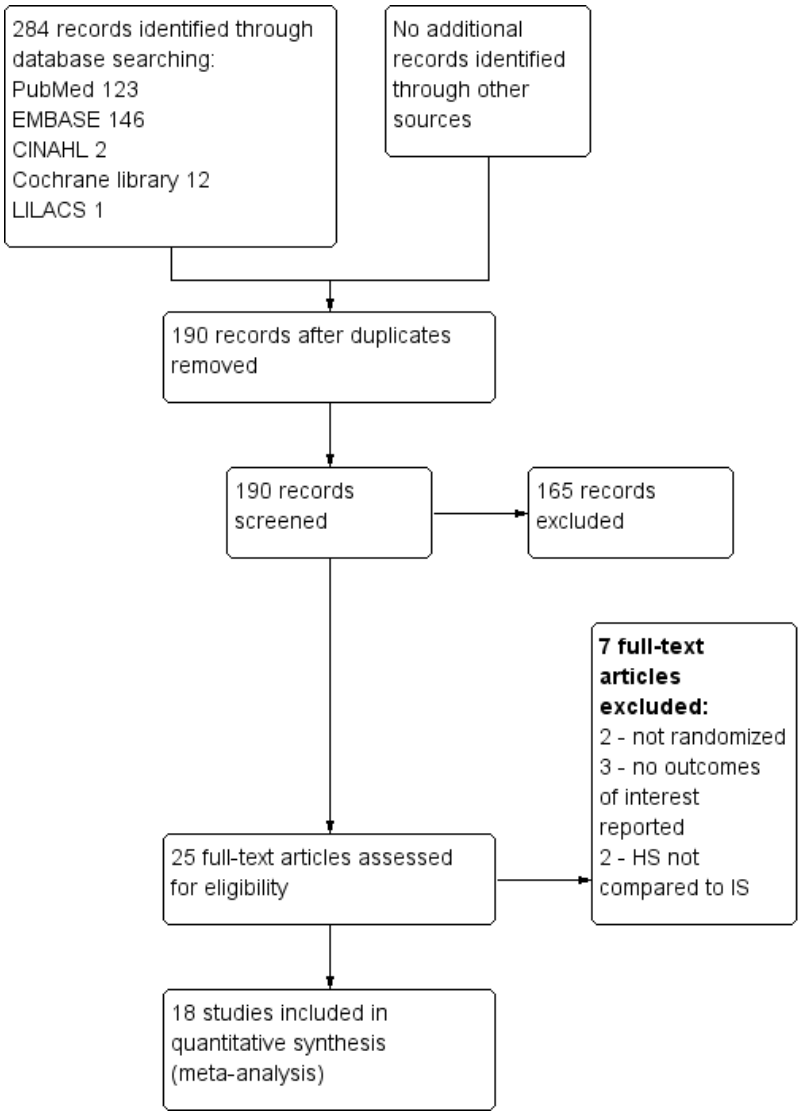
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Fluid balance (L) by type of surgery	8	737	Mean Difference(IV, Random, 95% CI)	-1.92 [-2.61, -1.22]
3.1.1 Aortic surgery	3	138	Mean Difference(IV, Random, 95% CI)	-3.84 [-6.45, -1.23]
3.1.2 Neurosurgery	1	40	Mean Difference(IV, Random, 95% CI)	-1.20 [-1.59, -0.81]
3.1.3 Hepatobiliary surgery	1	259	Mean Difference(IV, Random, 95% CI)	-0.53 [-2.20, 1.14]
3.1.4 Coronary artery bypass surgery	3	300	Mean Difference(IV, Random, 95% CI)	-1.24 [-1.92, -0.57]
3.2 Fluid balance (L) by dose of HS	8	737	Mean Difference(IV, Random, 95% CI)	-1.91 [-2.61, -1.22]
3.2.1 < 7.1 mL 3% HS/kg	1	40	Mean Difference(IV, Random, 95% CI)	-1.20 [-1.59, -0.81]
3.2.2 7.1 - 10 mL 3% HS/kg	3	308	Mean Difference(IV, Random, 95% CI)	-0.92 [-1.22, -0.62]
3.2.3 > 10 mL 3% HS/kg	4	389	Mean Difference(IV, Random, 95% CI)	-3.08 [-5.23, -0.94]

3.3 Fluid balance (L) by volume given to control group	8	737	Mean Difference(IV, Random, 95% CI)	-1.91 [-2.61, -1.22]
3.3.1 < 2000 mL	0	0	Mean Difference(IV, Random, 95% CI)	Not estimable
3.3.2 2000 - 5000 mL	4	328	Mean Difference(IV, Random, 95% CI)	-1.31 [-1.92, -0.70]
3.3.3 > 5000 mL	4	409	Mean Difference(IV, Random, 95% CI)	-2.87 [-5.29, -0.44]
3.4 Total volume of crystalloid administered (L) by type of surgery	13	871	Mean Difference(IV, Random, 95% CI)	-0.91 [-1.24, -0.59]
3.4.1 Cardiovascular surgery	7	429	Mean Difference(IV, Random, 95% CI)	-1.14 [-1.71, -0.57]
3.4.2 Non-cardiovascular surgery	6	442	Mean Difference(IV, Random, 95% CI)	-0.78 [-1.05, -0.50]
3.5 Total volume of crystalloid administered (L) by dose of HS	13	871	Mean Difference(IV, Random, 95% CI)	-0.91 [-1.24, -0.59]
3.5.1 < 7.1 mL 3% HS/kg	4	143	Mean Difference(IV, Random, 95% CI)	-0.77 [-1.19, -0.35]
3.5.2 7.1 - 10 mL 3% HS/kg	5	339	Mean Difference(IV, Random, 95% CI)	-0.76 [-1.25, -0.27]
3.5.3 > 10 mL 3% HS/kg	4	389	Mean Difference(IV, Random, 95% CI)	-2.50 [-4.99, -0.02]
3.6 Diuresis during study period (L) by type of surgery	9	777	Mean Difference(IV, Random, 95% CI)	0.11 [-0.10, 0.31]
3.6.1 Cardiovascular surgery	6	438	Mean Difference(IV, Random, 95% CI)	0.15 [-0.22, 0.52]
3.6.2 Non-cardiovascular surgery	3	339	Mean Difference(IV, Random, 95% CI)	0.00 [-0.30, 0.30]
3.7 Diuresis during study period (L) by dose of HS	9	777	Mean Difference(IV, Random, 95% CI)	0.10 [-0.10, 0.30]
3.7.1 < 7.1 mL 3% HS/kg	1	40	Mean Difference(IV, Random, 95% CI)	-0.16 [-0.54, 0.22]
3.7.2 7.1 - 10 mL 3% HS/kg	4	348	Mean Difference(IV, Random, 95% CI)	0.00 [-0.12, 0.13]
3.7.3 > 10 mL 3% HS/kg	4	389	Mean Difference(IV, Random, 95% CI)	0.31 [-0.50, 1.11]
3.8 Diuresis during study period (L) by volume given to control group	9	777	Mean Difference(IV, Random, 95% CI)	0.09 [-0.11, 0.30]
3.8.1 < 2000 mL	2	68	Mean Difference(IV, Random, 95% CI)	0.00 [-0.16, 0.17]
3.8.2 2000 - 5000 mL	3	300	Mean Difference(IV, Random, 95% CI)	0.33 [-0.19, 0.85]
3.8.3 > 5000 mL	4	409	Mean Difference(IV, Random, 95% CI)	-0.16 [-0.48, 0.17]
3.9 Peak serum sodium (meq/L) by type of surgery	16	780	Mean Difference(IV, Random, 95% CI)	7.73 [5.84, 9.62]
3.9.1 Cardiovascular surgery	7	469	Mean Difference(IV, Random, 95% CI)	10.61 [6.91, 14.31]
3.9.2 Transurethral resection of the prostate	3	87	Mean Difference(IV, Random, 95% CI)	4.01 [1.86, 6.16]
3.9.3 Other surgery	6	224	Mean Difference(IV, Random, 95% CI)	6.52 [3.64, 9.40]
3.10 Peak serum sodium (meq/L) by dose of HS	16	780	Mean Difference(IV, Random, 95% CI)	7.73 [5.84, 9.62]
3.10.1 < 7.1 mL 3% HS/kg	6	218	Mean Difference(IV, Random, 95% CI)	5.31 [2.00, 8.63]
3.10.2 7.1 - 10 mL 3% HS/kg	6	418	Mean Difference(IV, Random, 95% CI)	8.93 [5.16, 12.70]
3.10.3 > 10 mL 3% HS/kg	4	144	Mean Difference(IV, Random, 95% CI)	9.75 [5.50, 13.99]

3.11 Peak serum sodium (meq/L) by volume given to control group	11	619	Mean Difference(IV, Random, 95% CI)	9.10 [6.66, 11.53]
3.11.1 < 2000 mL/kg	4	141	Mean Difference(IV, Random, 95% CI)	4.94 [3.53, 6.34]
3.11.2 2000 - 5000 mL	4	328	Mean Difference(IV, Random, 95% CI)	9.05 [4.54, 13.56]
3.11.3 > 5000 mL	3	150	Mean Difference(IV, Random, 95% CI)	13.93 [11.44, 16.42]
3.12 Final serum sodium (meq/L) by type of surgery	12	640	Mean Difference(IV, Random, 95% CI)	3.45 [2.46, 4.44]
3.12.1 Cardiovascular surgery	6	390	Mean Difference(IV, Random, 95% CI)	3.91 [2.55, 5.28]
3.12.2 Transurethral resection of prostate	1	40	Mean Difference(IV, Random, 95% CI)	2.00 [0.45, 3.55]
3.12.3 Other surgery	5	210	Mean Difference(IV, Random, 95% CI)	3.05 [0.77, 5.32]
3.13 Final serum sodium (meq/L) by dose of HS	12	640	Mean Difference(IV, Random, 95% CI)	3.45 [2.46, 4.44]
3.13.1 < 7.1 mL 3% HS/kg	3	140	Mean Difference(IV, Random, 95% CI)	3.69 [1.70, 5.68]
3.13.2 7.1 - 10 mL 3% HS/kg	6	370	Mean Difference(IV, Random, 95% CI)	2.63 [1.17, 4.10]
3.13.3 > 10 mL 3% HS/kg	3	130	Mean Difference(IV, Random, 95% CI)	5.56 [3.16, 7.96]
3.14 Final serum sodium (meq/L) by volume given to control group	9	333	Mean Difference(IV, Random, 95% CI)	3.73 [2.29, 5.17]
3.14.1 < 2000 mL	3	111	Mean Difference(IV, Random, 95% CI)	2.32 [-0.74, 5.39]
3.14.2 2000 - 5000 mL	3	72	Mean Difference(IV, Random, 95% CI)	3.14 [1.02, 5.27]
3.14.3 > 5000 mL	3	150	Mean Difference(IV, Random, 95% CI)	5.70 [3.98, 7.43]

Figures

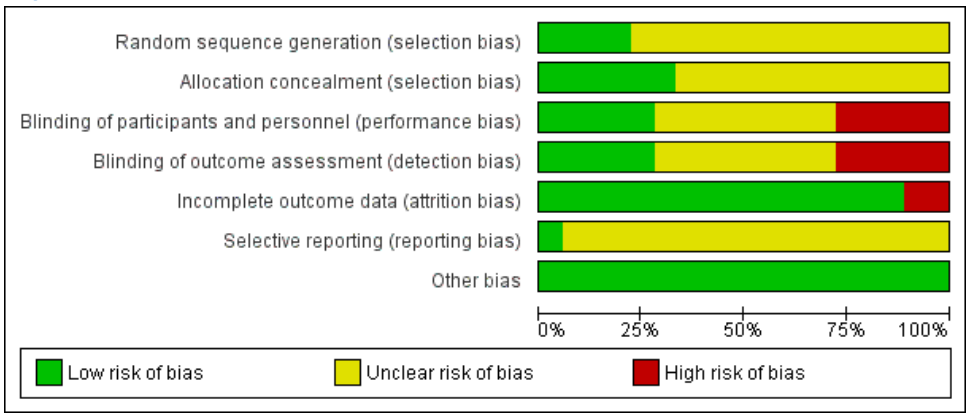
Figure 1



Caption

Study flow diagram.

