Hypertonic saline for peri-operative fluid management (Review)

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[Intervention Review]

Hypertonic saline for peri-operative fluid management

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ABSTRACT

Background

Fluid excess may place patients undergoing surgery at risk for various complications. Hypertonic saline (HS) maintains intravascular volume with less intravenous fluid than isotonic salt (IS) solutions, but may increase serum sodium.

Objectives

To determine the benefits and harms of HS versus IS solutions administered to patients undergoing surgery.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library*) Issue 1, 2009; MEDLINE (1966 to 2009); EMBASE (1980 to 2009); LILACS (to August 2009) and CINAHL (1982 to 2009) without language restrictions.

Selection criteria

We included randomized clinical trials where HS was compared to IS in patients undergoing surgery, irrespective of blinding, language, and publication status.

Data collection and analysis

We assessed the impact of HS administration on mortality, organ failure, fluid balance, serum sodium, serum osmolarity, diuresis and physiologic measures of cardiovascular function. We pooled data using odds ratio or mean difference (MD) for binary and continuous outcomes, respectively, using random-effects models.

Main results

We included 15 studies with 614 participants. One death in each group and no other serious adverse events were reported. While all patients were in a positive fluid balance postoperatively, the excess was significantly less in HS patients (standardized mean difference (SMD) -1.43L, 95% confidence interval (CI) 0.8 to 2.1 L less; P < 0.00001). Patients treated with HS received significantly less fluid than IS-treated patients (MD -2.4L 95% (CI) 1.5 to 3.2 L less; P < 0.00001) without differences in diuresis between the groups. Maximum intraoperative cardiac index was significantly increased with HS (SMD 0.6 L/min/M2 higher, 95% CI 0.1 to 1.0, P = 0.02) but Intraoperative pulmonary artery wedge pressure remained unchanged. While the maximum serum sodium and the serum sodium at the end of the study were significantly higher in HS patients, the level remained within normal limits (136 to 146 meq/L).

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Authors' conclusions

HS reduces the volume of intravenous fluid required to maintain patients undergoing surgery but transiently increases serum sodium. It is not known if HS effects patient survival and morbidity but it should be tested in randomized clinical trials that are designed and powered to test these outcomes.

PLAIN LANGUAGE SUMMARY

Hypertonic saline for peri-operative fluid management

Patients usually require intravenous fluids during surgery. Sometimes large volumes of fluid are given during operations in order to maintain adequate blood pressure, but these volumes may leave patients with an excessive fluid load in the post-operative period. Hypertonic saline has a higher sodium concentration than isotonic solutions which have concentrations similar to the blood stream. Hypertonic saline might benefit patients undergoing surgery by reducing the total volume of fluid required. This review includes 15 trials comparing hypertonic saline to isotonic saline in patients undergoing surgery. These trials suggests that less fluid is required for maintenance of arterial blood pressure and blood volume in these patients during surgery if hypertonic saline is given. Kidney function was good in both groups but the serum sodium was higher in patients given hypertonic saline. The trials were too small to see important differences in patient survival or organ failure.

BACKGROUND

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 saline (HS) administration have been demonstrated in experimental and clinical studies (Kolsen-Petersen 2004; Rizoli 2006). Several randomized clinical trials (RCTs) of HS resuscitation in critically ill patients have been performed. A systematic review of HS compared to isotonic solution 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).

Standard perioperative care includes isotonic salt (IS) solution administration to counter conditions which may cause transient intra-operative 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 solution has been shown to increase the weight of patients undergoing elective major surgery by an average of three to six kilograms (kg) (Grocott 2005). While most patients tolerate the additional fluid well, postoperative improvement or reversal of the conditions outlined above may place patients with compromised cardiovascular or renal function at increased risk for development of pulmonary oedema. Patients without cardiovascular or renal risk factors may also be adversely affected by perioperative fluid gain. A recent RCT demonstrated that perioperative fluid restriction resulted in fewer major or minor postoperative complications compared to traditional care in 172 adult patients 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 patients at risk for cardiac or cerebral ischaemia. Indeed supplemental perioperative fluid administration has been shown to improve tissue oxygenation (Arkilic 2003).

HS has the potential to reduce the total volume of fluid administered during operative procedures by allowing patients to draw fluid from the interstitium (and other body compartments) to counter perioperative 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). Notwith-

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standing, several risks have been associated with HS including the potential hypernatraemia, metabolic acidosis and vasodilatation. Several RCTs of prophylactic HS administration in the perioperative 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 perioperative fluid management.

OBJECTIVES

To determine the benefits and harms of HS versus IS solutions administered to patients 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 operative procedures, regardless of language or publication status.

Types of participants

We included patients undergoing any surgical procedures.

Types of interventions

We included perioperative 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 nonsurgical patient populations (burns, trauma and head injury).

Types of outcome measures

Primary outcomes

1. Mortality
2. Organ failure. Organ failure was recorded if it was so defined by each trial or if any of the following occurred: 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). For studies that only reported weight change, we applied a conversion factor, wherein 1 kg = 1 L, to calculate fluid balance.
4. Total volume of intravenous fluid
5. Perioperative diuresis
6. Maximum serum sodium concentration in the perioperative period
7. Final serum sodium
8. Duration of endotracheal intubation after operation
9. Duration of stay in intensive care after operation
10. Duration of stay in hospital after operation
11. We recorded any reported serious adverse events such as myocardial infarction, cerebrovascular accidents or central pontine myelinolysis.

Other outcomes

12. We collected data regarding actual fluid balance, serum osmolarity and perioperative haemodynamic parameters if they were reported by individual trials.

Search methods for identification of studies

Electronic searches

We searched the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library* Issue 1, 2009); MEDLINE (1966 to August 2009); EMBASE (1980 to 2009 week 18); CINAHL (1982 to August 2009 week 1) and LILACS (to August 2009) for RCTs comparing hypertonic and balanced salt solution administration in the perioperative period. 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 April 2007. We updated this search to August 2009 (see Appendix 6).
We limited the publication types to clinical trials, controlled clinical trials, RCTs, multi-centre studies and meta-analyses.
In addition we searched trial registries including http://clinicaltrials.gov/, http://www.controlled-trials.com/ and http://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.
We did not apply any language restrictions.

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Searching other resources

We hand searched 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

Trial identification

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

Data abstraction

Data were abstracted independently by at least two of the authors from the studies using standardized forms developed for this review. We wrote to primary study authors for information regarding missing data or data that was 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 using a standardized form.

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

1. patients (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).

If standard error of the mean was recorded in a study, we converted it to standard deviation.

Methodological quality

We followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We used Review Manager Version 5.0(RevMan 5.0). We assessed factors related to applicability of findings, validity of individual studies, and certain design characteristics that affect interpretation of results, including double-blinding and adherence to the intention-to-treat principle. We evaluated the included studies for selection, performance, attrition and detection bias. All three authors independently assessed the methodological quality of the included studies including the generation of allocation sequence (evaluated adequate (if the allocation sequence was generated by a computer or random number table), unclear (if the trial was described as randomized, but the method used for the allocation sequence generation was not described) or inadequate (if a system involving dates, names, or admittance numbers were used)), allocation concealment (evaluated as A (adequate), B (unclear), C (inadequate) or D (not used)) and adherence to the intention-to-treat principle. We resolved differences of opinion through discussion until consensus was achieved.

Analysis

We assessed statistical heterogeneity using the I^2 statistic (Higgins 2002). We used a random-effects model anticipating between study, as well as within study, heterogeneity (DerSimonian 1986). We performed subgroup analyses where appropriate. We summarized dichotomous and continuous outcomes using the odds ratio (OR) and mean difference (using the inverse variance method), respectively. We calculated an overall standardized mean difference (SMD).

We performed subgroup analysis, where appropriate, by calculation of an OR or SMD in each subgroup and examination of the 95% confidence intervals (CI). A lack of overlap between two CI in the subgroup analyses was interpreted to represent a statistically significant difference. We conducted all analyses using the intention-to-treat principle where possible. If analysis based on this principle was not possible, we stated this clearly.

Sensitivity analyses

We performed sensitivity analyses for missing data and study quality.

Missing data: We employed sensitivity analyses using different approaches for imputing missing data. For the best-case scenario we assumed that none of the originally enrolled patients missing from the primary analysis in the treatment group developed the negative outcome of interest, whilst all those missing from the control group did. For the worst-case scenario we assumed the converse.

Study quality: We performed analysis based on the presence or absence of a reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors.

Subgroup analysis

When appropriate after consideration of statistical and clinical heterogeneity, we performed subgroup analyses based on:

1. operation type
2. dose of HS (trials were stratified into three comparisons according to the dose of HS which was calculated as the volume of 3% HS required to give the same amount of sodium: 7 ml/kg or less (comparison 01); 7.1 - 10 ml/kg (comparison 02); > 10

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ml/kg (comparison 03). These dose stratifications were chosen 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 patients: < 2 L (comparison 01); 2 L to 5 L (comparison 02); > 5 L (comparison 03). These volume stratifications were chosen in advance of the review on the basis of an anticipated range of peri-operative fluid administration)

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

From 215 potential reports identified by the initial search strategy, 18 reports met the criteria for further assessment (Figure 1). Of these 18 references, we excluded three studies after detailed review because they were not randomized (Auler 1987; Shao 2005) or did not report any of the outcomes of interest (Auler 1992) (see Characteristics of excluded studies). No ongoing or recently completed studies were identified in registries of clinical trials including http://clinicaltrials.gov/; http://www.controlled-trials.com/; and http://www.ifpma.org/clinicaltrials.html.

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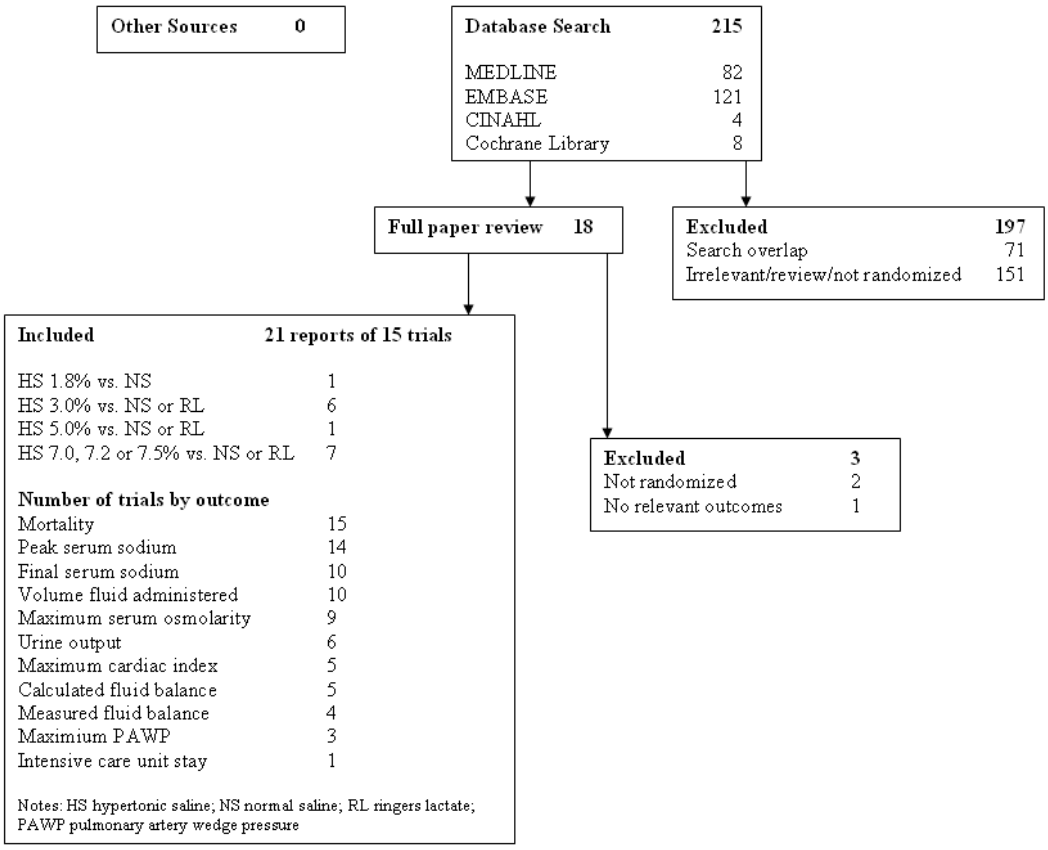
Figure 1. Searching results



Fifteen studies including 614 participants met our inclusion criteria (Baraka 1994; Bruegger 2005; Cross 1989; Durasnel 1999; Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kolsen-Petersen 2004; Shackford 1983; Shackford 1987; 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 (two trials) (Cross 1989; Jarvela 2001); hysterectomy (one trial) (Kolsen-Petersen 2004); hernia repair (one trial) (Wang 1997); general surgery (one trial) (Durasnel 1999). Anaesthetic techniques included: general anaesthesia (eight trials) (Bruegger 2005; Cross 1989; Jarvela 2001; Kato 1996; Kolsen-Petersen 2004; Shackford 1983; Shackford 1987; 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 nine countries. 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 included studies had small sample sizes, enrolling between 20 and 72 patients. The interval between the first and last study was approximately 22 years (1983 to 2005). None of the studies were designed to determine differences in mortality but instead focused on fluid and haemodynamic measurement during the perioperative period. Follow-up extended into the postoperative period in eight trials (Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Kato 1996; Kolsen-Petersen 2004; Shackford 1983; Shackford 1987) for durations ranging from the stay in the recovery unit to the hospital stay while the other trials confined their observations to the period of anaesthesia. Two studies reported results with standard error which were converted to standard deviation by multiplica-

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tion with the square root of the number in the group (Shackford 1983; Shackford 1987).

Risk of bias in included studies

Randomization

Randomization procedures were described in all but four trials (Ishikawa 1996; Kimura 1994; Wang 1997; Younes 1988). Adequate allocation concealment was reported in one trial (Kolsen-Petersen 2004). We verified the adequacy of allocation concealment in two further trials (Jarvela 2000; Jarvela 2001) through correspondence with the principal investigator. We could not reliably assess allocation concealment from the published reports of the remaining studies.

Participant baseline characteristics

Baseline parameters were reported in each study and appeared to be similar in both study groups in all trials.

Blinding

All studies blinded therapy to participants and investigators.

Compliance with protocol

Of the 614 enrolled participants, 607 completed the protocol. Three participants in the HS group failed to complete the study, one because of consent withdrawal (Kolsen-Petersen 2004); one for an anaphylactic reaction to another medication (Kolsen-Petersen 2004); and one without a reason specified (Durasnel 1999). Three participants in the IS group failed to complete the protocol, one because of an urgent return to the operating room for control of haemorrhage (Kolsen-Petersen 2004); one because of a transfer to another hospital (Kolsen-Petersen 2004) and one without a reason specified (Durasnel 1999). One enrolled patient failed to complete the protocol but neither the reason nor the group were specified (Ishikawa 1996).

Intention-to-treat analysis

No patients who completed the protocol were lost to follow up and intention-to-treat analysis was used in all studies.

Effects of interventions

Primary outcomes

1. Mortality

All trials were presumed to have reported all deaths because other outcomes such as serum sodium were reported at the end of the study period. Only two deaths were reported by the included trials for an overall survival rate of 99.7%. Both deaths occurred in one trial, one in each group (Shackford 1983).

2. Organ failure

No episodes of organ failure were reported by any of the included trials.

Secondary outcomes

3. Fluid balance

(Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5)

Perioperative fluid balance was calculated in five trials with 230 participants (Bruegger 2005; Cross 1989; Jarvela 2001; Shackford 1983; Shackford 1987). Overall, the fluid balance was positive in both groups but this positive balance was significantly less with HS administration than with IS administration (SMD -1.43L, 95% confidence interval (CI) 0.8 to 2.1 L less; $P < 0.00001$; $I^2 = 76\%$). Subgroup analysis suggested no significant effect of the type of surgery (Analysis 3.1), dose of HS given (Analysis 3.2), the total volume of fluid transfused (Analysis 3.3) or study quality (Analysis 3.4). Actual fluid balance (Analysis 3.5) was reported by four trials with 158 participants (Bruegger 2005; Cross 1989; Shackford 1983; Shackford 1987). The positive fluid balance was significantly less in the HS group compared to the IS group (SMD -1.63L, 95% CI 0.9 to 2.3L less; $P < 0.00001$; $I^2 = 69\%$), a result almost identical to the calculated balance.

4. Intravenous fluid volume administered

(Analysis 4.1; Analysis 4.2; Analysis 4.3)

The volume of intravenous fluid administered to patients was reported in six trials with 270 patients (Bruegger 2005; Cross 1989; Jarvela 2001; Shackford 1983; Shackford 1987) Patients in the HS group received considerably less fluid intravenously than patients in the IS groups (SMD -2.4L 95% (CI) 1.5 to 3.2 less; $P < 0.00001$; $I^2 = 90\%$). The high degree of heterogeneity for this outcome was not explained by subgroup analysis according to type of surgery (Analysis 4.1) or the dose of HS (Analysis 4.2). Funnel plot analysis showed this outcome to cluster symmetrically (Figure 2) except for two outliers from studies (Shackford 1983, Shackford 1987) that used considerably more HS than other trials. However, exclusion of these two trials from the analysis did not eliminate heterogeneity. Total fluid transfusion in IS groups exceeded that in HS groups for each subgroup analysed. Sensitivity analysis by

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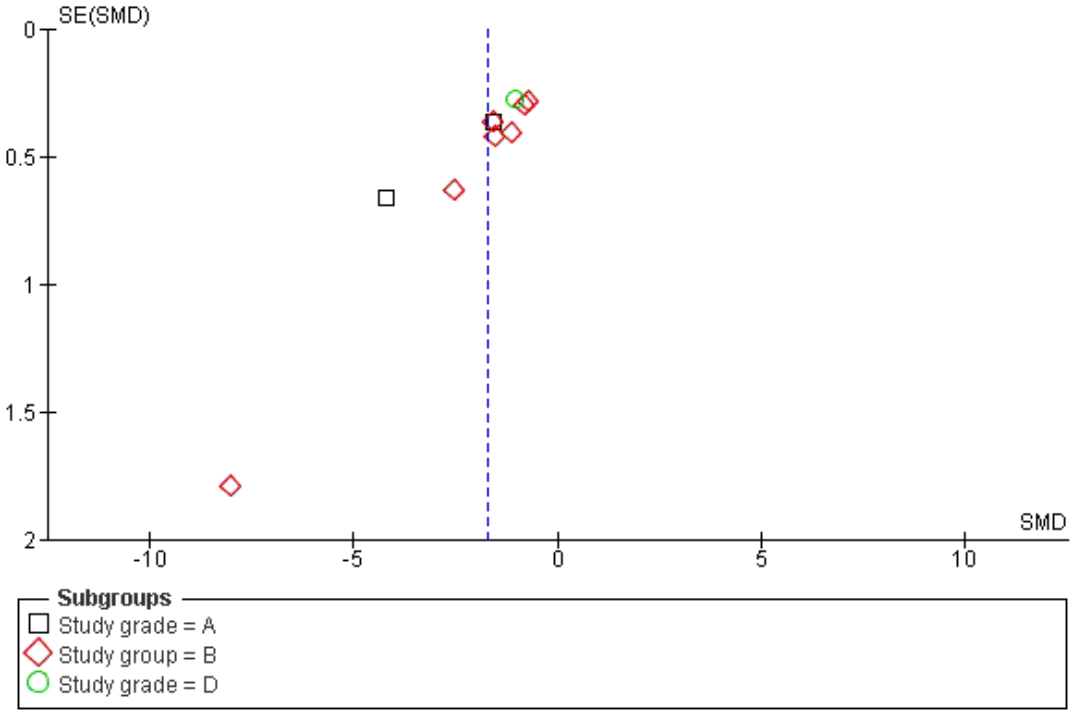
study quality (Analysis 4.3) did not alter the outcome. No heterogeneity was seen in the two studies where quality was graded as A but it was present in the other groups.