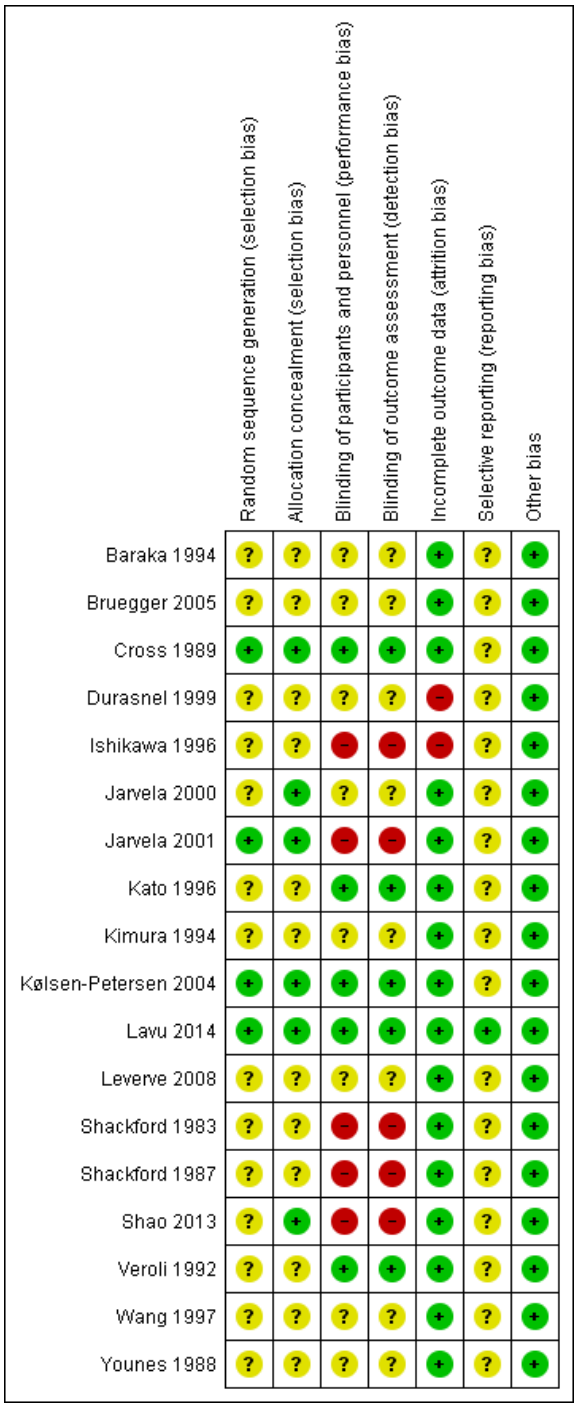
Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

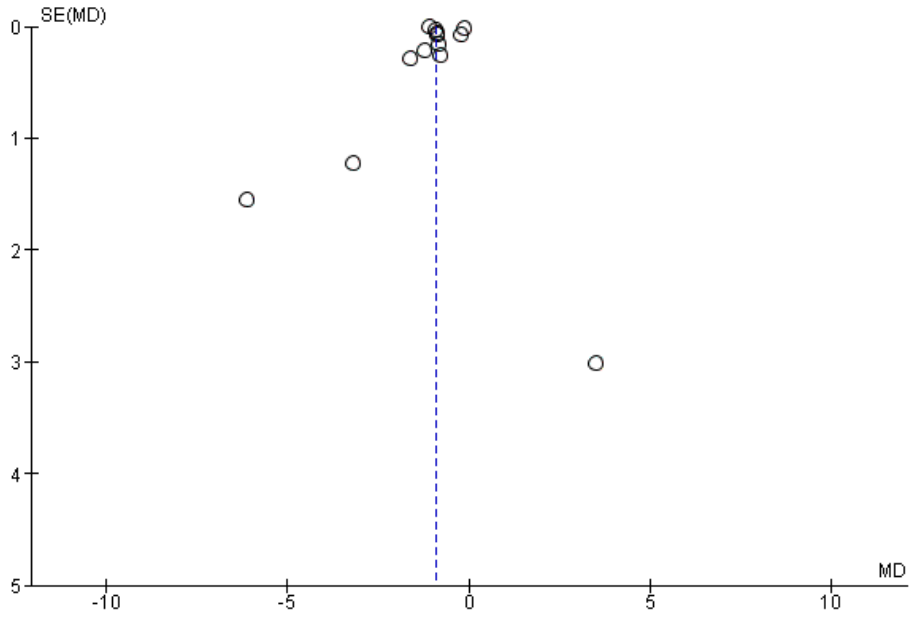
Figure 3



Caption

Risk of bias summary: review authors' judgements about each 'Risk of bias' item for each included study.

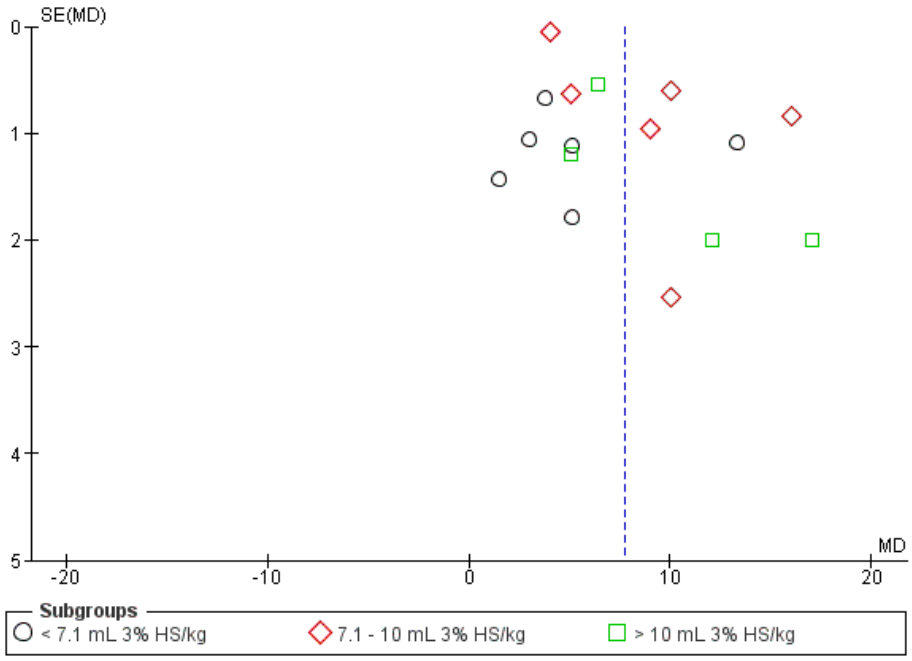
Figure 4 (Analysis 1.4)



Caption

Funnel plot of comparison: 1 Hypertonic salt versus isotonic salt solution for peri-operative resuscitation, outcome: 1.4 Total volume of crystalloid administered (L).

Figure 5 (Analysis 3.10)



Caption

Funnel plot of comparison: 3 Subgroup analysis - hypertonic salt versus isotonic salt solution for peri-operative resuscitation, outcome: 3.10 Peak serum sodium (meq/L) by dose of HS.

Sources of support

Internal sources

- Lawson Health Research Institute, Canada
  LHRF F9738 (V McAlister Research Fund)
- University of Western Ontario, Canada
  Division of General Surgery Research Fund

External sources

- No external funds sought or received, Other

Feedback

Appendices

1 MEDLINE (Ovid SP) 1946 to April 2007.

#1 explode saline solution, hypertonic/ all subheadings
#2 explode hypertonic solutions/ all subheadings
#3 (hypertonic NaCl) or (hypertonic saline) or (hypertonic solution*)
#4 Ringer's solution/ all subheadings
#5 #1 or #2 or #3 or #4
#6 #5 not (explode glucose solution, hypertonic / all subheadings)
#7 #6 not colloid*
#8 explode surgical procedures, operative/ all subheadings
#9 explode specialties, surgical/ all subheadings
#10 explode surgery/ all subheadings
#11 (surg* near procedur*) or surger* or operat*
#12 #8 or #9 or #10 or #11
#13 #7 and #12
#14 RANDOMIZED-CONTROLLED-TRIAL in PT
#15 CONTROLLED-CLINICAL-TRIAL in PT
#16 explode RANDOMIZED-CONTROLLED-TRIALS/ all subheadings
#17 explode RANDOM-ALLOCATION/ all subheadings
#18 explode DOUBLE-BLIND-METHOD/ all subheadings
#19 explode SINGLE-BLIND-METHOD/ all subheadings
#20 #14 or #15 or #16 or #17 or #18 or #19
#21 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#22 #20 not #21
#23 CLINICAL-TRIAL in PT
#24 explode CLINICAL-TRIALS / all subheadings
#25 (clin* near trial*) in TI
#26 (clin* near trial*) in AB
#27 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#28 (#27 in TI) or (#27 in AB)
#29 explode PLACEBOS/ all subheadings
#30 placebo* in TI
#31 placebo* in AB
#32 random* in TI
#33 random* in AB
#34 explode RESEARCH-DESIGN/ all subheadings
#35 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#37 #35 not #36
#38 #37 not #22
#39 TG=COMPARATIVE-STUDY
#40 explode EVALUATION-STUDIES/ all subheadings
#41 explode FOLLOW-UP-STUDIES/ all subheadings
#42 explode PROSPECTIVE-STUDIES/ all subheadings
#43 control* or prospectiv* or volunteer*
#44 (#43 in TI) or (#43 in AB)
#45 #39 or #40 or #41 or #42 or #43 or #44
#46 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#47 #45 not #46
#48 #47 not (#22 or #38)
#49 #22 or #38 or #48
#50 #13 and #49

2 EMBASE (Ovid SP) 1974 to April 2007.

#1 saline solution

#2 explode "hypertonic-solution" / all SUBHEADINGS in DEM,DER,DRM,DRR

#3 (hypertonic NaCl) or (hypertonic saline) or (hypertonic solution*)

#4 "Ringer-solution" / all SUBHEADINGS in DEM,DER,DRM,DRR

#5 sodium chloride in TI, AB

#6 #1 or #2 or #3 or #4 or #5

#7 #6 not (glucose or fructose)

#8 explode surgery/ all subheadings

#9 (surg* near procedur*) or surger* or operat*

#10 "surgical-technique" / all SUBHEADINGS in DEM,DER,DRM,DRR

#11 #8 or #9 or #10

#12 #7 and #11

#13 explode "randomized-controlled-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR

#14 (randomi?ed controlled trial*) in TI, AB

#15 random*

#16 explode "randomization-" / all SUBHEADINGS in DEM,DER,DRM,DRR

#17 randomi?ation

#18 explode "clinical-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR

#19 clinical near trial*

#20 explode multicenter-study / all subheadings

#21 multi?cent*

#22 explode phase-4-clinical-trial / all subheadings or explode double-blind-procedure / all subheadings or explode single-blind-procedure / all subheadings

#23 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI, AB, TW

#24 ((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in TI,AB

#25 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

#26 (human) in DER

#27 (animal or nonhuman) in DER

#28 #26 and #27

#29 #27 not #28

#30 #25 not #29

#31 #12 and #30

3 CINAHL (1982 to April 2007)

#1 explode "Saline-Solution-Hypertonic" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#2 explode "Hypertonic-Solutions" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#3 (hypertonic NaCl) or (hypertonic saline) or (hypertonic solution*)

#4 explode "Lactated-Ringer's-Solution" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#5 explode "Sodium-Chloride" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#6 #1 or #2 or #3 or #4 or #5

#7 #6 not (glucose or fructose)

#8 explode "Surgery-Operative" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#9 (surg* near procedur*) or (surg* and procedur*)or surger* or operat*

#10 #8 or #9

#11 #7 and #10

#12 Randomized Clinical Trial*

#13 Controlled Clinical Trial*

#14 explode "Random-Assignment" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#15 "Double-Blind-Studies" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#16 "Single-Blind-Studies" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#17 explode "Clinical-Trials" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#18 (clin* near trial*) in TI

#19 (clin* near trial*) in AB

#20 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)

#21 (#20 in TI) or (#20 in AB)

#22 "Placebos-" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#23 placebo* in TI

#24 placebo* in AB

#25 random* in TI

#26 random* in AB

#27 "Study-Design" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#28 "Comparative-Studies" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#29 explode "Evaluation-Research" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#30 "Prospective-Studies" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

#31 control* or prospectiv* or volunteer*

#32 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 sheep or dog* or cat* or guinea?pig* or mouse or experimental animal*

#34 explode animals/ all topical subheadings / all age subheadings

#35 #33 or #34

#36 human*

#37 #35 not (#34 and #35)

#38 #32 not #37

#39 #11 and #38

4 LILACS (1982 to April 8, 2016)

"HYPERTONIC" or "HYPERTONIC SALINE SOLUTION/" or "HYPERTONIC SOLUTION, SALINE/" or "HYPERTONIC SOLUTIONS/" or "RINGER" or "SODIUM CHLORIDE" or "SODIUM CHLORIDE SOLUTION, HYPERTONIC/" [Words] and "SURGERY" or "SURGICAL" or "OPERATION" or "surg$" or "operat$" [Words]

5 CENTRAL, (*The Cochrane Library, April 2007*)

#1 MeSH descriptor Sodium Chloride explode all trees
#2 MeSH descriptor Saline Solution, Hypertonic explode all trees
#3 ((hypertonic in All Text and NaCl in All Text) or (hypertonic in All Text and saline in All Text) or (hypertonic in All Text and solution* in All Text))
#4 (Ringer's in All Text and solution in All Text)
#5 (#1 or #2 or #3 or #4)
#6 MeSH descriptor Glucose Solution, Hypertonic explode all trees
#7 (#5 and not #6)
#8 (#7 and not colloid* in All Text)
#9 MeSH descriptor surgical procedures, operative explode all trees
#10 MeSH descriptor Specialties, Surgical explode all trees
#11 MeSH descriptor Specialties, Dental explode all trees
#12 MeSH descriptor Surgery explode all trees
#13 (surg* in All Text near/6 procedur* in All Text)
#14 (surger* in All Text or operat* in All Text)
#15 (#9 or #10 or #11 or #12 or #13 or #14)
#16 (#8 and #15)
5 not #36
#38 #37 not #22
#39 TG=COMPARATIVE-STUDY
#40 explode EVALUATION-STUDIES/ all subheadings
#41 explode FOLLOW-UP-STUDIES/ all subheadings
#42 explode PROSPECTIVE-STUDIES/ all subheadings
#43 control* or prospectiv* or volunteer*
#44 (#43 in TI) or (#43 in AB)
#45 #39 or #40 or #41 or #42 or #43 or #44
#46 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#47 #45 not #46
#48 #47 not (#22 or #38)
#49 #22 or #38 or #48
#50 #13 and #49