Figure 2. Funnel plot of comparison: 4 Total volume of crystalloid administered (L), outcome: 4.3 Volume of crystalloid administered (sensitivity analysis by study quality).



5. Perioperative diuresis

(Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5)

Urine output during the trial was reported in six trials including 270 participants (Bruegger 2005; Cross 1989; Jarvela 2000; Jarvela 2001; Shackford 1983; Shackford 1987). There was no difference in perioperative urine output between the two groups;(Analysis 5.1 SMD +0.2 L, (95% CI -0.2 to +0.6), P = 0.78, I^2 = 68%). Stratification by type of surgery (Analysis 5.1) or dose of HS (Analysis 5.2) did not affect the degree of heterogeneity. However heterogeneity was eliminated when the trials were stratified by the total volume of crystalloid use in the IS group (Analysis 5.4). Sensitivity analysis by study quality (Analysis 5.5) did not change the outcome or the heterogeneity of the studies.

6. Maximum serum sodium

(Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4)

The maximum serum sodium was measured in all of the trials except one (Durasnel 1999), and included 532 participants. Maximum serum sodium was higher in the HS group than the IS group (SMD +2.24 meq/L more with HS, 95% CI 1.6 to 2.9, P < 0.00001, I^2 = 88%). The maximum serum sodium ranged between 136 and 159 in HS groups compared to between 137 and 143 meq/L in the IS groups. The maximum serum sodium was higher with HS in each subgroup. Subgroup analysis by type of surgery (Analysis 6.1) or by volume of crystalloid administered (Analysis 6.3) did not alter the outcome or the heterogeneity between trials. Stratification of subgroups by dose of HS (Analysis 6.2) showed the increase in peak serum sodium with HS to be related to the dose of HS administered (MD +3.6 meq/L, 95%

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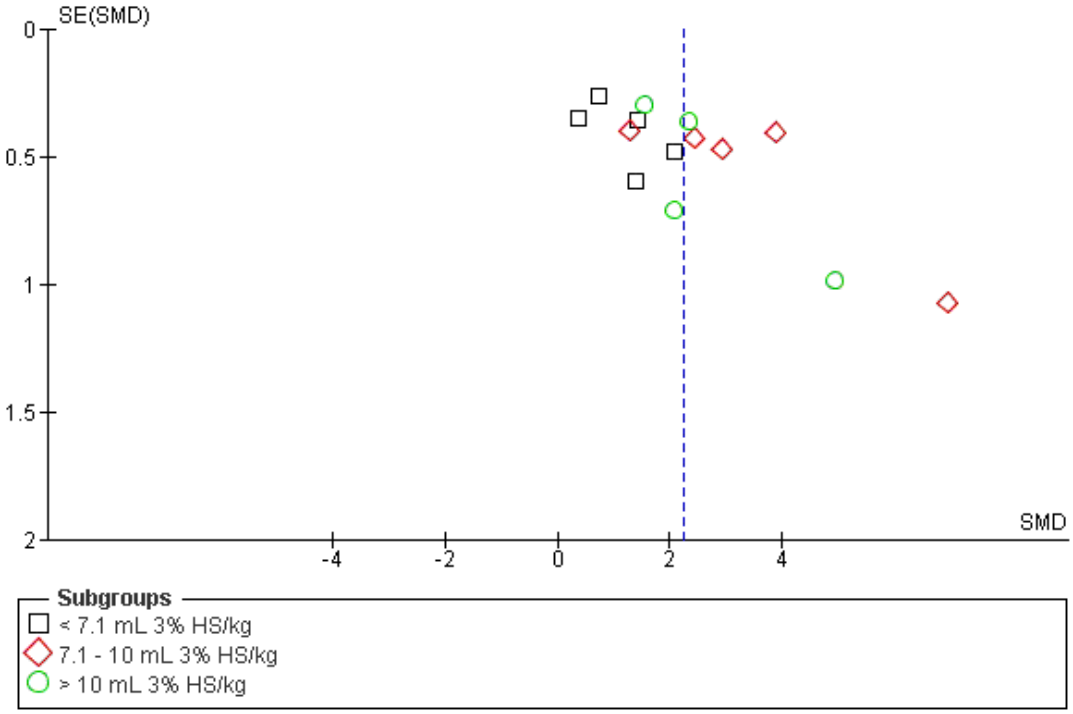
CI 2.6 to 4.8 where the dose equivalent of 3% HS was 7 ml/kg or less compared to MD +9.98 meq/L, 95% CI 6.1 to 13.9 where dose was > 7 ml 3% HS/kg). Funnel plot analysis which showed peak serum sodium of each study to cluster symmetrically around a positive MD in the HS group illustrates the relationship between dose of HS and increase in peak sodium (Figure 3). Sensitivity analysis by study quality did not change the outcome or the heterogeneity of the studies (Analysis 6.4).

Figure 3. Funnel plot of comparison: 6 Peak serum sodium (meq/L), outcome: 6.2 Peak serum sodium (stratified by dose of HS).



7. Final serum sodium

(Analysis 7.1; Analysis 7.2; Analysis 7.3; Analysis 7.4; Analysis 7.5)

By the end of the study period the difference between the groups in serum sodium was considerably reduced (SMD 1.07 meq/L higher with HS, 95% CI 0.6 to 1.5, P < 0.00001, I^2 = 90%) and the range for average final serum sodium was within normal limits: 136 to 146 meq/L and 136 to 140 in the HS and IS groups respectively (Analysis 7.1). Neither the outcome nor heterogeneity were altered in subgroup analysis by surgery type (Analysis 7.4), dose of HS (Analysis 7.2) or volume of crystalloid (Analysis 7.3). Funnel plot analysis is similar to that observed with peak serum sodium except that the difference between HS and IS has been reduced (Figure 4).

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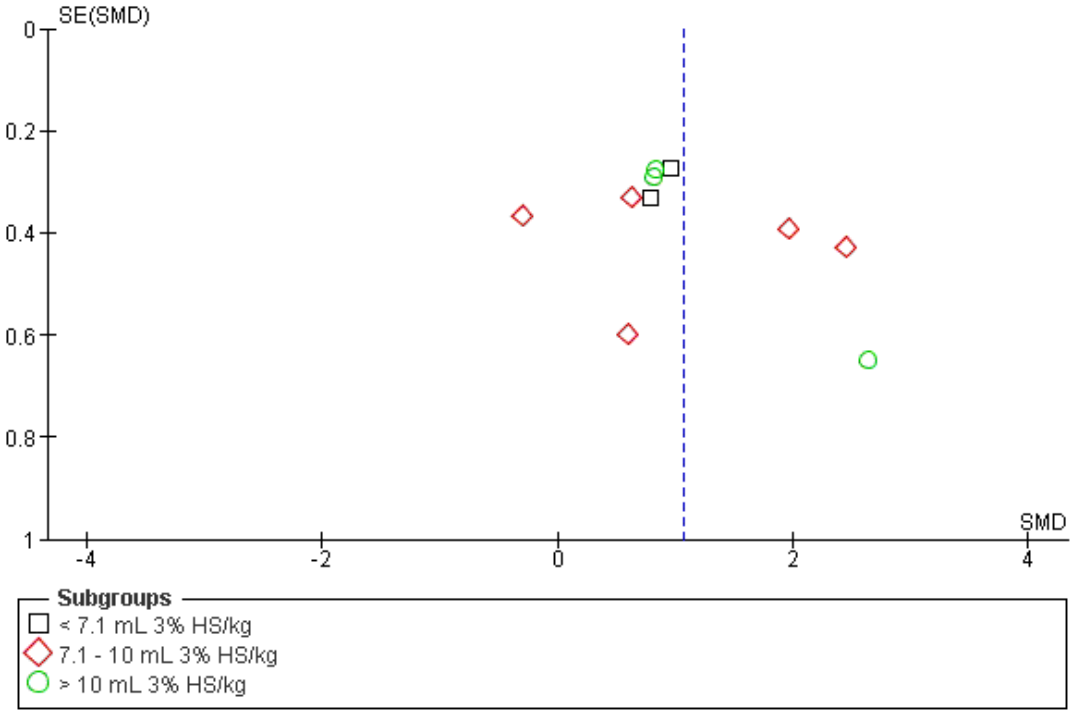
Figure 4. Funnel plot of comparison: 7 Final serum sodium (meq/L), outcome: 7.2 Final serum sodium (stratified by dose of HS given).



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

The duration of mechanical ventilation and the length of stay in hospital were not reported in any of the trials. 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 ans IS groups respectively (P = 0.63).

11. Adverse events

No serious adverse events such as myocardial infarction, cerebrovascular accident or central pontine myelinolysis were reported in these trials.

12. Serum osmolarity, haemodynamic parameters

(Analysis 12.1; Analysis 12.2; Analysis 12.3)

Trials in which maximum serum osmolarity (Analysis 12.1) was measured (Ishikawa 1996; Jarvela 2000; Jarvela 2001; Kato 1996; Kimura 1994; Kolsen-Petersen 2004; Shackford 1983; Shackford 1987; Younes 1988) showed an increase with HS that was similar to the increase in serum sodium (SMD 2.7 mOsm / kg H2O higher with HS, 95% CI 1.7 to 3.7, P < 0.00001, I^2 = 90%). Several groups measured haemodynamic parameters (Cross 1989; Jarvela 2000; Jarvela 2001; Shackford 1983; Shackford 1987). Maximum intraoperative cardiac index (Analysis 12.3) was significantly increased with HS (SMD 0.6 L/min/M2 higher with HS, 95% CI 0.1 to 1.0, P = 0.02, I^2 = 59%) but intraoperative pulmonary artery wedge pressure (Analysis 12.2) remained unchanged by HS (SMD 0, 95% CI -0.3 to +0.3, P = 0.98, I^2 = 0).