6 Search update: April 2007 to April 8, 2016

Search strategy for EMBASE (Ovid SP)

#1. exp sodium chloride/ or Ringer solution/
#2. exp hypertonic solution/
#3. (hypertonic adj3 (NaCl or saline or solution*)).mp.
#4. #1 or #2 or #3
#5. (glucose or fructose).mp.
#6. #4 not #5
#7. surgery/ or ((surg* adj3 procedur*) or surger* or operat*).ti,ab.
#8. (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).mp. not (animal not (human and animal)).sh.
#9. #6 and #7 and #8

Search strategy for MEDLINE (Ovid SP)

#1. saline solution, hypertonic/ or hypertonic solutions/
#2. (hypertonic adj3 (NaCl or saline or solution*)).mp. or ringer.mp.
#3. #1 or #2
#4. exp glucose solution, hypertonic/ or colloid*.mp.
#5. #3 not #4
#6. exp surgical procedures, operative/ or exp specialties, surgical/ or exp surgery/
#7. ((surg* adj3 procedur*) or surger* or operat*).mp.
#8. #6 or #7
#9. #8 and #5
#10. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
#11. #9 and #10

Search strategy for CINAHL (EBASCOhost)

S1. (MM "Saline Solution, Hypertonic") or (MM "Hypertonic Solutions")
S2. (MH "Lactated Ringer's Solution")
S3. TX (hypertonic and (NaCl or saline or solution*)) or Ringer
S4. (MH "Sodium Chloride")
S5. S1 or S2 or S3 or S4
S6. TX glucose or fructose
S7. S5 not S6
S8. (MH "Surgery, Operative")
S9. TX surger* or operat*
S10. S8 or S9
S11. S7 and S10

Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Saline Solution, Hypertonic explode all trees
#2 MeSH descriptor Hypertonic Solutions explode all trees
#3 (hypertonic NaCl) or (hypertonic saline) or (hypertonic solution*)
#4 Ringer* near solution*
#5 Sodium Chloride
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Glucose Solution, Hypertonic, this term only
#8 (#6 AND NOT #7)
#9 MeSH descriptor Surgical Procedures, Operative explode all trees
#10 MeSH descriptor Specialties, Surgical explode all trees
#11 MeSH descriptor Surgery explode all trees
#12 (surg* near procedur*) or surger* or operat*
#13 (#9 OR #10 OR #11 OR #12)
#14 (#8 AND #13)

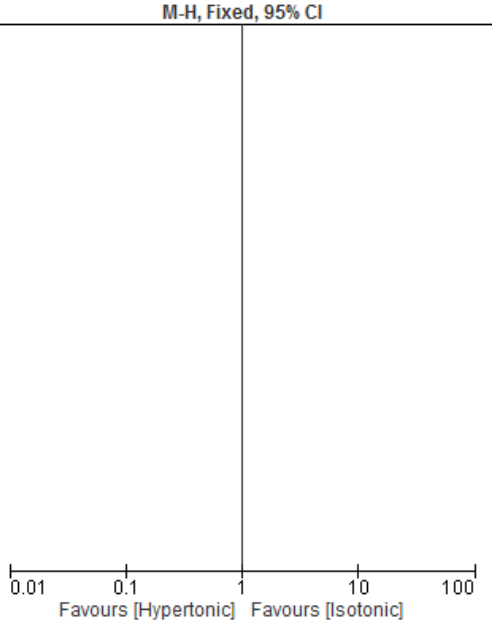
Graphs

1 - Hypertonic salt versus isotonic salt solution for peri-operative resuscitation

1.1 Mortality during the study period

Study or Subgroup	Hypertonic Saline Events	Total	Isotonic Solution Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baraka 1994	0	17	0	16		Not estimable
Bruegger 2005	0	14	0	14		Not estimable
Cross 1989	0	11	0	9		Not estimable
Durasnel 1999	0	24	0	24		Not estimable
Ishikawa 1996	0	8	0	7		Not estimable
Jarvela 2000	0	20	0	20		Not estimable
Jarvela 2001	0	36	0	36		Not estimable
Kato 1996	0	20	0	20		Not estimable
Kimura 1994	0	7	0	7		Not estimable
Kølsen-Petersen 2004	0	19	0	20		Not estimable
Lavu 2014	0	131	0	128		Not estimable
Leverve 2008	0	109	0	99		Not estimable
Shackford 1983	0	30	0	28		Not estimable
Shackford 1987	0	26	0	26		Not estimable
Shao 2013	0	20	0	20		Not estimable
Veroli 1992	0	10	0	20		Not estimable
Wang 1997	0	30	0	30		Not estimable
Younes 1988	0	13	0	18		Not estimable
Total (95% CI)		**545**		**542**		**Not estimable**
Total events	0		0			

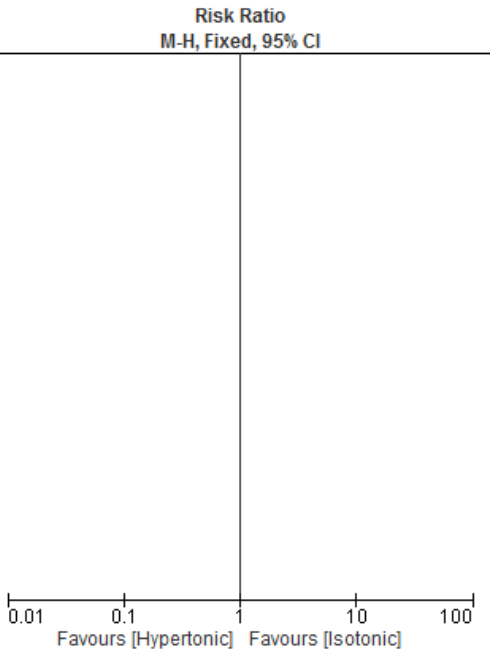
Heterogeneity: Not applicable
Test for overall effect: Not applicable



1.2 Serious adverse events during the study period

Study or Subgroup	Hypertonic Events	Total	Isotonic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baraka 1994	0	17	0	16		Not estimable
Bruegger 2005	0	14	0	14		Not estimable
Cross 1989	0	11	0	9		Not estimable
Durasnel 1999	0	24	0	24		Not estimable
Ishikawa 1996	0	8	0	7		Not estimable
Jarvela 2000	0	20	0	20		Not estimable
Jarvela 2001	0	36	0	36		Not estimable
Kato 1996	0	20	0	20		Not estimable
Kimura 1994	0	7	0	7		Not estimable
Kølsen-Petersen 2004	0	19	0	20		Not estimable
Lavu 2014	0	131	0	128		Not estimable
Leverve 2008	0	109	0	99		Not estimable
Shackford 1983	0	30	0	28		Not estimable
Shackford 1987	0	26	0	26		Not estimable
Shao 2013	0	20	0	20		Not estimable
Veroli 1992	0	10	0	20		Not estimable
Wang 1997	0	30	0	30		Not estimable
Younes 1988	0	13	0	18		Not estimable
Total (95% CI)		**545**		**542**		**Not estimable**
Total events	0		0			

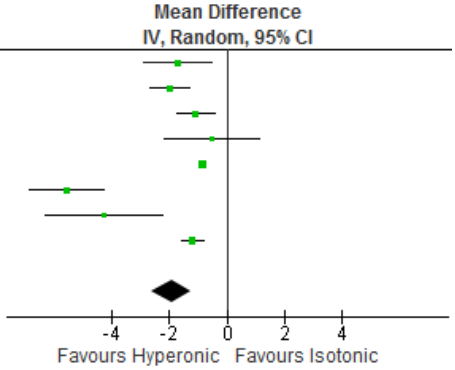
Heterogeneity: Not applicable
Test for overall effect: Not applicable



1.3 Fluid balance (L) measured at the end of the recovery period

Study or Subgroup	Hypertonic salt solution Mean	SD	Total	Isotonic salt solution Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bruegger 2005	3.6	2	14	5.31	1.1	14	11.3%	-1.71 [-2.91, -0.51]
Cross 1989	-1.72	0.73	11	0.27	0.83	9	14.6%	-1.99 [-2.68, -1.30]
Jarvela 2001	0.8	1.5	36	1.9	1.4	36	14.7%	-1.10 [-1.77, -0.43]
Lavu 2014	6.47	7.9	131	7	5.63	128	8.6%	-0.53 [-2.20, 1.14]
Leverve 2008	-0.79	0.07	109	0.04	0.12	99	17.1%	-0.83 [-0.86, -0.80]
Shackford 1983	4.2	1.6	30	9.8	3.2	28	10.6%	-5.60 [-6.92, -4.28]
Shackford 1987	5.5	1.5	26	9.8	5.1	26	6.9%	-4.30 [-6.34, -2.26]
Shao 2013	2.24	0.71	20	3.44	0.55	20	16.2%	-1.20 [-1.59, -0.81]
Total (95% CI)			**377**			**360**	**100.0%**	**-1.92 [-2.61, -1.22]**

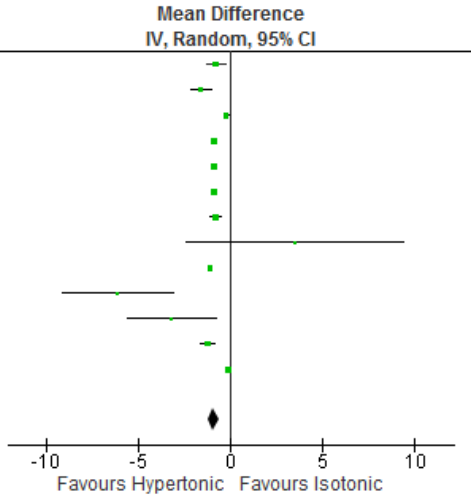
Heterogeneity: Tau² = 0.74; Chi² = 78.26, df = 7 (P < 0.00001); I² = 91%
Test for overall effect: Z = 5.40 (P < 0.00001)



1.4 Total volume of crystalloid administered (L)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bruegger 2005	1.92	0.7	14	2.72	0.68	14	8.3%	-0.80 [-1.31, -0.29]
Cross 1989	4.17	0.41	11	5.77	0.79	9	7.9%	-1.60 [-2.17, -1.03]
Durasnel 1999	0.39	0.22	24	0.62	0.32	24	10.3%	-0.23 [-0.39, -0.07]
Ishikawa 1996	0.1	0.02	8	0.98	0.15	7	10.4%	-0.88 [-0.99, -0.77]
Jarvela 2000	0.13	0.03	20	1.03	0.16	20	10.4%	-0.90 [-0.97, -0.83]
Jarvela 2001	0.55	0.18	16	1.44	0.23	16	10.3%	-0.89 [-1.03, -0.75]
Kato 1996	0.81	0.35	20	1.62	0.62	20	9.6%	-0.81 [-1.12, -0.50]
Lavu 2014	30.05	30.19	131	26.56	16.27	128	0.3%	3.49 [-2.40, 9.38]
Leverve 2008	1.32	0.07	109	2.43	0.12	99	10.5%	-1.11 [-1.14, -1.08]
Shackford 1983	6.4	4.6	30	12.5	6.9	28	1.0%	-6.10 [-9.14, -3.06]
Shackford 1987	6.3	2.4	26	9.5	5.8	26	1.5%	-3.20 [-5.61, -0.79]
Shao 2013	4.26	0.67	20	5.5	0.68	20	8.9%	-1.24 [-1.66, -0.82]
Younes 1988	0.7	0.05	18	0.81	0.09	13	10.5%	-0.11 [-0.16, -0.06]
Total (95% CI)			**447**			**424**	**100.0%**	**-0.91 [-1.24, -0.59]**

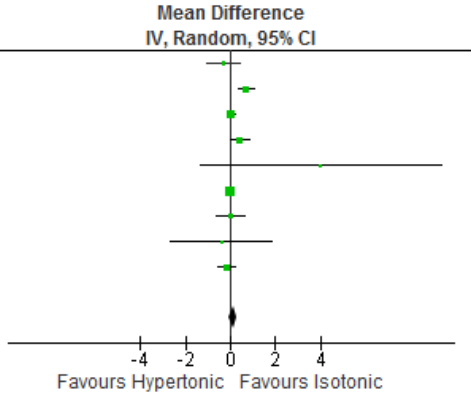
Heterogeneity: Tau² = 0.26; Chi² = 1147.77, df = 12 (P < 0.00001); I² = 99%
Test for overall effect: Z = 5.50 (P < 0.00001)



1.5 Diuresis during study period (L)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bruegger 2005	1.2	0.55	14	1.5	1.33	14	5.5%	-0.30 [-1.05, 0.45]
Cross 1989	4.5	0.5	11	3.8	0.25	9	14.8%	0.70 [0.36, 1.04]
Jarvela 2000	0.45	0.28	20	0.43	0.27	20	21.6%	0.02 [-0.15, 0.19]
Jarvela 2001	3.35	1.04	36	2.94	0.85	36	11.5%	0.41 [-0.03, 0.85]
Lavu 2014	23.58	27.86	131	19.56	13.74	128	0.1%	4.02 [-1.31, 9.35]
Leverve 2008	1.57	0.1	109	1.61	0.15	99	25.5%	-0.04 [-0.08, -0.00]
Shackford 1983	1.8	0.8	30	1.8	1.6	28	6.8%	0.00 [-0.66, 0.66]
Shackford 1987	0.7	0.7	26	1.1	5.8	26	0.8%	-0.40 [-2.65, 1.85]
Shao 2013	1.43	0.57	20	1.59	0.65	20	13.4%	-0.16 [-0.54, 0.22]
Total (95% CI)			**397**			**380**	**100.0%**	**0.11 [-0.09, 0.31]**

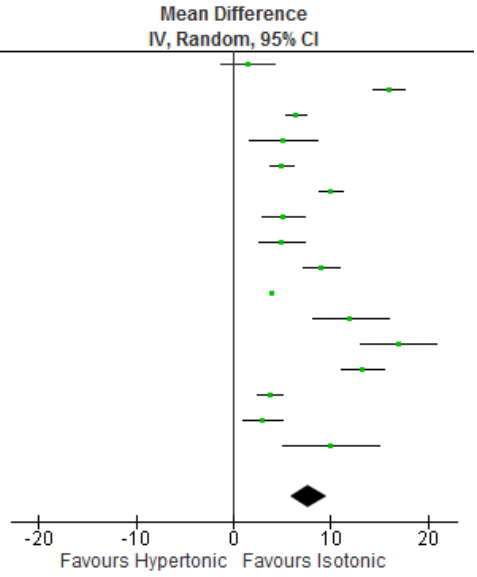
Heterogeneity: Tau² = 0.04; Chi² = 25.74, df = 8 (P = 0.001); I² = 69%
Test for overall effect: Z = 1.07 (P = 0.28)



1.6 Peak serum sodium (meq/L)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baraka 1994	138.5	5	17	137	3	16	6.1%	1.50 [-1.29, 4.29]
Bruegger 2005	159	3	14	143	1	14	6.6%	16.00 [14.34, 17.66]
Cross 1989	145.4	1.4	11	139	1	9	6.8%	6.40 [5.35, 7.45]
Ishikawa 1996	144.1	3.4	8	139	3.5	7	5.6%	5.10 [1.60, 8.60]
Jarvela 2000	145	2	20	140	2	20	6.8%	5.00 [3.76, 6.24]
Jarvela 2001	150	3	36	140	2	36	6.8%	10.00 [8.82, 11.18]
Kato 1996	145	4.4	20	139.9	2.4	20	6.4%	5.10 [2.90, 7.30]
Kimura 1994	142	1	7	137	3	7	6.3%	5.00 [2.66, 7.34]
Kølsen-Petersen 2004	150	3	19	141	3	20	6.5%	9.00 [7.12, 10.88]
Leverve 2008	140	0.4	109	136	0.4	99	7.0%	4.00 [3.89, 4.11]
Shackford 1983	151	7.6	30	139	7.6	28	5.4%	12.00 [8.09, 15.91]
Shackford 1987	157	7.2	26	140	7.2	26	5.4%	17.00 [13.09, 20.91]
Shao 2013	152.5	4.4	20	139.2	2.1	20	6.4%	13.30 [11.16, 15.44]
Veroli 1992	143.7	1.7	10	139.95	1.8	20	6.8%	3.75 [2.43, 5.07]
Wang 1997	142	5	30	139	3	30	6.4%	3.00 [0.91, 5.09]
Younes 1988	147	9	18	137	5	13	4.7%	10.00 [5.03, 14.97]
Total (95% CI)			**395**			**385**	**100.0%**	**7.73 [5.84, 9.62]**

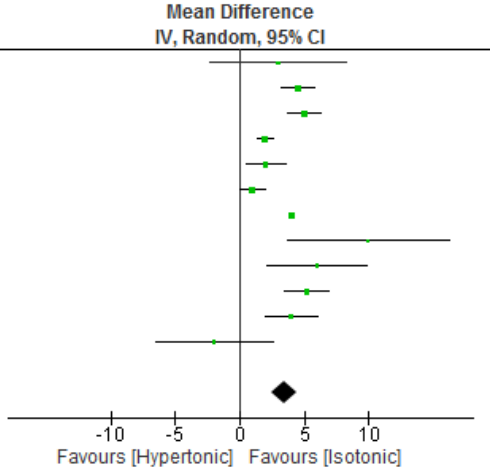
Heterogeneity: Tau² = 13.29; Chi² = 482.15, df = 15 (P < 0.00001); I² = 97%
Test for overall effect: Z = 8.02 (P < 0.00001)



1.7 Final serum sodium (meq/L)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bruegger 2005	143	5.3	6	140	4	6	2.7%	3.00 [-2.31, 8.31]
Cross 1989	144	2	11	139.5	1	9	10.7%	4.50 [3.15, 5.85]
Jarvela 2000	145	2	20	140	2	20	11.0%	5.00 [3.76, 6.24]
Jarvela 2001	141	1	20	139	1	20	12.7%	2.00 [1.38, 2.62]
Kato 1996	140.6	2.6	20	138.6	2.4	20	10.1%	2.00 [0.45, 3.55]
Kølsen-Petersen 2004	139	2	19	138	1	20	11.8%	1.00 [-0.00, 2.00]
Leverve 2008	140	0.4	109	136	0.4	99	13.3%	4.00 [3.89, 4.11]
Shackford 1983	146	7.6	30	136	15.2	28	2.1%	10.00 [3.75, 16.25]
Shackford 1987	145	7.2	26	139	7.2	26	4.3%	6.00 [2.09, 9.91]
Shao 2013	141.5	2.5	20	136.3	3.1	20	9.4%	5.20 [3.45, 6.95]
Wang 1997	142	5	30	138	3	30	8.4%	4.00 [1.91, 6.09]
Younes 1988	136	7	18	138	6	13	3.4%	-2.00 [-6.59, 2.59]
Total (95% CI)			**329**			**311**	**100.0%**	**3.45 [2.46, 4.44]**

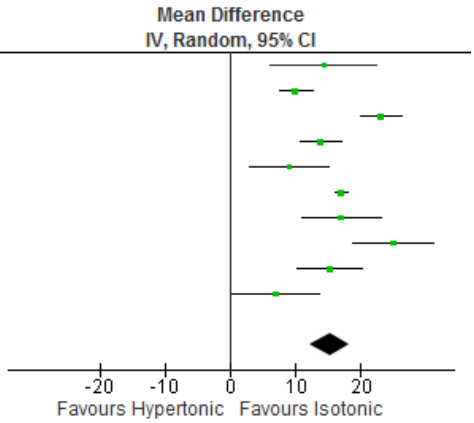
Heterogeneity: Tau² = 1.90; Chi² = 94.45, df = 11 (P < 0.00001); I² = 88%
Test for overall effect: Z = 6.84 (P < 0.00001)



1.8 Maximum intraoperative serum osmolarity (mOsm/kg H2O)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ishikawa 1996	295.8	4.4	8	281.5	10.2	7	6.8%	14.30 [6.15, 22.45]
Jarvela 2000	302	5	20	292	3	20	12.3%	10.00 [7.44, 12.56]
Jarvela 2001	313	6	20	290	4	20	11.7%	23.00 [19.84, 26.16]
Kato 1996	298.2	6.1	20	284.3	3.5	20	11.8%	13.90 [10.82, 16.98]
Kimura 1994	296	4	7	287	7	7	8.8%	9.00 [3.03, 14.97]
Kølsen-Petersen 2004	302	2	19	285	0.5	20	13.3%	17.00 [16.07, 17.93]
Shackford 1983	301	15.2	30	284	7.6	28	8.7%	17.00 [10.88, 23.12]
Shackford 1987	309	14.4	26	284	7.2	26	8.6%	25.00 [18.81, 31.19]
Shao 2013	328.7	8.7	20	313.5	7.4	20	9.8%	15.20 [10.19, 20.21]
Younes 1988	327	11	18	320	8	13	8.1%	7.00 [0.31, 13.69]
Total (95% CI)			**188**			**181**	**100.0%**	**15.29 [12.27, 18.31]**

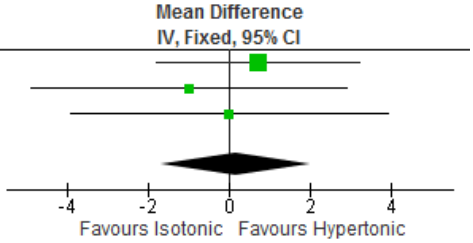
Heterogeneity: Tau² = 17.66; Chi² = 66.36, df = 9 (P < 0.00001); I² = 86%
Test for overall effect: Z = 9.91 (P < 0.00001)



1.9 Maximum intraoperative pulmonary artery wedge pressure (mm Hg)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jarvela 2001	9.1	3.5	20	8.4	4.5	20	55.1%	0.70 [-1.80, 3.20]
Shackford 1983	10	7.6	30	11	7.6	28	22.4%	-1.00 [-4.91, 2.91]
Shackford 1987	11	7.2	26	11	7.2	26	22.5%	0.00 [-3.91, 3.91]
Total (95% CI)			**76**			**74**	**100.0%**	**0.16 [-1.69, 2.02]**

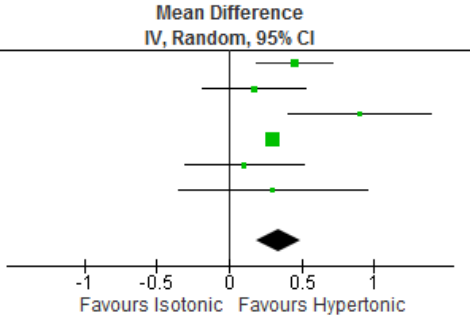
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)



1.10 Maximum intraoperative cardiac index (L/min/M²)

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	3.1	0.3	11	2.65	0.3	9	19.1%	0.45 [0.19, 0.71]
Jarvela 2000	3.19	0.5	20	3.02	0.65	20	12.8%	0.17 [-0.19, 0.53]
Jarvela 2001	3.2	1	20	2.3	0.5	20	7.9%	0.90 [0.41, 1.39]
Leverve 2008	3.1	0.1	109	2.8	0.1	99	45.1%	0.30 [0.27, 0.33]
Shackford 1983	3.1	0.8	30	3	0.8	28	10.4%	0.10 [-0.31, 0.51]
Shackford 1987	3.7	1.2	26	3.4	1.2	26	4.8%	0.30 [-0.35, 0.95]
Total (95% CI)			**216**			**202**	**100.0%**	**0.34 [0.19, 0.49]**

Heterogeneity: Tau² = 0.01; Chi² = 8.39, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 4.39 (P < 0.0001)

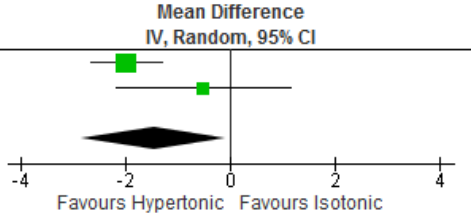


2 - Sensitivity analysis - hypertonic salt versus isotonic salt solution for peri-operative resuscitation

2.1 Fluid balance (L) measured during the study period: studies at low risk of bias

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	-1.72	0.73	11	0.27	0.83	9	64.1%	-1.99 [-2.68, -1.30]
Lavu 2014	6.47	7.9	131	7	5.63	128	35.9%	-0.53 [-2.20, 1.14]
Total (95% CI)			**142**			**137**	**100.0%**	**-1.47 [-2.84, -0.09]**

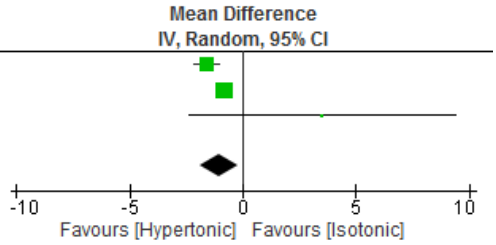
Heterogeneity: Tau² = 0.64; Chi² = 2.51, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 2.09 (P = 0.04)



2.2 Total volume of crystalloid administered (L): studies at low risk of bias

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	4.17	0.41	11	5.77	0.79	9	45.2%	-1.60 [-2.17, -1.03]
Kato 1996	0.81	0.35	20	1.62	0.62	20	52.9%	-0.81 [-1.12, -0.50]
Lavu 2014	30.05	30.19	131	26.56	16.27	128	2.0%	3.49 [-2.40, 9.38]
Total (95% CI)			**162**			**157**	**100.0%**	**-1.08 [-1.92, -0.24]**

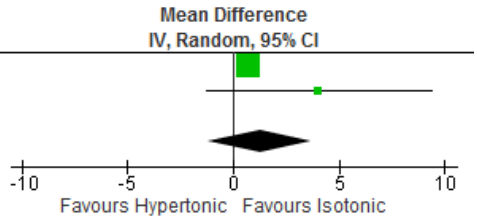
Heterogeneity: Tau² = 0.32; Chi² = 7.90, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 2.53 (P = 0.01)