DISCUSSION

There were no differences with respect to mortality or major morbidity between the treatment arms of this meta-analysis. A preliminary survey carried out before designing this meta-analysis suggested that trials of perioperative 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. As

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expected, we found no trials that were designed to measure differences in mortality or serious adverse events and in general the study periods of the included trials were insufficient to determine the impact of the interventions on mortality. Only one death and no organ failures were reported in 297 patients who received HS, just as in the IS group. Neither the trials nor the meta-analysis are sufficiently powered to determine the impact of HS on perioperative mortality or morbidity. The low mortality rate in the IS group suggests that normal risk patients were studied and in which adequate power would require many times the number of patients collected in this meta-analysis. However the absence of excess mortality or morbidity in the HS group despite a wide range of doses administered suggests that HS is safe. Therefore an alternative strategy for consideration is to study perioperative HS in a population at higher risk of death or major morbidity.

Meta-analysis of the outcomes measured by the trials was performed on less clinically relevant outcomes in order to provide a picture of the impact of HS on perioperative fluid management. HS significantly reduces the positive fluid balance experienced by patients undergoing surgery. This observation was independent of the type of surgery or perioperative fluid protocol. HS conserved fluid at lower doses as much as at higher doses.

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, considerable heterogeneity was observed in perioperative diuresis even though there was no significant difference in diuresis between the test group, HS, and the control. Stratification by the volume of intravenous fluid eliminated heterogeneity. This makes clinical sense in that diuresis is directly related to the volume of fluid infused. It also highlights the variability in the fluid regimen used in these trials. While such variability increases the clinical applicability of the review, it also contributes to heterogeneity of the observations. Other potential sources of heterogeneity such as concommitant medications were not amenable to investigation because of lack of information.

Perioperative diuresis was similar in the HS and IS patients suggesting that adequate intravascular volumes were maintained throughout surgery despite the fact that HS patients received significantly less intravenous fluid than IS patients. HS increased the intraoperative cardiac index. All of the patient groups completed surgery with a positive fluid balance. 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 patients undergoing surgery. HS increased serum sodium and osmolarity in a dose related manner. 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.

Is there a potential therapeutic window for HS in patients undergoing surgery, where perioperative weight gain can be minimized without a risk of significant hypernatraemia?In hyponatraemic patients, 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 patients 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 patients had normal serum sodium levels at baseline and we did not find any case reports in the literature of central pontine myelinolysis in patients who received HS. 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 perioperatively 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 perioperative fluid excess would improve clinically relevant outcomes but it provides the basis for an RCT.

AUTHORS' CONCLUSIONS

Implications for practice

Small volumes of HS reduced the positive fluid balance and transiently increased serum sodium in patients undergoing surgery. The impact of HS on clinically relevant outcomes was not tested by the trials analysed and we cannot recommend routine perioperative use of HS across the surgical population. HS may be useful when fluid restriction is required in selected individuals or clinical situations.

Implications for research

HS administration to patients undergoing surgery should be compared to standard practice using RCTs of high methodological rigour in order to determine any impact on patient 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 group in these trials. The duration of any future trial should be sufficient to cover the period of perioperative mortality or major morbidity which is usually considered to be 60 days or at least the postoperative hospital stay.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baraka 1994

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: Lebanon Language: English Single centre Inclusion criteria: consenting adult male patients 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
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	Mortality Peak serum sodium Haemodynamic parameters
Notes	

Risk of bias

Item	Authors' judgement	Description

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Baraka 1994 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Bruegger 2005

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: no Additional features to blind fluid administered: no Control of co-interventions: no Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: Germany Language: English Single centre Inclusion criteria: patients undergoing elective infrarenal aortic aneurysm repair Exclusion criteria: ASA IV; renal dysfunction; congestive heart failure; recent brain infarction; contra-indication to starch or dextran Number eligible: Not specified Number enrolled: 28 (HS 14; NS 14) Number completed study: 28
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: yes Study Period: duration of surgery plus 72 hours
Outcomes	Mortality Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Notes	Different colloids given to experimental and control groups
Risk of bias	

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Bruegger 2005 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cross 1989

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: USA Language: English Inclusion criteria: consenting patients 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
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 Post-operative 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	Mortality LOS hospital LOS ICU Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output

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Cross 1989 (*Continued*)

	Haemodynamic parameters
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Durasnel 1999

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: Niger Language: French Single centre Inclusion criteria: consenting adult patients 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 (one from each group excluded, cause not given)
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	Mortality Haemodynamic parameters Fluid volume transfused

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Durasnel 1999 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Ishikawa 1996

Methods	Publication type: full article Allocation random: unclear Allocation concealment: not described 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: no (one patient in RL group excluded during study) Intention-to-treat analysis: yes
Participants	Country: Japan Language: Japanese Inclusion criteria: Patients 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: 23
Interventions	Hypertonic saline group IV solution: 7.2% HS Dose: 1.8 ml / kg Duration: 20 minute Post-operative 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
Notes	Translations supplied by Dr Hideaki Tanaka and Dr Yoshihisa Morita
Risk of bias	

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Ishikawa 1996 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jarvela 2000

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: Finland Language: English Single centre Inclusion criteria: consenting fit patients have 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
Interventions	Hypertonic saline group IV solution: 7.5% HS Dose: 4 ml/kg Duration: 30 minute Post-operative 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	Mortality Fluid volume transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters

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Jarvela 2000 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Jarvela 2001

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described 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
Participants	Country: Finland Language: English Single centre Inclusion criteria: Patients 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
Interventions	Hypertonic saline group IV solution: 7.5% HS Dose: 4 ml/kg Duration: 30 minute Post-operative 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: 4% albumin to maintain cardiac index at 2.5 L / min / m2 Co-interventions applied differentially between groups: no Study Period: duration of surgery and post-operative period until next morning
Outcomes	Mortality Fluid volume transfused Weight gain Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters Extubation times
Notes	

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Jarvela 2001 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Kato 1996

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: no Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: Japan Language: English Inclusion criteria: consenting patients 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
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 Post-operative maintenance: Co-interventions: Co-interventions applied differentially between groups: no Study Period: duration of surgery plus first post-operative day.
Outcomes	Mortality Fluid volume transfused Peak serum sodium Haemodynamic parameters
Notes	

Risk of bias

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Kato 1996 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kimura 1994

Methods	Publication type: full article Allocation random: unclear Allocation concealment: not described 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: unclear
Participants	Country: Japan Language: Japanese Inclusion criteria: patients 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
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
Notes	Translation provided by Dr Hideaki Tanaka and Dr Yoshihisa Morita

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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Kolsen-Petersen 2004

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described 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
Participants	Country: Denmark Language: English Inclusion criteria: adult female patients 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 (one HS patient withdrew consent; one HS had anaphylactoid reaction to anaesthetic agent; one NS-4 patient transferred to another hospital; one NS-32 patient returned to the operating room for haemorrhage)
Interventions	Hypertonic saline group IV solution: 7.5% NaCl Dose: 4 ml / kg Duration: over 10 minutes before hysterectomy Post-operative maintenance: not specified Isotonic salt solution group IV solution: NS Dose - two groups: 'NS-4' received 4 ml / kg; 'NS-32' received 32 ml / kg Duration: over 10 minutes before hysterectomy Post-operative 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	Mortality Peak serum sodium Urine output Immunological parameters
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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Shackford 1983

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described 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
Participants	Country: USA Language: English Inclusion criteria: patients undergoing aortic surgery Exclusion criteria: not specified Number eligible: 61 Number enrolled: 58 (HS 30; ISS 28) Number completed study: 58
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 Post-operative maintenance: D5/0.25NaCl Isotonic salt solution group IV solution: RL Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Post-operative maintenance: D5/0.25NaCl Co-interventions: Co-interventions applied differentially between groups: no Study Period: duration of hospital stay for surgery
Outcomes	Mortality Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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Shackford 1987

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described 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
Participants	Country: USA Language: English Inclusion criteria: Patients 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
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 Post-operative maintenance: D5/0.25NaCl Isotonic salt solution group IV solution: RL Dose: titrated to maintain CVP within 3 torr of preoperative value Duration: during operation Post-operative maintenance: D5/0.25NaCl Co-interventions: Co-interventions applied differentially between groups: no Study Period: duration of surgery plus first four post-operative days
Outcomes	Fluid volume transfused Blood transfused Fluid loss Fluid balance Weight change Peak serum sodium Urine output
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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Veroli 1992

Methods	Publication type: full article Allocation random: yes Allocation concealment: not described Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: yes (second anaesthetist) Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: yes
Participants	Country: France Language: English Inclusion criteria: consenting patients 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
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	Mortality Fluid volume transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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Wang 1997

Methods	Publication type: full article Allocation random: unclear Allocation concealment: not described 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
Participants	Country: China Language: English Single centre Inclusion criteria: consenting fit patients 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
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
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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Younes 1988

Methods	Publication type: full article Allocation random: unclear Allocation concealment: not described 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
Participants	Country: Brazil Language: Portuguese Single centre Inclusion criteria: Adult patients 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
Interventions	Hypertonic saline group IV solution: 7.5% HS Dose: 4 ml / kg Duration: 15 minute bolus Post-operative 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 Post-operative 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	Mortality LOS hospital LOS ICU Fluid volume transfused Blood transfused Fluid loss Fluid balance Peak serum sodium Urine output Haemodynamic parameters
Notes	Translation provided by Ms. Christiane Baldwin
Risk of bias	

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Younes 1988 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ASA: American Society Anesthesiology classification
HS: hypertonic saline
HSL: hypertonic saline lactate
NS: normal saline (154 meq Na per litre)
RL: Ringer's Lactate (130 meq Na per litre)
HSL: hypertonic sodium lactate
D5/0.45NS: dextrose 5% in 0.45% saline
ISS: isotonic salt solution
IV: intravenous
LOS: length of stay
ICU: intensive care unit

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Characteristics of excluded studies *[ordered by study ID]*

Auler 1987	Consecutive patients enrolled. Study not randomized
Auler 1992	Study of intraoperative respiratory physiology but did not measure outcomes such as weight gain, fluid balance or peak serum sodium or determine postoperative survival.
Shao 2005	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)".