2.3 Diuresis during study period (L): studies at low risk of bias

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	4.5	0.5	11	3.8	0.25	9	83.4%	0.70 [0.36, 1.04]
Lavu 2014	23.58	27.86	131	19.56	13.74	128	16.6%	4.02 [-1.31, 9.35]
Total (95% CI)			**142**			**137**	**100.0%**	**1.25 [-1.17, 3.67]**

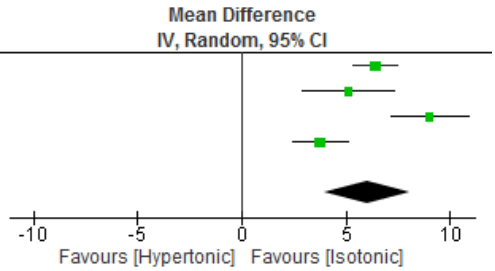
Heterogeneity: Tau² = 1.80; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.01 (P = 0.31)



2.4 Peak serum sodium (meq/L): studies at low risk of bias

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	145.4	1.4	11	139	1	9	27.5%	6.40 [5.35, 7.45]
Kato 1996	145	4.4	20	139.9	2.4	20	22.2%	5.10 [2.90, 7.30]
Kølsen-Petersen 2004	150	3	19	141	3	20	23.8%	9.00 [7.12, 10.88]
Veroli 1992	143.7	1.7	10	139.95	1.8	20	26.5%	3.75 [2.43, 5.07]
Total (95% CI)			**60**			**69**	**100.0%**	**6.03 [3.96, 8.09]**

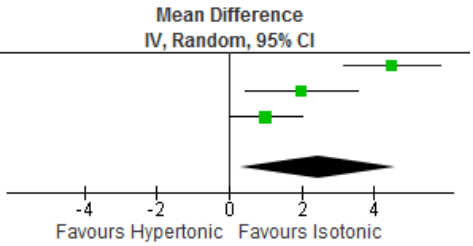
Heterogeneity: Tau² = 3.74; Chi² = 22.01, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 5.72 (P < 0.00001)



2.5 Final serum sodium (meq/L): studies at low risk of bias

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cross 1989	144	2	11	139.5	1	9	33.1%	4.50 [3.15, 5.85]
Kato 1996	140.6	2.6	20	138.6	2.4	20	31.8%	2.00 [0.45, 3.55]
Kølsen-Petersen 2004	139	2	19	138	1	20	35.2%	1.00 [-0.00, 2.00]
Total (95% CI)			**50**			**49**	**100.0%**	**2.48 [0.33, 4.62]**

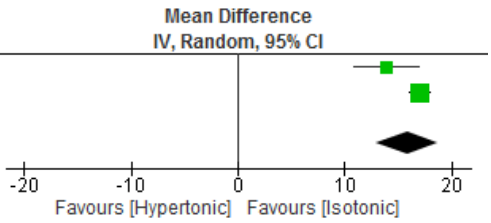
Heterogeneity: Tau² = 3.16; Chi² = 16.73, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 2.26 (P = 0.02)



2.6 Maximum intraoperative serum osmolarity (mOsm/kg H2O): studies at low risk of bias

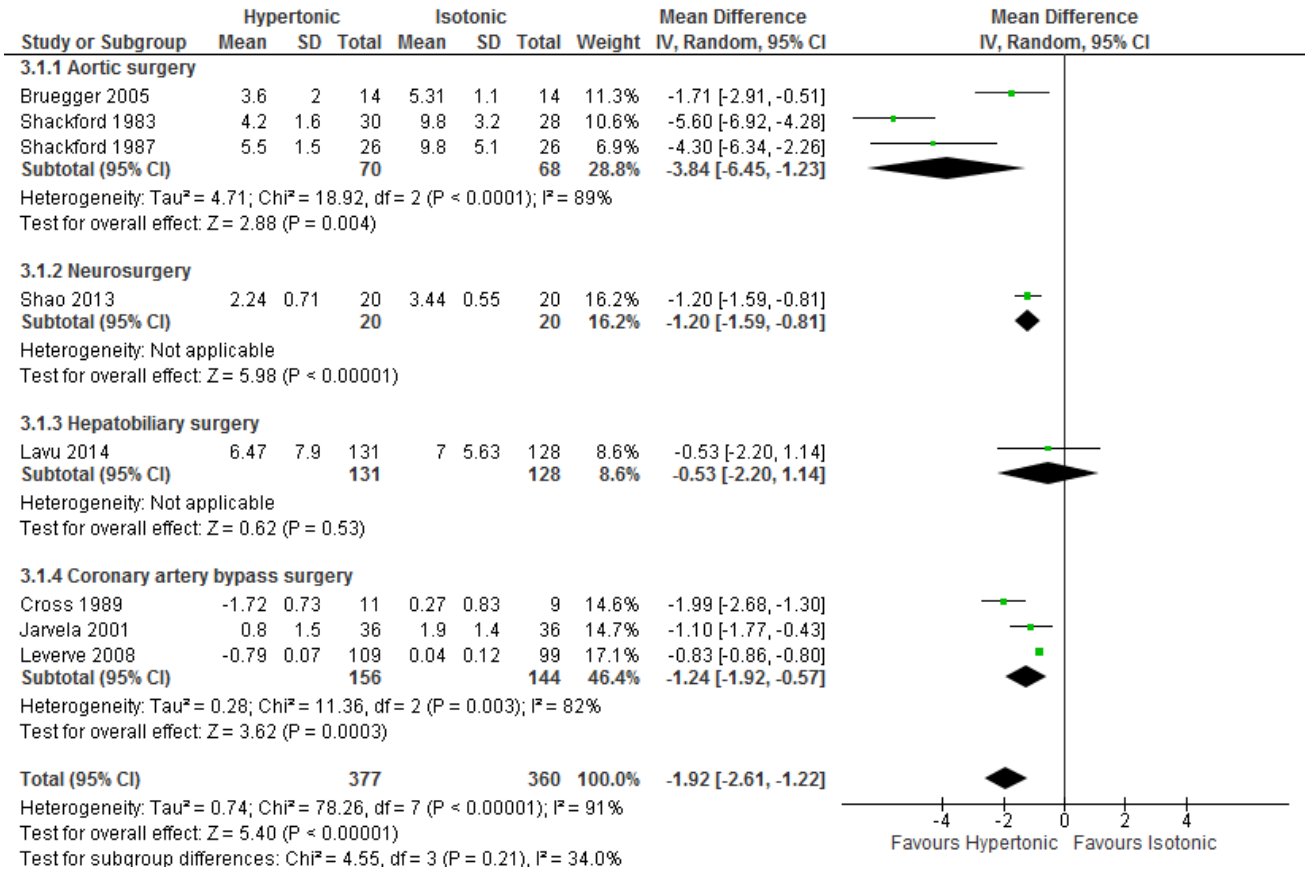
Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kato 1996	298.2	6.1	20	284.3	3.5	20	38.3%	13.90 [10.82, 16.98]
Kølsen-Petersen 2004	302	2	19	285	0.5	20	61.7%	17.00 [16.07, 17.93]
Total (95% CI)			**39**			**40**	**100.0%**	**15.81 [12.86, 18.77]**

Heterogeneity: Tau² = 3.46; Chi² = 3.56, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 10.49 (P < 0.00001)

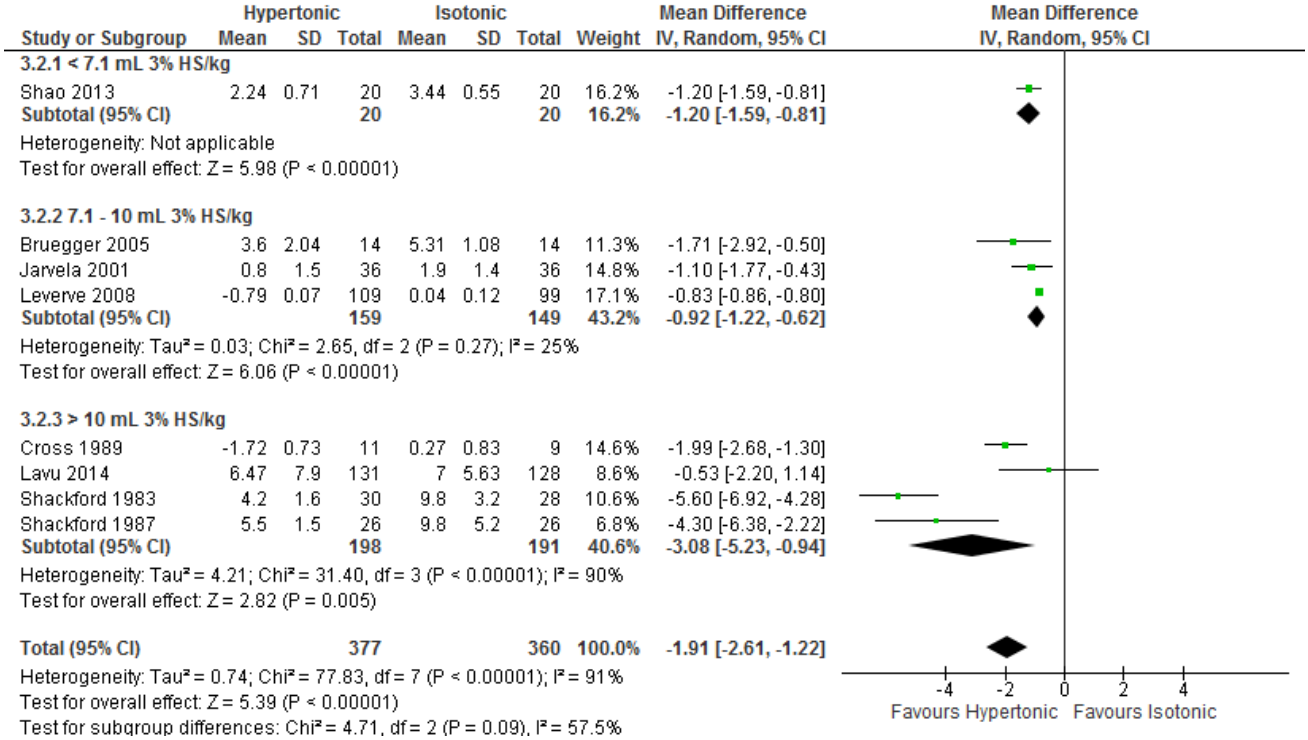


3 - Subgroup analysis - hypertonic salt versus isotonic salt solution for peri-operative resuscitation

3.1 Fluid balance (L) by type of surgery

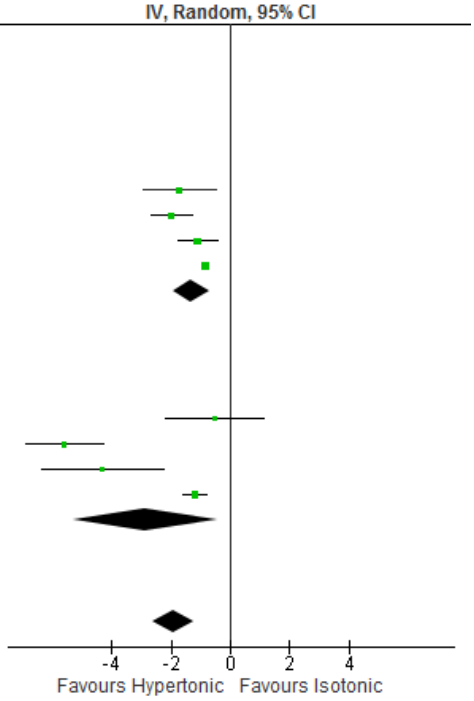


3.2 Fluid balance (L) by dose of HS



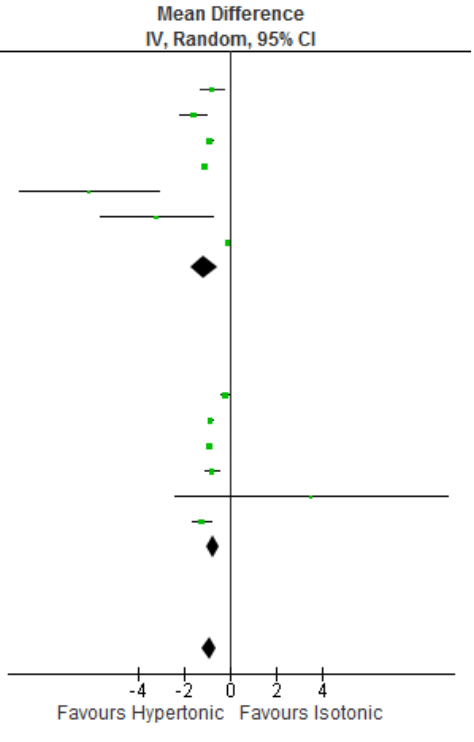
3.3 Fluid balance (L) by volume given to control group

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 < 2000 mL								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.3.2 2000 - 5000 mL								
Bruegger 2005	3.6	2.04	14	5.31	1.08	14	11.3%	-1.71 [-2.92, -0.50]
Cross 1989	-1.72	0.73	11	0.27	0.83	9	14.6%	-1.99 [-2.68, -1.30]
Jarvela 2001	0.8	1.5	36	1.9	1.4	36	14.8%	-1.10 [-1.77, -0.43]
Leverve 2008	-0.79	0.07	109	0.04	0.12	99	17.1%	-0.83 [-0.86, -0.80]
Subtotal (95% CI)			**170**			**158**	**57.8%**	**-1.31 [-1.92, -0.70]**
Heterogeneity: Tau² = 0.27; Chi² = 13.39, df = 3 (P = 0.004); I² = 78%								
Test for overall effect: Z = 4.21 (P < 0.0001)								
3.3.3 > 5000 mL								
Lavu 2014	6.47	7.9	131	7	5.63	128	8.6%	-0.53 [-2.20, 1.14]
Shackford 1983	4.2	1.6	30	9.8	3.2	28	10.6%	-5.60 [-6.92, -4.28]
Shackford 1987	5.5	1.5	26	9.8	5.2	26	6.8%	-4.30 [-6.38, -2.22]
Shao 2013	2.24	0.71	20	3.44	0.55	20	16.2%	-1.20 [-1.59, -0.81]
Subtotal (95% CI)			**207**			**202**	**42.2%**	**-2.87 [-5.29, -0.44]**
Heterogeneity: Tau² = 5.54; Chi² = 47.49, df = 3 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 2.32 (P = 0.02)								
Total (95% CI)			**377**			**360**	**100.0%**	**-1.91 [-2.61, -1.22]**
Heterogeneity: Tau² = 0.74; Chi² = 77.83, df = 7 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 5.39 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.49, df = 1 (P = 0.22), I² = 32.8%								



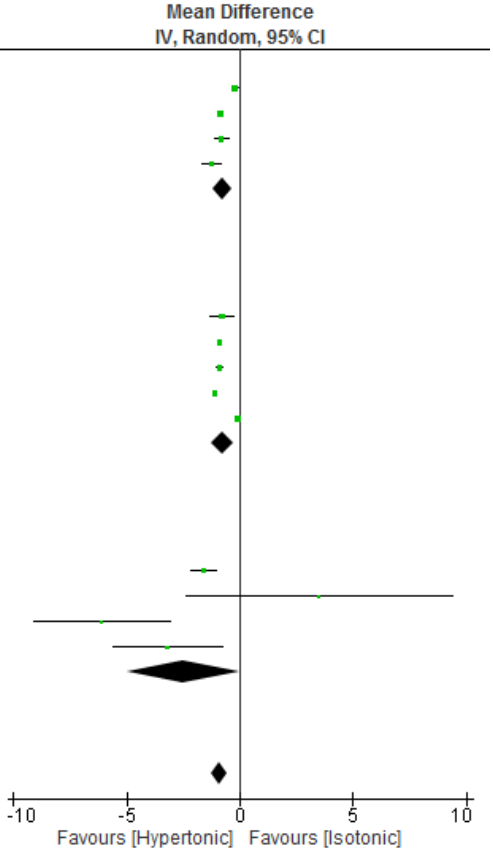
3.4 Total volume of crystalloid administered (L) by type of surgery

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 Cardiovascular surgery								
Bruegger 2005	1.92	0.7	14	2.72	0.68	14	8.3%	-0.80 [-1.31, -0.29]
Cross 1989	4.17	0.41	11	5.77	0.79	9	7.9%	-1.60 [-2.17, -1.03]
Jarvela 2001	0.55	0.18	16	1.44	0.23	16	10.3%	-0.89 [-1.03, -0.75]
Leverve 2008	1.32	0.07	109	2.43	0.12	99	10.5%	-1.11 [-1.14, -1.08]
Shackford 1983	6.4	4.6	30	12.5	6.9	28	1.0%	-6.10 [-9.14, -3.06]
Shackford 1987	6.3	2.4	26	9.5	5.8	26	1.5%	-3.20 [-5.61, -0.79]
Younes 1988	0.7	0.05	18	0.81	0.09	13	10.5%	-0.11 [-0.16, -0.06]
Subtotal (95% CI)			**224**			**205**	**50.1%**	**-1.14 [-1.71, -0.57]**
Heterogeneity: Tau² = 0.43; Chi² = 1070.54, df = 6 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 3.89 (P < 0.0001)								
3.4.2 Non-cardiovascular surgery								
Durasnel 1999	0.39	0.22	24	0.62	0.32	24	10.3%	-0.23 [-0.39, -0.07]
Ishikawa 1996	0.1	0.02	8	0.98	0.15	7	10.4%	-0.88 [-0.99, -0.77]
Jarvela 2000	0.13	0.03	20	1.03	0.16	20	10.4%	-0.90 [-0.97, -0.83]
Kato 1996	0.81	0.35	20	1.62	0.62	20	9.6%	-0.81 [-1.12, -0.50]
Lavu 2014	30.05	30.19	131	26.56	16.27	128	0.3%	3.49 [-2.40, 9.38]
Shao 2013	4.26	0.67	20	5.5	0.68	20	8.9%	-1.24 [-1.66, -0.82]
Subtotal (95% CI)			**223**			**219**	**49.9%**	**-0.78 [-1.05, -0.50]**
Heterogeneity: Tau² = 0.08; Chi² = 67.23, df = 5 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 5.56 (P < 0.00001)								
Total (95% CI)			**447**			**424**	**100.0%**	**-0.91 [-1.24, -0.59]**
Heterogeneity: Tau² = 0.26; Chi² = 1147.77, df = 12 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 5.50 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.7%								



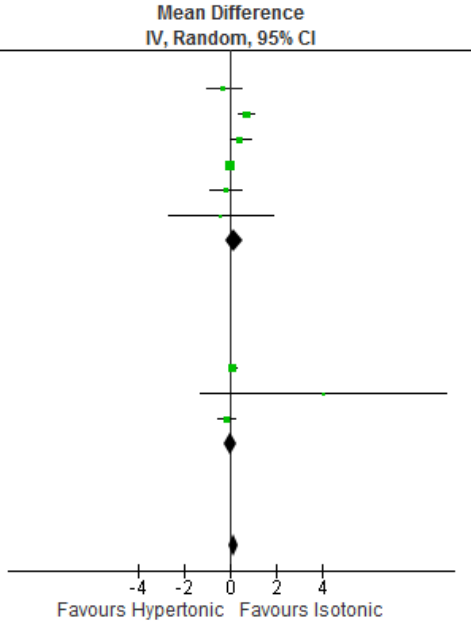
3.5 Total volume of crystalloid administered (L) by dose of HS

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.5.1 < 7.1 mL 3% HS/kg								
Durasnel 1999	0.39	0.22	24	0.62	0.32	24	10.3%	-0.23 [-0.39, -0.07]
Ishikawa 1996	0.1	0.02	8	0.98	0.15	7	10.4%	-0.88 [-0.99, -0.77]
Kato 1996	0.81	0.35	20	1.62	0.62	20	9.6%	-0.81 [-1.12, -0.50]
Shao 2013	4.26	0.67	20	5.5	0.68	20	8.9%	-1.24 [-1.66, -0.82]
Subtotal (95% CI)			**72**			**71**	**39.1%**	**-0.77 [-1.19, -0.35]**
Heterogeneity: Tau² = 0.16; Chi² = 51.94, df = 3 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
3.5.2 7.1 - 10 mL 3% HS/kg								
Bruegger 2005	1.92	0.7	14	2.72	0.68	14	8.3%	-0.80 [-1.31, -0.29]
Jarvela 2000	0.13	0.03	20	1.03	0.16	20	10.4%	-0.90 [-0.97, -0.83]
Jarvela 2001	0.55	0.18	16	1.44	0.23	16	10.3%	-0.89 [-1.03, -0.75]
Leverve 2008	1.32	0.07	109	2.43	0.12	99	10.5%	-1.11 [-1.14, -1.08]
Younes 1988	0.7	0.05	18	0.81	0.09	13	10.5%	-0.11 [-0.16, -0.06]
Subtotal (95% CI)			**177**			**162**	**50.0%**	**-0.76 [-1.25, -0.27]**
Heterogeneity: Tau² = 0.30; Chi² = 1050.31, df = 4 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 3.06 (P = 0.002)								
3.5.3 > 10 mL 3% HS/kg								
Cross 1989	4.17	0.41	11	5.77	0.79	9	7.9%	-1.60 [-2.17, -1.03]
Lavu 2014	30.05	30.19	131	26.56	16.27	128	0.3%	3.49 [-2.40, 9.38]
Shackford 1983	6.4	4.6	30	12.5	6.9	28	1.0%	-6.10 [-9.14, -3.06]
Shackford 1987	6.3	2.4	26	9.5	5.8	26	1.5%	-3.20 [-5.61, -0.79]
Subtotal (95% CI)			**198**			**191**	**10.8%**	**-2.50 [-4.99, -0.02]**
Heterogeneity: Tau² = 4.31; Chi² = 12.55, df = 3 (P = 0.006); I² = 76%								
Test for overall effect: Z = 1.98 (P = 0.05)								
Total (95% CI)			**447**			**424**	**100.0%**	**-0.91 [-1.24, -0.59]**
Heterogeneity: Tau² = 0.26; Chi² = 1147.77, df = 12 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 5.50 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.86, df = 2 (P = 0.40), I² = 0%								



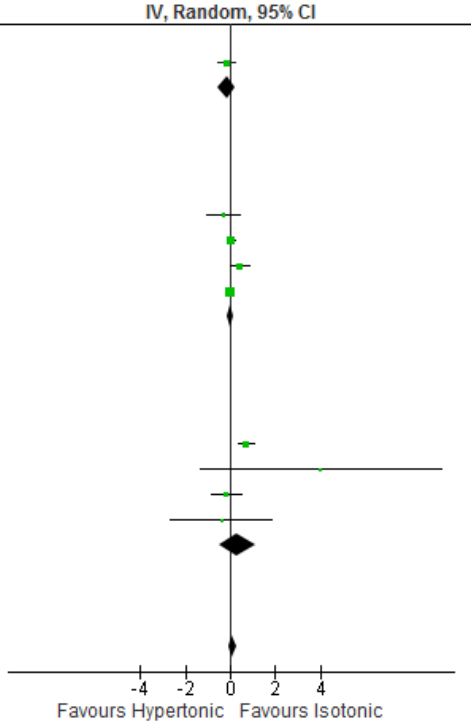
3.6 Diuresis during study period (L) by type of surgery

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.6.1 Cardiovascular surgery								
Bruegger 2005	1.2	0.55	14	1.5	1.33	14	5.7%	-0.30 [-1.05, 0.45]
Cross 1989	4.5	0.5	11	3.8	0.25	9	14.9%	0.70 [0.36, 1.04]
Jarvela 2001	3.36	1.04	36	2.94	0.85	36	11.7%	0.42 [-0.02, 0.86]
Leverve 2008	1.57	0.1	109	1.61	0.15	99	24.9%	-0.04 [-0.08, -0.00]
Shackford 1983	1.6	0.8	30	1.8	1.6	28	7.0%	-0.20 [-0.86, 0.46]
Shackford 1987	0.7	0.7	26	1.1	5.8	26	0.8%	-0.40 [-2.65, 1.85]
Subtotal (95% CI)			**226**			**212**	**65.0%**	**0.15 [-0.22, 0.52]**
Heterogeneity: Tau² = 0.13; Chi² = 23.17, df = 5 (P = 0.0003); I² = 78%								
Test for overall effect: Z = 0.79 (P = 0.43)								
3.6.2 Non-cardiovascular surgery								
Jarvela 2000	0.5	0.28	20	0.43	0.27	20	21.3%	0.07 [-0.10, 0.24]
Lavu 2014	23.58	27.86	131	19.56	13.74	128	0.1%	4.02 [-1.31, 9.35]
Shao 2013	1.43	0.57	20	1.59	0.65	20	13.5%	-0.16 [-0.54, 0.22]
Subtotal (95% CI)			**171**			**168**	**35.0%**	**0.00 [-0.30, 0.30]**
Heterogeneity: Tau² = 0.03; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 0.01 (P = 1.00)								
Total (95% CI)			**397**			**380**	**100.0%**	**0.11 [-0.10, 0.31]**
Heterogeneity: Tau² = 0.04; Chi² = 27.13, df = 8 (P = 0.0007); I² = 71%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%								



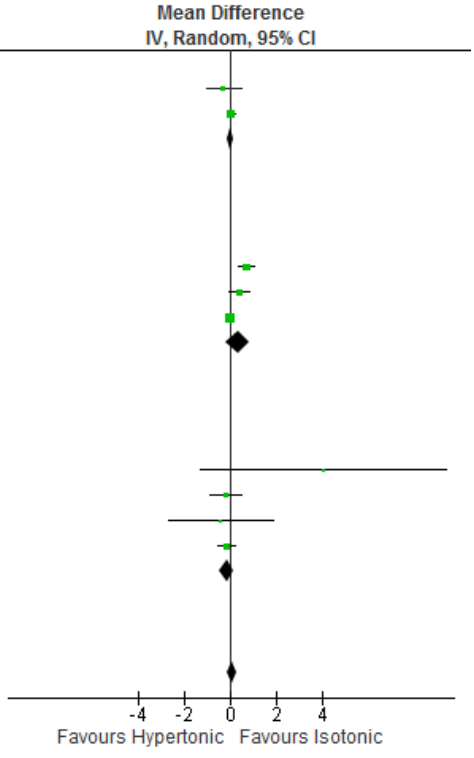
3.7 Diuresis during study period (L) by dose of HS