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DATA AND ANALYSES

Comparison 3. Fluid balance (L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Calculated fluid balance (stratified for surgery type)	5	230	Std. Mean Difference (IV, Random, 95% CI)	-1.43 [-2.05, -0.80]
1.1 Coronary artery bypass surgery	2	92	Std. Mean Difference (IV, Random, 95% CI)	-1.51 [-3.17, 0.15]
1.2 Aortic surgery	3	138	Std. Mean Difference (IV, Random, 95% CI)	-1.46 [-2.21, -0.72]
2 Calculated fluid balance (stratified for dose of HS given)	5	230	Std. Mean Difference (IV, Random, 95% CI)	-1.42 [-2.05, -0.79]
2.1 < 7.1 mL 3% HS/kg	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
2.2 7.1 - 10 mL 3% HS/kg	2	100	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-1.23, -0.41]
2.3 > 10 mL 3% HS/kg	3	130	Std. Mean Difference (IV, Random, 95% CI)	-1.84 [-2.72, -0.97]
3 Calculated fluid balance (stratified for volume given in control group)	5	230	Std. Mean Difference (IV, Random, 95% CI)	-1.42 [-2.05, -0.79]
3.1 < 2000 mL	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 2000 - 5000 mL	3	120	Std. Mean Difference (IV, Random, 95% CI)	-1.24 [-2.07, -0.42]
3.3 > 5000 mL	2	110	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.72, -0.57]
4 Calculated fluid balance (sensitivity analysis by study quality)	5	230	Std. Mean Difference (IV, Random, 95% CI)	-1.45 [-2.11, -0.79]
4.1 Study grade = A	1	72	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.23, -0.27]
4.2 Study group = B	3	100	Std. Mean Difference (IV, Random, 95% CI)	-1.37 [-2.07, -0.67]
4.3 Study group = D	1	58	Std. Mean Difference (IV, Random, 95% CI)	-2.32 [-1.00, -1.65]
5 Actual fluid balance (L)	4	158	Std. Mean Difference (IV, Random, 95% CI)	-1.63 [-2.32, -0.93]

Comparison 4. Total volume of crystalloid administered (L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Volume of crystalloid administered (stratified for type of surgery)	10	364	Std. Mean Difference (IV, Random, 95% CI)	-2.35 [-3.21, -1.49]
1.1 Cardiovascular surgery	6	221	Std. Mean Difference (IV, Random, 95% CI)	-1.70 [-2.48, -0.93]
1.2 Non cardiovascular surgery	4	143	Std. Mean Difference (IV, Random, 95% CI)	-4.04 [-6.46, -1.62]
2 Volume of crystalloid administered (stratified by dose of HS)	10	364	Std. Mean Difference (IV, Random, 95% CI)	-2.35 [-3.21, -1.49]
2.1 < 7.1 mL 3% HS/kg	3	103	Std. Mean Difference (IV, Random, 95% CI)	-2.24 [-3.93, -0.56]
2.2 7.1 - 10 mL 3% HS/kg	4	131	Std. Mean Difference (IV, Random, 95% CI)	-3.49 [-5.72, -1.26]

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2.3 > 10 mL 3% HS/kg	3	130	Std. Mean Difference (IV, Random, 95% CI)	-1.22 [-1.98, -0.46]
3 Volume of crystalloid administered (sensitivity analysis by study quality)	10	364	Std. Mean Difference (IV, Random, 95% CI)	-1.70 [-2.29, -1.12]
3.1 Study grade = A	2	72	Std. Mean Difference (IV, Random, 95% CI)	-2.83 [-5.40, -0.26]
3.2 Study group = B	7	234	Std. Mean Difference (IV, Random, 95% CI)	-1.51 [-2.17, -0.86]
3.3 Study grade = D	1	58	Std. Mean Difference (IV, Random, 95% CI)	-1.03 [-1.58, -0.48]

Comparison 5. Diuresis during study period (L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diuresis during study period (L)	6	270	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.19, 0.58]
2 Diuresis during study period (stratified by dose of HS)	6	270	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.23, 0.57]
2.1 < 7.1 mL 3% HS/kg	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
2.2 7.1 - 10 mL 3% HS/kg	3	140	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.25, 0.55]
2.3 > 10 mL 3% HS/kg	3	130	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.51, 1.17]
3 Diuresis during study period (stratified for type of surgery)	6	270	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.20, 0.61]
3.1 Cardiovascular surgery	5	230	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.29, 0.70]
3.2 Non cardiovascular surgery	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.37, 0.87]
4 Diuresis during study period (stratified for volume of crystalloid infused)	6	270	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.23, 0.57]
4.1 < 2000 mL	2	68	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.55, 0.40]
4.2 2000 - 5000 mL	2	92	Std. Mean Difference (IV, Random, 95% CI)	0.94 [-0.25, 2.12]
4.3 > 5000 mL	2	110	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.50, 0.25]
5 Diuresis during study period (sensitivity analysis by study quality)	6	270	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.23, 0.57]
5.1 Study grade = A	2	112	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.08, 0.66]
5.2 Study grade = B	3	100	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.64, 1.30]
5.3 Study grade = D	1	58	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.67, 0.36]

Comparison 6. Peak serum sodium (meq/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak serum sodium (stratified by type of surgery)	14	532	Std. Mean Difference (IV, Random, 95% CI)	2.24 [1.59, 2.89]
1.1 Cardiovascular surgery	6	261	Std. Mean Difference (IV, Random, 95% CI)	3.20 [1.98, 4.42]
1.2 Transurethral resection of the prostate	3	87	Std. Mean Difference (IV, Random, 95% CI)	1.17 [0.22, 2.11]

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1.3 Other surgery	5	184	Std. Mean Difference (IV, Random, 95% CI)	1.89 [0.97, 2.81]
2 Peak serum sodium (stratified by dose of HS)	14	532	Std. Mean Difference (IV, Random, 95% CI)	2.24 [1.59, 2.89]
2.1 < 7.1 mL 3% HS/kg	5	178	Std. Mean Difference (IV, Random, 95% CI)	1.11 [0.54, 1.68]
2.2 7.1 - 10 mL 3% HS/kg	5	210	Std. Mean Difference (IV, Random, 95% CI)	3.26 [1.96, 4.57]
2.3 > 10 mL 3% HS/kg	4	144	Std. Mean Difference (IV, Random, 95% CI)	2.43 [1.44, 3.41]
3 Peak serum sodium (stratified by volume given in control group)	9	371	Std. Mean Difference (IV, Random, 95% CI)	2.69 [1.89, 3.48]
3.1 < 2000 mL/kg	4	141	Std. Mean Difference (IV, Random, 95% CI)	1.76 [1.22, 2.31]
3.2 2000 - 5000 mL	3	120	Std. Mean Difference (IV, Random, 95% CI)	5.06 [3.28, 6.84]
3.3 > 5000 mL	2	110	Std. Mean Difference (IV, Random, 95% CI)	1.91 [1.16, 2.67]
4 Peak serum sodium (sensitivity analysis by study quality)	14	532	Mean Difference (IV, Random, 95% CI)	7.64 [5.47, 9.80]
4.1 Study grade = A	2	112	Mean Difference (IV, Random, 95% CI)	7.50 [2.60, 12.40]
4.2 Study grade = B	11	362	Mean Difference (IV, Random, 95% CI)	7.33 [4.59, 10.08]
4.3 Study grade = D	1	58	Mean Difference (IV, Random, 95% CI)	12.0 [8.09, 15.91]

Comparison 7. Final serum sodium (meq/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final serum sodium (all studies)	10	392	Std. Mean Difference (IV, Random, 95% CI)	1.07 [0.60, 1.54]
2 Final serum sodium (stratified by dose of HS given)	10	392	Std. Mean Difference (IV, Random, 95% CI)	1.07 [0.60, 1.54]
2.1 < 7.1 mL 3% HS/kg	2	100	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.47, 1.30]
2.2 7.1 - 10 mL 3% HS/kg	5	162	Std. Mean Difference (IV, Random, 95% CI)	1.07 [0.06, 2.07]
2.3 > 10 mL 3% HS/kg	3	130	Std. Mean Difference (IV, Random, 95% CI)	1.21 [0.43, 2.00]
3 Final serum sodium (stratified by volume given in control group)	8	293	Std. Mean Difference (IV, Random, 95% CI)	1.17 [0.55, 1.79]
3.1 < 2000 mL	3	111	Std. Mean Difference (IV, Random, 95% CI)	0.96 [-0.49, 2.42]
3.2 2000 - 5000 mL	3	72	Std. Mean Difference (IV, Random, 95% CI)	1.73 [0.68, 2.78]
3.3 > 5000 mL	2	110	Std. Mean Difference (IV, Random, 95% CI)	0.83 [0.43, 1.22]
4 Final serum sodium (stratified by type of surgery)	10	392	Std. Mean Difference (IV, Random, 95% CI)	1.07 [0.60, 1.54]
4.1 Cardiovascular surgery	5	182	Std. Mean Difference (IV, Random, 95% CI)	1.28 [0.65, 1.91]
4.2 Transurethral resection of prostate	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.78 [0.14, 1.43]
4.3 Other surgery	4	170	Std. Mean Difference (IV, Random, 95% CI)	0.91 [-0.04, 1.87]
5 Final serum sodium (sensitivity analysis by study quality)	10	392	Mean Difference (IV, Random, 95% CI)	3.18 [1.91, 4.44]
5.1 Study grade = A	2	80	Mean Difference (IV, Random, 95% CI)	3.45 [0.51, 6.39]
5.2 Study grade = B	7	254	Mean Difference (IV, Random, 95% CI)	2.74 [1.11, 4.38]
5.3 Study grade = D	1	58	Mean Difference (IV, Random, 95% CI)	10.0 [3.75, 16.25]