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.7.1 < 7.1 mL 3% HS/kg								
Shao 2013	1.43	0.57	20	1.59	0.65	20	13.4%	-0.16 [-0.54, 0.22]
Subtotal (95% CI)			**20**			**20**	**13.4%**	**-0.16 [-0.54, 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
3.7.2 7.1 - 10 mL 3% HS/kg								
Bruegger 2005	1.2	0.55	14	1.5	1.33	14	5.6%	-0.30 [-1.05, 0.45]
Jarvela 2000	0.45	0.28	20	0.43	0.27	20	21.6%	0.02 [-0.15, 0.19]
Jarvela 2001	3.35	1.04	36	2.94	0.85	36	11.5%	0.41 [-0.03, 0.85]
Leverve 2008	1.57	0.1	109	1.61	0.15	99	25.3%	-0.04 [-0.08, -0.00]
Subtotal (95% CI)			**179**			**169**	**64.0%**	**0.00 [-0.12, 0.13]**
Heterogeneity: Tau² = 0.01; Chi² = 4.90, df = 3 (P = 0.18); I² = 39%								
Test for overall effect: Z = 0.04 (P = 0.97)								
3.7.3 > 10 mL 3% HS/kg								
Cross 1989	4.5	0.5	11	3.8	0.25	9	14.8%	0.70 [0.36, 1.04]
Lavu 2014	23.58	27.86	131	19.56	13.74	128	0.1%	4.02 [-1.31, 9.35]
Shackford 1983	1.6	0.8	30	1.8	1.6	28	6.8%	-0.20 [-0.86, 0.46]
Shackford 1987	0.7	0.7	26	1.1	5.8	26	0.8%	-0.40 [-2.65, 1.85]
Subtotal (95% CI)			**198**			**191**	**22.6%**	**0.31 [-0.50, 1.11]**
Heterogeneity: Tau² = 0.32; Chi² = 7.98, df = 3 (P = 0.05); I² = 62%								
Test for overall effect: Z = 0.75 (P = 0.46)								
Total (95% CI)			**397**			**380**	**100.0%**	**0.10 [-0.10, 0.30]**
Heterogeneity: Tau² = 0.04; Chi² = 25.99, df = 8 (P = 0.001); I² = 69%								
Test for overall effect: Z = 0.94 (P = 0.35)								
Test for subgroup differences: Chi² = 1.23, df = 2 (P = 0.54), I² = 0%								



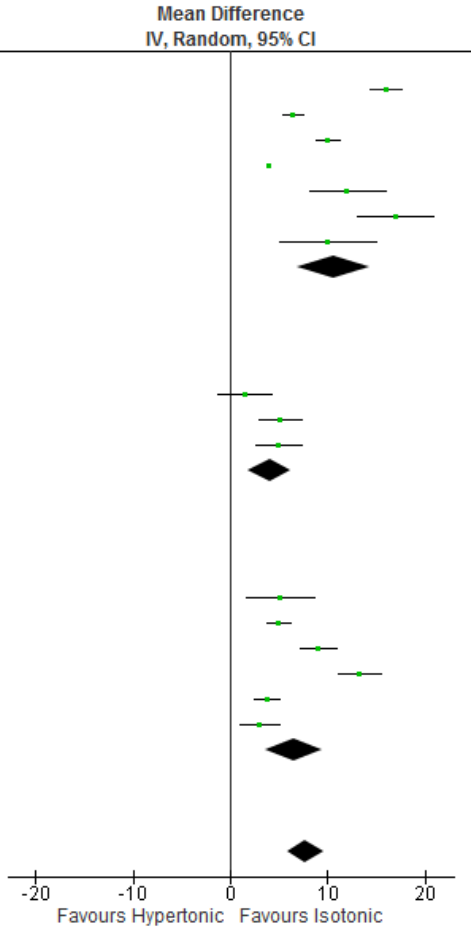
3.8 Diuresis during study period (L) by volume given to control group

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.8.1 < 2000 mL								
Bruegger 2005	1.2	0.55	14	1.5	1.33	14	5.5%	-0.30 [-1.05, 0.45]
Jarvela 2000	0.45	0.28	20	0.43	0.27	20	21.6%	0.02 [-0.15, 0.19]
Subtotal (95% CI)			**34**			**34**	**27.2%**	**0.00 [-0.16, 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
3.8.2 2000 - 5000 mL								
Cross 1989	4.5	0.5	11	3.8	0.25	9	14.8%	0.70 [0.36, 1.04]
Jarvela 2001	3.34	1.04	36	2.94	0.85	36	11.5%	0.40 [-0.04, 0.84]
Leverve 2008	1.57	0.1	109	1.61	0.15	99	25.4%	-0.04 [-0.08, -0.00]
Subtotal (95% CI)			**156**			**144**	**51.8%**	**0.33 [-0.19, 0.85]**
Heterogeneity: Tau² = 0.19; Chi² = 21.96, df = 2 (P < 0.0001); I² = 91%								
Test for overall effect: Z = 1.25 (P = 0.21)								
3.8.3 > 5000 mL								
Lavu 2014	23.58	27.86	131	19.56	13.74	128	0.1%	4.02 [-1.31, 9.35]
Shackford 1983	1.6	0.8	30	1.8	1.6	28	6.8%	-0.20 [-0.86, 0.46]
Shackford 1987	0.7	0.7	26	1.1	5.8	26	0.8%	-0.40 [-2.65, 1.85]
Shao 2013	1.43	0.57	20	1.59	0.65	20	13.4%	-0.16 [-0.54, 0.22]
Subtotal (95% CI)			**207**			**202**	**21.1%**	**-0.16 [-0.48, 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 3 (P = 0.49); I² = 0%								
Test for overall effect: Z = 0.96 (P = 0.34)								
Total (95% CI)			**397**			**380**	**100.0%**	**0.09 [-0.11, 0.30]**
Heterogeneity: Tau² = 0.04; Chi² = 25.81, df = 8 (P = 0.001); I² = 69%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 2.48, df = 2 (P = 0.29), I² = 19.4%								



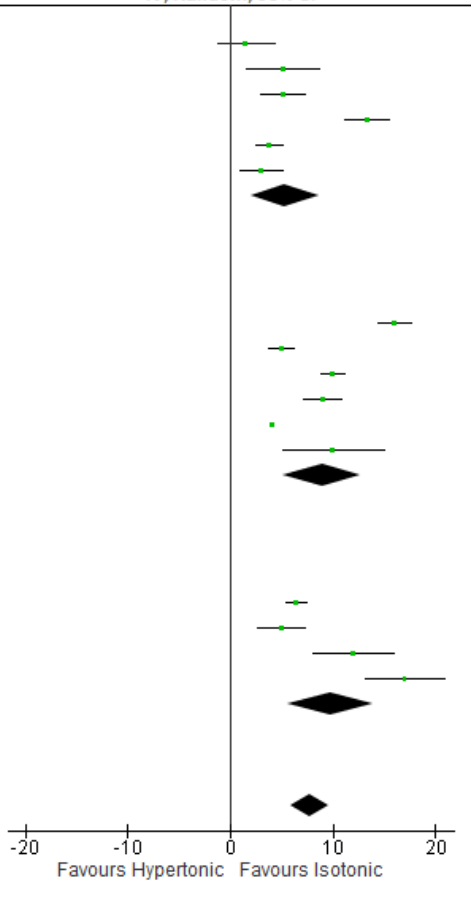
3.9 Peak serum sodium (meq/L) by type of surgery

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.9.1 Cardiovascular surgery								
Bruegger 2005	159	3	14	143	1	14	6.6%	16.00 [14.34, 17.66]
Cross 1989	145.4	1.4	11	139	1	9	6.8%	6.40 [5.35, 7.45]
Jarvela 2001	150	3	36	140	2	36	6.8%	10.00 [8.82, 11.18]
Leverve 2008	140	0.4	109	136	0.4	99	7.0%	4.00 [3.89, 4.11]
Shackford 1983	151	7.6	30	139	7.6	28	5.4%	12.00 [8.09, 15.91]
Shackford 1987	157	7.2	26	140	7.2	26	5.4%	17.00 [13.09, 20.91]
Younes 1988	147	9	18	137	5	13	4.7%	10.00 [5.03, 14.97]
Subtotal (95% CI)			**244**			**225**	**42.7%**	**10.61 [6.91, 14.31]**
Heterogeneity: Tau² = 22.85; Chi² = 378.33, df = 6 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 5.63 (P < 0.00001)								
3.9.2 Transurethral resection of the prostate								
Baraka 1994	138.5	5	17	137	3	16	6.1%	1.50 [-1.29, 4.29]
Kato 1996	145	4.4	20	139.9	2.4	20	6.4%	5.10 [2.90, 7.30]
Kimura 1994	142	1	7	137	3	7	6.3%	5.00 [2.66, 7.34]
Subtotal (95% CI)			**44**			**43**	**18.7%**	**4.01 [1.86, 6.16]**
Heterogeneity: Tau² = 2.06; Chi² = 4.68, df = 2 (P = 0.10); I² = 57%								
Test for overall effect: Z = 3.66 (P = 0.0003)								
3.9.3 Other surgery								
Ishikawa 1996	144.1	3.4	8	139	3.5	7	5.6%	5.10 [1.60, 8.60]
Jarvela 2000	145	2	20	140	2	20	6.8%	5.00 [3.76, 6.24]
Kølsen-Petersen 2004	150	3	19	141	3	20	6.5%	9.00 [7.12, 10.88]
Shao 2013	152.5	4.4	20	139.2	2.1	20	6.4%	13.30 [11.16, 15.44]
Veroli 1992	143.7	1.7	10	139.95	1.8	20	6.8%	3.75 [2.43, 5.07]
Wang 1997	142	5	30	139	3	30	6.4%	3.00 [0.91, 5.09]
Subtotal (95% CI)			**107**			**117**	**38.5%**	**6.52 [3.64, 9.40]**
Heterogeneity: Tau² = 11.78; Chi² = 76.37, df = 5 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.44 (P < 0.00001)								
Total (95% CI)			**395**			**385**	**100.0%**	**7.73 [5.84, 9.62]**
Heterogeneity: Tau² = 13.29; Chi² = 482.15, df = 15 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 8.02 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.40, df = 2 (P = 0.009), I² = 78.7%								



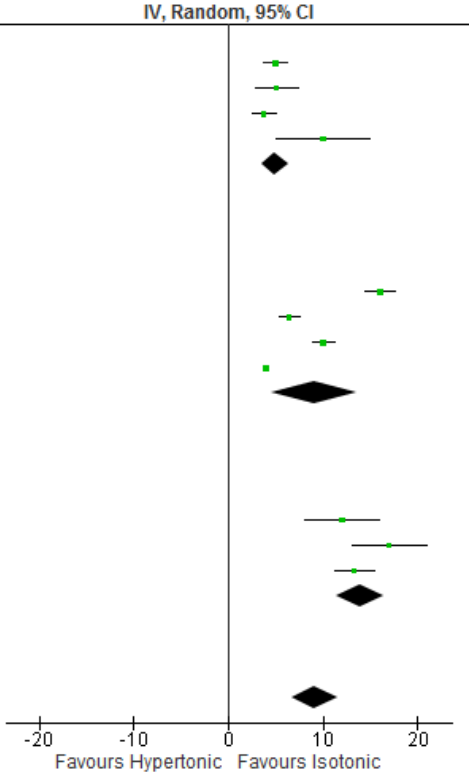
3.10 Peak serum sodium (meq/L) by dose of HS

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.10.1 < 7.1 mL 3% HS/kg								
Baraka 1994	138.5	5	17	137	3	16	6.1%	1.50 [-1.29, 4.29]
Ishikawa 1996	144.1	3.4	8	139	3.5	7	5.6%	5.10 [1.60, 8.60]
Kato 1996	145	4.4	20	139.9	2.4	20	6.4%	5.10 [2.90, 7.30]
Shao 2013	152.5	4.4	20	139.2	2.1	20	6.4%	13.30 [11.16, 15.44]
Veroli 1992	143.7	1.7	10	139.95	1.8	20	6.8%	3.75 [2.43, 5.07]
Wang 1997	142	5	30	139	3	30	6.4%	3.00 [0.91, 5.09]
Subtotal (95% CI)			**105**			**113**	**37.7%**	**5.31 [2.00, 8.63]**
Heterogeneity: Tau² = 15.64; Chi² = 70.87, df = 5 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.14 (P = 0.002)								
3.10.2 7.1 - 10 mL 3% HS/kg								
Bruegger 2005	159	3	14	143	1	14	6.6%	16.00 [14.34, 17.66]
Jarvela 2000	145	2	20	140	2	20	6.8%	5.00 [3.76, 6.24]
Jarvela 2001	150	3	36	140	2	36	6.8%	10.00 [8.82, 11.18]
Kølsen-Petersen 2004	150	3	19	141	3	20	6.5%	9.00 [7.12, 10.88]
Leverve 2008	140	0.4	109	136	0.4	99	7.0%	4.00 [3.89, 4.11]
Younes 1988	147	9	18	137	5	13	4.7%	10.00 [5.03, 14.97]
Subtotal (95% CI)			**216**			**202**	**38.4%**	**8.93 [5.16, 12.70]**
Heterogeneity: Tau² = 20.94; Chi² = 331.09, df = 5 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
3.10.3 > 10 mL 3% HS/kg								
Cross 1989	145.4	1.4	11	139	1	9	6.8%	6.40 [5.35, 7.45]
Kimura 1994	142	1	7	137	3	7	6.3%	5.00 [2.66, 7.34]
Shackford 1983	151	7.6	30	139	7.6	28	5.4%	12.00 [8.09, 15.91]
Shackford 1987	157	7.2	26	140	7.2	26	5.4%	17.00 [13.09, 20.91]
Subtotal (95% CI)			**74**			**70**	**23.9%**	**9.75 [5.50, 13.99]**
Heterogeneity: Tau² = 16.51; Chi² = 35.37, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 4.50 (P < 0.00001)								
Total (95% CI)			**395**			**385**	**100.0%**	**7.73 [5.84, 9.62]**
Heterogeneity: Tau² = 13.29; Chi² = 482.15, df = 15 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 8.02 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.29, df = 2 (P = 0.19), I² = 39.2%								