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Comparison 12. Other outcomes of interest

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum intraoperative serum osmolarity (mOsm/kg H2O)	9	329	Std. Mean Difference (IV, Random, 95% CI)	2.72 [1.73, 3.71]
2 Maximum intraoperative pulmonary artery wedge pressure (mm Hg)	3	150	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.33, 0.32]
3 Maximum intraoperative cardiac index (L/min/M2)	5	210	Std. Mean Difference (IV, Random, 95% CI)	0.55 [0.10, 1.00]

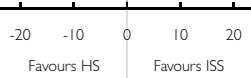
Analysis 3.1. Comparison 3 Fluid balance (L), Outcome 1 Calculated fluid balance (stratified for surgery type).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 3 Fluid balance (L)

Outcome: 1 Calculated fluid balance (stratified for surgery type)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Coronary artery bypass surgery							
Cross 1989	11	-1.72 (0.73)	9	0.27 (0.83)		13.5 %	-2.46 [-3.68, -1.23]
Jarvela 2001	36	0.8 (1.5)	36	1.9 (1.4)		23.9 %	-0.75 [-1.23, -0.27]
Subtotal (95% CI)	**47**		**45**			**37.4 %**	**-1.51 [-3.17, 0.15]**
Heterogeneity: Tau^2 = 1.23; Chi^2 = 6.47, df = 1 (P = 0.01); I^2 =85%							
Test for overall effect: Z = 1.78 (P = 0.076)							
2 Aortic surgery							
Shackford 1983	30	4.2 (1.6)	28	9.8 (3.2)		21.2 %	-2.21 [-2.87, -1.55]
Shackford 1987	26	5.5 (1.5)	26	9.8 (5.1)		22.3 %	-1.13 [-1.72, -0.54]
Bruegger 2005	14	3.6 (2)	14	5.31 (1.1)		19.2 %	-1.03 [-1.82, -0.23]
Subtotal (95% CI)	**70**		**68**			**62.6 %**	**-1.46 [-2.21, -0.72]**
Heterogeneity: Tau^2 = 0.31; Chi^2 = 7.26, df = 2 (P = 0.03); I^2 =72%							
Test for overall effect: Z = 3.85 (P = 0.00012)							
Total (95% CI)	**117**		**113**			**100.0 %**	**-1.43 [-2.05, -0.80]**
Heterogeneity: Tau^2 = 0.37; Chi^2 = 16.42, df = 4 (P = 0.003); I^2 =76%							
Test for overall effect: Z = 4.46 (P < 0.00001)							



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Analysis 3.2. Comparison 3 Fluid balance (L), Outcome 2 Calculated fluid balance (stratified for dose of HS given).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 3 Fluid balance (L)

Outcome: 2 Calculated fluid balance (stratified for dose of HS given)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 7.1 mL 3% HS/kg							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 7.1 - 10 mL 3% HS/kg							
Bruegger 2005	14	3.6 (2.04)	14	5.31 (1.08)		19.2 %	-1.02 [-1.81, -0.22]
Jarvela 2001	36	0.8 (1.5)	36	1.9 (1.4)		23.8 %	-0.75 [-1.23, -0.27]
Subtotal (95% CI)	**50**		**50**			**43.0 %**	**-0.82 [-1.23, -0.41]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 3.92 (P = 0.000087)							
3 > 10 mL 3% HS/kg							
Cross 1989	11	-1.72 (0.73)	9	0.27 (0.83)		13.5 %	-2.46 [-3.68, -1.23]
Shackford 1983	30	4.2 (1.6)	28	9.8 (3.2)		21.2 %	-2.21 [-2.87, -1.55]
Shackford 1987	26	5.5 (1.5)	26	9.8 (5.2)		22.3 %	-1.11 [-1.69, -0.52]
Subtotal (95% CI)	**67**		**63**			**57.0 %**	**-1.84 [-2.72, -0.97]**
Heterogeneity: Tau^2 = 0.43; Chi^2 = 7.65, df = 2 (P = 0.02); I^2 =74%							
Test for overall effect: Z = 4.13 (P = 0.000037)							
Total (95% CI)	**117**		**113**			**100.0 %**	**-1.42 [-2.05, -0.79]**
Heterogeneity: Tau^2 = 0.37; Chi^2 = 16.51, df = 4 (P = 0.002); I^2 =76%							
Test for overall effect: Z = 4.43 (P < 0.00001)							

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Analysis 3.3. Comparison 3 Fluid balance (L), Outcome 3 Calculated fluid balance (stratified for volume given in control group).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 3 Fluid balance (L)

Outcome: 3 Calculated fluid balance (stratified for volume given in control group)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 2000 mL							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 2000 - 5000 mL							
Bruegger 2005	14	3.6 (2.04)	14	5.31 (1.08)		19.2 %	-1.02 [-1.81, -0.22]
Cross 1989	11	-1.72 (0.73)	9	0.27 (0.83)		13.5 %	-2.46 [-3.68, -1.23]
Jarvela 2001	36	0.8 (1.5)	36	1.9 (1.4)		23.8 %	-0.75 [-1.23, -0.27]
Subtotal (95% CI)	**61**		**59**			**56.5 %**	**-1.24 [-2.07, -0.42]**
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 6.48$, df = 2 (P = 0.04); $I^2 = 69\%$							
Test for overall effect: Z = 2.97 (P = 0.0030)							
3 > 5000 mL							
Shackford 1983	30	4.2 (1.6)	28	9.8 (3.2)		21.2 %	-2.21 [-2.87, -1.55]
Shackford 1987	26	5.5 (1.5)	26	9.8 (5.2)		22.3 %	-1.11 [-1.69, -0.52]
Subtotal (95% CI)	**56**		**54**			**43.5 %**	**-1.65 [-2.72, -0.57]**
Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 5.95$, df = 1 (P = 0.01); $I^2 = 83\%$							
Test for overall effect: Z = 2.99 (P = 0.0028)							
Total (95% CI)	**117**		**113**			**100.0 %**	**-1.42 [-2.05, -0.79]**
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 16.51$, df = 4 (P = 0.002); $I^2 = 76\%$							
Test for overall effect: Z = 4.43 (P < 0.00001)							

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Analysis 3.4. Comparison 3 Fluid balance (L), Outcome 4 Calculated fluid balance (sensitivity analysis by study quality).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 3 Fluid balance (L)

Outcome: 4 Calculated fluid balance (sensitivity analysis by study quality)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Study grade = A							
Jarvela 2001	36	0.8 (1.5)	36	1.9 (1.4)		23.5 %	-0.75 [-1.23, -0.27]
Subtotal (95% CI)	**36**		**36**			**23.5 %**	**-0.75 [-1.23, -0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.07 (P = 0.0021)							
2 Study group = B							
Bruegger 2005	14	3.6 (2.04)	14	5.31 (1.08)		19.3 %	-1.02 [-1.81, -0.22]
Cross 1989	11	-1.72 (0.73)	9	0.27 (0.83)		14.0 %	-2.46 [-3.68, -1.23]
Shackford 1987	26	5.5 (1.5)	26	9.8 (5.2)		22.2 %	-1.11 [-1.69, -0.52]
Subtotal (95% CI)	**51**		**49**			**55.5 %**	**-1.37 [-2.07, -0.67]**
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 4.29$, df = 2 (P = 0.12); $I^2 = 53\%$							
Test for overall effect: Z = 3.83 (P = 0.00013)							
3 Study group = D							
Shackford 1983	30	4.2 (1.6)	28	9.8 (3)		21.0 %	-2.32 [-3.00, -1.65]
Subtotal (95% CI)	**30**		**28**			**21.0 %**	**-2.32 [-3.00, -1.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.73 (P < 0.00001)							
Total (95% CI)	**117**		**113**			**100.0 %**	**-1.45 [-2.11, -0.79]**
Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 18.12$, df = 4 (P = 0.001); $I^2 = 78\%$							
Test for overall effect: Z = 4.30 (P = 0.000017)							

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Analysis 3.5. Comparison 3 Fluid balance (L), Outcome 5 Actual fluid balance (L).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 3 Fluid balance (L)

Outcome: 5 Actual fluid balance (L)

Study or subgroup	Hypertonic Saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bruegger 2005	14	3.6 (2.03)	14	5.3 (1.08)		25.2 %	-1.02 [-1.81, -0.22]
Cross 1989	11	-1.72 (0.73)	9	0.27 (0.83)		17.4 %	-2.46 [-3.68, -1.23]
Shackford 1983	30	4.2 (1.6)	28	9.8 (3.2)		27.9 %	-2.21 [-2.87, -1.55]
Shackford 1987	26	5.5 (1.5)	26	9.8 (5.2)		29.5 %	-1.11 [-1.69, -0.52]
Total (95% CI)	**81**		**77**			**100.0 %**	**-1.63 [-2.32, -0.93]**

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 9.83$, df = 3 (P = 0.02); $I^2 = 69\%$

Test for overall effect: Z = 4.56 (P < 0.00001)

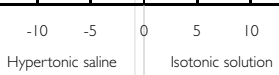
Analysis 4.1. Comparison 4 Total volume of crystalloid administered (L), Outcome 1 Volume of crystalloid administered (stratified for type of surgery).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 4 Total volume of crystalloid administered (L)

Outcome: 1 Volume of crystalloid administered (stratified for type of surgery)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Cardiovascular surgery							
Bruegger 2005	14	1.92 (0.7)	14	2.72 (0.68)		11.1 %	-1.13 [-1.93, -0.32]
Cross 1989	11	4.17 (0.41)	9	5.77 (0.79)		9.8 %	-2.52 [-3.75, -1.28]
Jarvela 2001	16	0.55 (0.18)	16	1.44 (0.23)		9.6 %	-4.20 [-5.50, -2.90]
Shackford 1983	30	6.4 (4.6)	28	12.5 (6.9)		11.7 %	-1.03 [-1.58, -0.48]
Shackford 1987	26	6.3 (2.4)	26	9.5 (5.8)		11.7 %	-0.71 [-1.27, -0.15]
Younes 1988	18	0.7 (0.05)	13	0.81 (0.09)		11.1 %	-1.54 [-2.37, -0.72]
Subtotal (95% CI)	**115**		**106**			**65.1 %**	**-1.70 [-2.48, -0.93]**



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Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Heterogeneity: Tau² = 0.74; Chi² = 28.50, df = 5 (P = 0.00003); I² =82%							
Test for overall effect: Z = 4.29 (P = 0.000018)							
2 Non cardiovascular surgery							
Durasnel 1999	24	0.39 (0.22)	24	0.62 (0.32)		11.7 %	-0.82 [-1.42, -0.23]
Ishikawa 1996	8	0.1 (0.02)	7	0.98 (0.15)		4.0 %	-8.04 [-11.55, -4.54]
Jarvela 2000	20	0.13 (0.03)	20	1.03 (0.16)		7.8 %	-7.66 [-9.54, -5.79]
Kato 1996	20	0.81 (0.35)	20	1.62 (0.62)		11.4 %	-1.58 [-2.30, -0.86]
Subtotal (95% CI)	**72**		**71**			**34.9 %**	**-4.04 [-6.46, -1.62]**
Heterogeneity: Tau² = 5.22; Chi² = 59.84, df = 3 (P<0.00001); I² =95%							
Test for overall effect: Z = 3.28 (P = 0.0011)							
Total (95% CI)	**187**		**177**			**100.0 %**	**-2.35 [-3.21, -1.49]**
Heterogeneity: Tau² = 1.56; Chi² = 89.63, df = 9 (P<0.00001); I² =90%							
Test for overall effect: Z = 5.36 (P < 0.00001)							

-10 -5 0 5 10

Hypertonic saline Isotonic solution

Analysis 4.2. Comparison 4 Total volume of crystalloid administered (L), Outcome 2 Volume of crystalloid administered (stratified by dose of HS).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 4 Total volume of crystalloid administered (L)

Outcome: 2 Volume of crystalloid administered (stratified by dose of HS)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 7.1 mL 3% HS/kg							
Durasnel 1999	24	0.39 (0.22)	24	0.62 (0.32)		11.7 %	-0.82 [-1.42, -0.23]
Ishikawa 1996	8	0.1 (0.02)	7	0.98 (0.15)		4.0 %	-8.04 [-11.55, -4.54]
Kato 1996	20	0.81 (0.35)	20	1.62 (0.62)		11.4 %	-1.58 [-2.30, -0.86]
Subtotal (95% CI)	**52**		**51**			**27.1 %**	**-2.24 [-3.93, -0.56]**
Heterogeneity: Tau² = 1.63; Chi² = 17.25, df = 2 (P = 0.00018); I² =88%							
Test for overall effect: Z = 2.61 (P = 0.0090)							
2 7.1 - 10 mL 3% HS/kg							
Bruegger 2005	14	1.92 (0.7)	14	2.72 (0.68)		11.1 %	-1.13 [-1.93, -0.32]

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Hypertonic saline Isotonic solution

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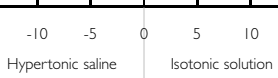
Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Jarvela 2000	20	0.13 (0.03)	20	1.03 (0.16)		7.8 %	-7.66 [-9.54, -5.79]
Jarvela 2001	16	0.55 (0.18)	16	1.44 (0.23)		9.6 %	-4.20 [-5.50, -2.90]
Younes 1988	18	0.7 (0.05)	13	0.81 (0.09)		11.1 %	-1.54 [-2.37, -0.72]
Subtotal (95% CI)	**68**		**63**			**39.6 %**	**-3.49 [-5.72, -1.26]**
Heterogeneity: $Tau^2 = 4.78$; $Chi^2 = 51.01$, df = 3 (P<0.00001); I^2 =94%							
Test for overall effect: Z = 3.06 (P = 0.0022)							
3 > 10 mL 3% HS/kg							
Cross 1989	11	4.17 (0.41)	9	5.77 (0.79)		9.8 %	-2.52 [-3.75, -1.28]
Shackford 1983	30	6.4 (4.6)	28	12.5 (6.9)		11.7 %	-1.03 [-1.58, -0.48]
Shackford 1987	26	6.3 (2.4)	26	9.5 (5.8)		11.7 %	-0.71 [-1.27, -0.15]
Subtotal (95% CI)	**67**		**63**			**33.3 %**	**-1.22 [-1.98, -0.46]**
Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 6.78$, df = 2 (P = 0.03); I^2 =71%							
Test for overall effect: Z = 3.16 (P = 0.0016)							
Total (95% CI)	**187**		**177**			**100.0 %**	**-2.35 [-3.21, -1.49]**
Heterogeneity: $Tau^2 = 1.56$; $Chi^2 = 89.63$, df = 9 (P<0.00001); I^2 =90%							
Test for overall effect: Z = 5.36 (P < 0.00001)							



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Analysis 4.3. Comparison 4 Total volume of crystalloid administered (L), Outcome 3 Volume of crystalloid administered (sensitivity analysis by study quality).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 4 Total volume of crystalloid administered (L)

Outcome: 3 Volume of crystalloid administered (sensitivity analysis by study quality)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Study grade = A							
Jarvela 2000	16	0.55 (0.18)	16	1.44 (0.23)		8.2 %	-4.20 [-5.50, -2.90]
Jarvela 2001	20	0.81 (0.35)	20	1.62 (0.62)		11.4 %	-1.58 [-2.30, -0.86]
Subtotal (95% CI)	**36**		**36**			**19.6 %**	**-2.83 [-5.40, -0.26]**
Heterogeneity: Tau² = 3.16; Chi² = 12.00, df = 1 (P = 0.00053); I² =92%							
Test for overall effect: Z = 2.16 (P = 0.031)							
2 Study group = B							
Bruegger 2005	14	1.92 (0.7)	14	2.72 (0.68)		10.9 %	-1.13 [-1.93, -0.32]
Cross 1989	11	4.17 (0.41)	9	5.77 (0.79)		8.5 %	-2.52 [-3.75, -1.28]
Durasnel 1999	24	0.39 (0.22)	24	0.62 (0.32)		12.1 %	-0.82 [-1.42, -0.23]
Ishikawa 1996	8	0.1 (0.02)	7	0.98 (0.15)		2.3 %	-8.04 [-11.55, -4.54]
Kato 1996	20	0.81 (0.35)	20	1.62 (0.62)		11.4 %	-1.58 [-2.30, -0.86]
Shackford 1987	26	6.3 (2.4)	26	9.5 (5.8)		12.2 %	-0.71 [-1.27, -0.15]
Younes 1988	18	0.7 (0.05)	13	0.81 (0.09)		10.8 %	-1.54 [-2.37, -0.72]
Subtotal (95% CI)	**121**		**113**			**68.2 %**	**-1.51 [-2.17, -0.86]**
Heterogeneity: Tau² = 0.53; Chi² = 25.24, df = 6 (P = 0.00031); I² =76%							
Test for overall effect: Z = 4.52 (P < 0.00001)							
3 Study grade = D							
Shackford 1983	30	6.4 (4.6)	28	12.5 (6.9)		12.3 %	-1.03 [-1.58, -0.48]
Subtotal (95% CI)	**30**		**28**			**12.3 %**	**-1.03 [-1.58, -0.48]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.68 (P = 0.00023)							
Total (95% CI)	**187**		**177**			**100.0 %**	**-1.70 [-2.29, -1.12]**
Heterogeneity: Tau² = 0.64; Chi² = 46.38, df = 9 (P<0.00001); I² =81%							
Test for overall effect: Z = 5.73 (P < 0.00001)							

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Analysis 5.1. Comparison 5 Diuresis during study period (L), Outcome 1 Diuresis during study period (L).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 5 Diuresis during study period (L)

Outcome: 1 Diuresis during study period (L)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bruegger 2005	14	1.2 (0.55)	14	1.5 (1.33)		14.2 %	-0.29 [-1.03, 0.46]
Cross 1989	11	4.5 (0.5)	9	3.8 (0.25)		9.3 %	1.64 [0.59, 2.69]
Jarvela 2000	20	0.45 (0.28)	20	0.43 (0.27)		17.0 %	0.07 [-0.55, 0.69]
Jarvela 2001	36	3.35 (1.04)	36	2.94 (0.85)		21.0 %	0.43 [-0.04, 0.89]
Shackford 1983	30	1.8 (0.8)	28	1.8 (1.6)		19.7 %	0.0 [-0.52, 0.52]
Shackford 1987	26	0.7 (0.7)	26	1.1 (5.8)		18.9 %	-0.10 [-0.64, 0.45]
Total (95% CI)	**137**		**133**			**100.0 %**	**0.20 [-0.19, 0.58]**

Heterogeneity: Tau² = 0.13; Chi² = 11.61, df = 5 (P = 0.04); I² =57%

Test for overall effect: Z = 1.00 (P = 0.32)

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Analysis 5.2. Comparison 5 Diuresis during study period (L), Outcome 2 Diuresis during study period (stratified by dose of HS).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 5 Diuresis during study period (L)