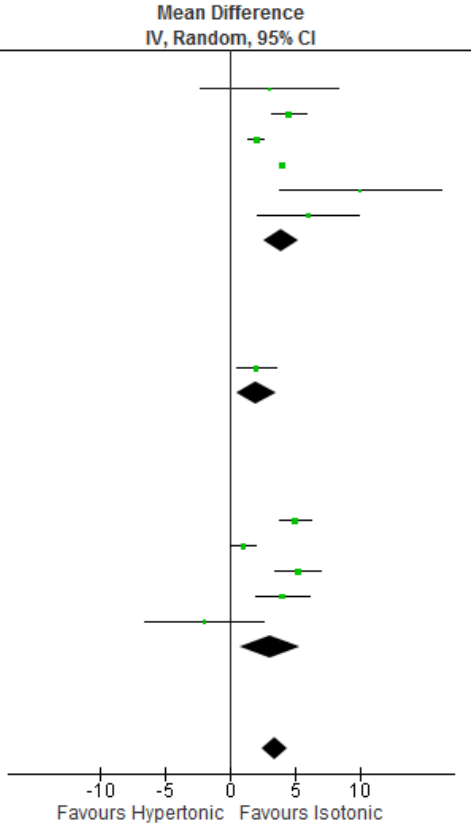
3.11 Peak serum sodium (meq/L) by volume given to control group

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.11.1 < 2000 mL/kg								
Jarvela 2000	145	2	20	140	2	20	9.7%	5.00 [3.76, 6.24]
Kato 1996	145	4.4	20	139.9	2.4	20	9.2%	5.10 [2.90, 7.30]
Veroli 1992	143.7	1.7	10	139.95	1.8	20	9.7%	3.75 [2.43, 5.07]
Younes 1988	147	9	18	137	5	13	7.1%	10.00 [5.03, 14.97]
Subtotal (95% CI)			**68**			**73**	**35.7%**	**4.94 [3.53, 6.34]**
Heterogeneity: Tau² = 1.04; Chi² = 6.72, df = 3 (P = 0.08); I² = 55%								
Test for overall effect: Z = 6.87 (P < 0.00001)								
3.11.2 2000 - 5000 mL								
Bruegger 2005	159	3	14	143	1	14	9.5%	16.00 [14.34, 17.66]
Cross 1989	145.4	1.4	11	139	1	9	9.8%	6.40 [5.35, 7.45]
Jarvela 2001	150	3	36	140	2	36	9.8%	10.00 [8.82, 11.18]
Leverve 2008	140	0.4	109	136	0.4	99	10.0%	4.00 [3.89, 4.11]
Subtotal (95% CI)			**170**			**158**	**39.1%**	**9.05 [4.54, 13.56]**
Heterogeneity: Tau² = 20.85; Chi² = 315.96, df = 3 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 3.93 (P < 0.0001)								
3.11.3 > 5000 mL								
Shackford 1983	151	7.6	30	139	7.6	28	7.9%	12.00 [8.09, 15.91]
Shackford 1987	157	7.2	26	140	7.2	26	7.9%	17.00 [13.09, 20.91]
Shao 2013	152.5	4.4	20	139.2	2.1	20	9.3%	13.30 [11.16, 15.44]
Subtotal (95% CI)			**76**			**74**	**25.2%**	**13.93 [11.44, 16.42]**
Heterogeneity: Tau² = 2.20; Chi² = 3.59, df = 2 (P = 0.17); I² = 44%								
Test for overall effect: Z = 10.95 (P < 0.00001)								
Total (95% CI)			**314**			**305**	**100.0%**	**9.10 [6.66, 11.53]**
Heterogeneity: Tau² = 15.47; Chi² = 451.49, df = 10 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 7.32 (P < 0.00001)								
Test for subgroup differences: Chi² = 38.57, df = 2 (P < 0.00001), I² = 94.8%								



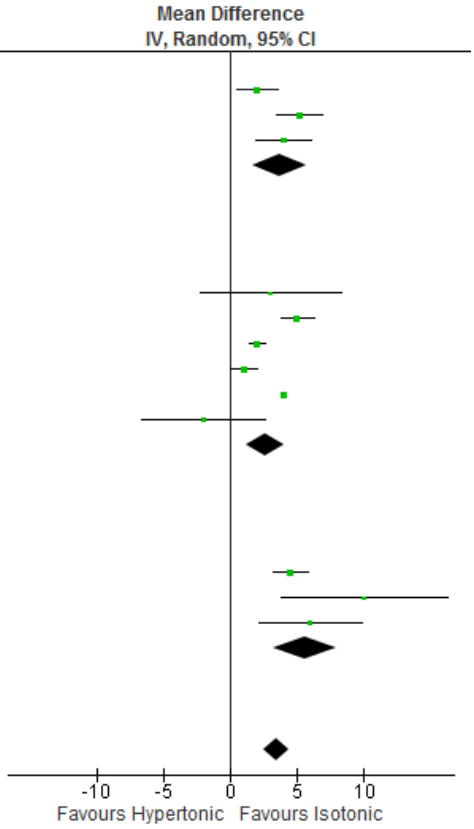
3.12 Final serum sodium (meq/L) by type of surgery

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.12.1 Cardiovascular surgery								
Bruegger 2005	143	5.3	6	140	4	6	2.7%	3.00 [-2.31, 8.31]
Cross 1989	144	2	11	139.5	1	9	10.7%	4.50 [3.15, 5.85]
Jarvela 2001	141	1	20	139	1	20	12.7%	2.00 [1.38, 2.62]
Leverve 2008	140	0.4	109	136	0.4	99	13.3%	4.00 [3.89, 4.11]
Shackford 1983	146	7.6	30	136	15.2	28	2.1%	10.00 [3.75, 16.25]
Shackford 1987	145	7.2	26	139	7.2	26	4.3%	6.00 [2.09, 9.91]
Subtotal (95% CI)			**202**			**188**	**45.9%**	**3.91 [2.55, 5.28]**
Heterogeneity: Tau² = 1.61; Chi² = 44.24, df = 5 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 5.62 (P < 0.00001)								
3.12.2 Transurethral resection of prostate								
Kato 1996	140.6	2.6	20	138.6	2.4	20	10.1%	2.00 [0.45, 3.55]
Subtotal (95% CI)			**20**			**20**	**10.1%**	**2.00 [0.45, 3.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.53 (P = 0.01)								
3.12.3 Other surgery								
Jarvela 2000	145	2	20	140	2	20	11.0%	5.00 [3.76, 6.24]
Kølsen-Petersen 2004	139	2	19	138	1	20	11.8%	1.00 [-0.00, 2.00]
Shao 2013	141.5	2.5	20	136.3	3.1	20	9.4%	5.20 [3.45, 6.95]
Wang 1997	142	5	30	138	3	30	8.4%	4.00 [1.91, 6.09]
Younes 1988	136	7	18	138	6	13	3.4%	-2.00 [-6.59, 2.59]
Subtotal (95% CI)			**107**			**103**	**44.0%**	**3.05 [0.77, 5.32]**
Heterogeneity: Tau² = 5.51; Chi² = 36.89, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.63 (P = 0.009)								
Total (95% CI)			**329**			**311**	**100.0%**	**3.45 [2.46, 4.44]**
Heterogeneity: Tau² = 1.90; Chi² = 94.45, df = 11 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 6.84 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.30, df = 2 (P = 0.19), I² = 39.4%								



3.13 Final serum sodium (meq/L) by dose of HS

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.13.1 < 7.1 mL 3% HS/kg								
Kato 1996	140.6	2.6	20	138.6	2.4	20	10.1%	2.00 [0.45, 3.55]
Shao 2013	141.5	2.5	20	136.3	3.1	20	9.4%	5.20 [3.45, 6.95]
Wang 1997	142	5	30	138	3	30	8.4%	4.00 [1.91, 6.09]
Subtotal (95% CI)			**70**			**70**	**27.9%**	**3.69 [1.70, 5.68]**
Heterogeneity: Tau² = 2.25; Chi² = 7.45, df = 2 (P = 0.02); I² = 73%								
Test for overall effect: Z = 3.64 (P = 0.0003)								
3.13.2 7.1 - 10 mL 3% HS/kg								
Bruegger 2005	143	5.3	6	140	4	6	2.7%	3.00 [-2.31, 8.31]
Jarvela 2000	145	2	20	140	2	20	11.0%	5.00 [3.76, 6.24]
Jarvela 2001	141	1	20	139	1	20	12.7%	2.00 [1.38, 2.62]
Kølsen-Petersen 2004	139	2	19	138	1	20	11.8%	1.00 [-0.00, 2.00]
Leverve 2008	140	0.4	109	136	0.4	99	13.3%	4.00 [3.89, 4.11]
Younes 1988	136	7	18	138	6	13	3.4%	-2.00 [-6.59, 2.59]
Subtotal (95% CI)			**192**			**178**	**55.0%**	**2.63 [1.17, 4.10]**
Heterogeneity: Tau² = 2.37; Chi² = 81.05, df = 5 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
3.13.3 > 10 mL 3% HS/kg								
Cross 1989	144	2	11	139.5	1	9	10.7%	4.50 [3.15, 5.85]
Shackford 1983	146	7.6	30	136	15.2	28	2.1%	10.00 [3.75, 16.25]
Shackford 1987	145	7.2	26	139	7.2	26	4.3%	6.00 [2.09, 9.91]
Subtotal (95% CI)			**67**			**63**	**17.1%**	**5.56 [3.16, 7.96]**
Heterogeneity: Tau² = 1.93; Chi² = 3.19, df = 2 (P = 0.20); I² = 37%								
Test for overall effect: Z = 4.54 (P < 0.00001)								
Total (95% CI)			**329**			**311**	**100.0%**	**3.45 [2.46, 4.44]**
Heterogeneity: Tau² = 1.90; Chi² = 94.45, df = 11 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 6.84 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.22, df = 2 (P = 0.12), I² = 52.6%								



3.14 Final serum sodium (meq/L) by volume given to control group

Study or Subgroup	Hypertonic Mean	SD	Total	Isotonic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.14.1 < 2000 mL								
Jarvela 2000	145	2	20	140	2	20	15.6%	5.00 [3.76, 6.24]
Kato 1996	140.6	2.6	20	138.6	2.4	20	14.7%	2.00 [0.45, 3.55]
Younes 1988	136	7	18	138	6	13	6.3%	-2.00 [-6.59, 2.59]
Subtotal (95% CI)			**58**			**53**	**36.6%**	**2.32 [-0.74, 5.39]**
Heterogeneity: Tau² = 5.73; Chi² = 14.70, df = 2 (P = 0.0006); I² = 86%								
Test for overall effect: Z = 1.49 (P = 0.14)								
3.14.2 2000 - 5000 mL								
Bruegger 2005	143	5.3	6	140	4	6	5.2%	3.00 [-2.31, 8.31]
Cross 1989	144	2	11	139.5	1	9	15.3%	4.50 [3.15, 5.85]
Jarvela 2001	141	1	20	139	1	20	17.1%	2.00 [1.38, 2.62]
Subtotal (95% CI)			**37**			**35**	**37.6%**	**3.14 [1.02, 5.27]**
Heterogeneity: Tau² = 2.40; Chi² = 10.92, df = 2 (P = 0.004); I² = 82%								
Test for overall effect: Z = 2.90 (P = 0.004)								
3.14.3 > 5000 mL								
Shackford 1983	146	7.6	30	136	15.2	28	4.1%	10.00 [3.75, 16.25]
Shackford 1987	145	7.2	26	139	7.2	26	7.7%	6.00 [2.09, 9.91]
Shao 2013	141.5	2.5	20	136.3	3.1	20	14.0%	5.20 [3.45, 6.95]
Subtotal (95% CI)			**76**			**74**	**25.8%**	**5.70 [3.98, 7.43]**
Heterogeneity: Tau² = 0.25; Chi² = 2.14, df = 2 (P = 0.34); I² = 7%								
Test for overall effect: Z = 6.48 (P < 0.00001)								
Total (95% CI)			**171**			**162**	**100.0%**	**3.73 [2.29, 5.17]**
Heterogeneity: Tau² = 3.06; Chi² = 44.06, df = 8 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 5.08 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.28, df = 2 (P = 0.07), I² = 62.1%