Outcome: 2 Diuresis during study period (stratified by dose of HS)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 7.1 mL 3% HS/kg							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 7.1 - 10 mL 3% HS/kg							
Bruegger 2005	14	1.2 (0.55)	14	1.5 (1.33)		14.4 %	-0.29 [-1.03, 0.46]
Jarvela 2000	20	0.45 (0.28)	20	0.43 (0.27)		17.0 %	0.07 [-0.55, 0.69]
Jarvela 2001	36	3.35 (1.04)	36	2.94 (0.85)		20.6 %	0.43 [-0.04, 0.89]
Subtotal (95% CI)	**70**		**70**			**52.1 %**	**0.15 [-0.25, 0.55]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.69$, df = 2 (P = 0.26); $I^2 = 26\%$							
Test for overall effect: Z = 0.75 (P = 0.45)							
3 > 10 mL 3% HS/kg							
Cross 1989	11	4.5 (0.5)	9	3.8 (0.25)		9.7 %	1.64 [0.59, 2.69]
Shackford 1983	30	1.6 (0.8)	28	1.8 (1.6)		19.5 %	-0.16 [-0.67, 0.36]
Shackford 1987	26	0.7 (0.7)	26	1.1 (5.8)		18.8 %	-0.10 [-0.64, 0.45]
Subtotal (95% CI)	**67**		**63**			**47.9 %**	**0.33 [-0.51, 1.17]**
Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 9.75$, df = 2 (P = 0.01); $I^2 = 79\%$							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)	**137**		**133**			**100.0 %**	**0.17 [-0.23, 0.57]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 12.63$, df = 5 (P = 0.03); $I^2 = 60\%$							
Test for overall effect: Z = 0.83 (P = 0.41)							

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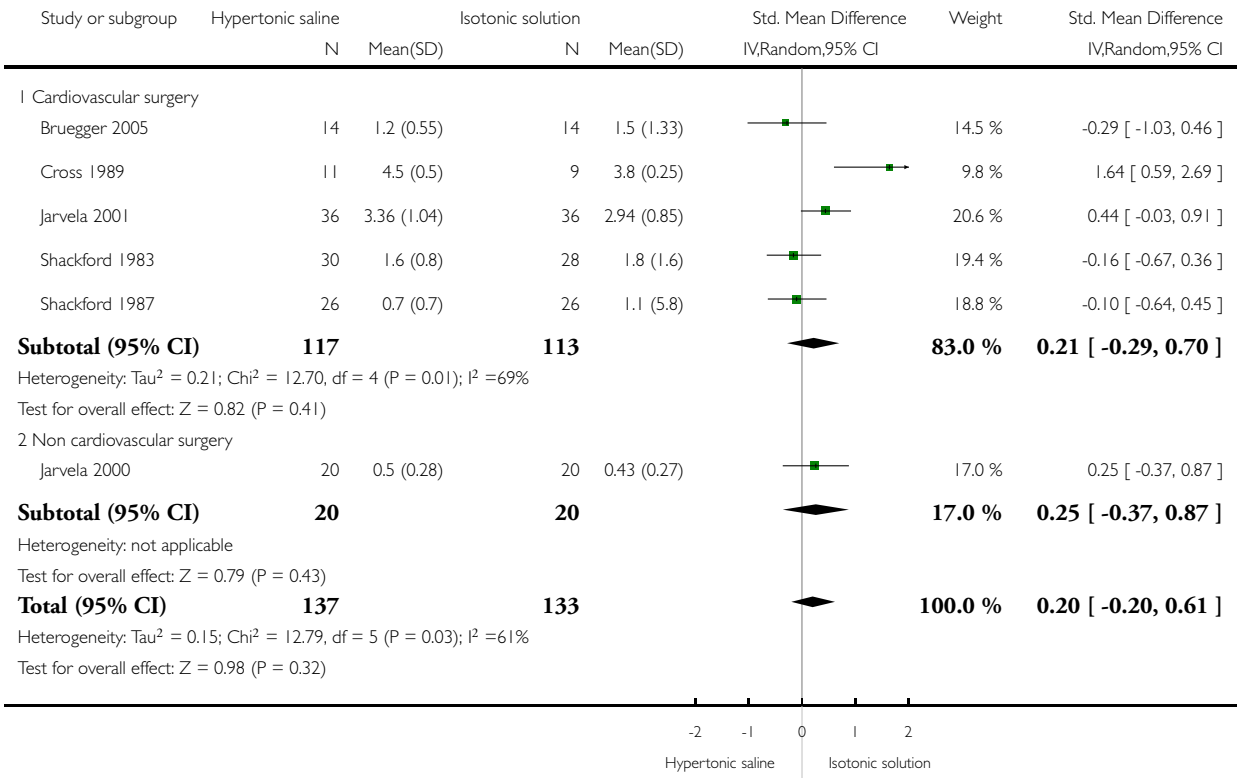
Analysis 5.3. Comparison 5 Diuresis during study period (L), Outcome 3 Diuresis during study period (stratified for type of surgery).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 5 Diuresis during study period (L)

Outcome: 3 Diuresis during study period (stratified for type of surgery)



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Analysis 5.4. Comparison 5 Diuresis during study period (L), Outcome 4 Diuresis during study period (stratified for volume of crystalloid infused).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 5 Diuresis during study period (L)

Outcome: 4 Diuresis during study period (stratified for volume of crystalloid infused)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 2000 mL							
Bruegger 2005	14	1.2 (0.55)	14	1.5 (1.33)		14.4 %	-0.29 [-1.03, 0.46]
Jarvela 2000	20	0.45 (0.28)	20	0.43 (0.27)		17.0 %	0.07 [-0.55, 0.69]
Subtotal (95% CI)	**34**		**34**			**31.4 %**	**-0.07 [-0.55, 0.40]**
Heterogeneity: Tau² = 0.0; Chi² = 0.52, df = 1 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 0.31 (P = 0.76)							
2 2000 - 5000 mL							
Cross 1989	11	4.5 (0.5)	9	3.8 (0.25)		9.6 %	1.64 [0.59, 2.69]
Jarvela 2001	36	3.34 (1.04)	36	2.94 (0.85)		20.7 %	0.42 [-0.05, 0.88]
Subtotal (95% CI)	**47**		**45**			**30.3 %**	**0.94 [-0.25, 2.12]**
Heterogeneity: Tau² = 0.58; Chi² = 4.38, df = 1 (P = 0.04); I² =77%							
Test for overall effect: Z = 1.55 (P = 0.12)							
3 > 5000 mL							
Shackford 1983	30	1.6 (0.8)	28	1.8 (1.6)		19.5 %	-0.16 [-0.67, 0.36]
Shackford 1987	26	0.7 (0.7)	26	1.1 (5.8)		18.8 %	-0.10 [-0.64, 0.45]
Subtotal (95% CI)	**56**		**54**			**38.3 %**	**-0.13 [-0.50, 0.25]**
Heterogeneity: Tau² = 0.0; Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%							
Test for overall effect: Z = 0.67 (P = 0.50)							
Total (95% CI)	**137**		**133**			**100.0 %**	**0.17 [-0.23, 0.57]**
Heterogeneity: Tau² = 0.14; Chi² = 12.53, df = 5 (P = 0.03); I² =60%							
Test for overall effect: Z = 0.82 (P = 0.41)							

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Analysis 5.5. Comparison 5 Diuresis during study period (L), Outcome 5 Diuresis during study period (sensitivity analysis by study quality).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 5 Diuresis during study period (L)

Outcome: 5 Diuresis during study period (sensitivity analysis by study quality)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Study grade = A							
Jarvela 2000	20	0.45 (0.28)	20	0.43 (0.27)		17.0 %	0.07 [-0.55, 0.69]
Jarvela 2001	36	3.34 (1.04)	36	2.94 (0.85)		20.7 %	0.42 [-0.05, 0.88]
Subtotal (95% CI)	**56**		**56**			**37.7 %**	**0.29 [-0.08, 0.66]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%							
Test for overall effect: Z = 1.53 (P = 0.13)							
2 Study grade = B							
Bruegger 2005	14	1.2 (0.55)	14	1.5 (1.33)		14.4 %	-0.29 [-1.03, 0.46]
Cross 1989	11	4.5 (0.5)	9	3.8 (0.25)		9.6 %	1.64 [0.59, 2.69]
Shackford 1987	26	0.7 (0.7)	26	1.1 (5.8)		18.8 %	-0.10 [-0.64, 0.45]
Subtotal (95% CI)	**51**		**49**			**42.8 %**	**0.33 [-0.64, 1.30]**
Heterogeneity: Tau^2 = 0.58; Chi^2 = 9.84, df = 2 (P = 0.01); I^2 =80%							
Test for overall effect: Z = 0.67 (P = 0.50)							
3 Study grade = D							
Shackford 1983	30	1.6 (0.8)	28	1.8 (1.6)		19.5 %	-0.16 [-0.67, 0.36]
Subtotal (95% CI)	**30**		**28**			**19.5 %**	**-0.16 [-0.67, 0.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
Total (95% CI)	**137**		**133**			**100.0 %**	**0.17 [-0.23, 0.57]**
Heterogeneity: Tau^2 = 0.14; Chi^2 = 12.53, df = 5 (P = 0.03); I^2 =60%							
Test for overall effect: Z = 0.82 (P = 0.41)							

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Analysis 6.1. Comparison 6 Peak serum sodium (meq/L), Outcome 1 Peak serum sodium (stratified by type of surgery).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 6 Peak serum sodium (meq/L)

Outcome: 1 Peak serum sodium (stratified by type of surgery)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Cardiovascular surgery							
Bruegger 2005	14	159 (3)	14	143 (1)		4.6 %	6.95 [4.85, 9.04]
Cross 1989	11	145.4 (1.4)	9	139 (1)		4.9 %	4.95 [3.02, 6.88]
Jarvela 2001	36	150 (3)	36	140 (2)		7.7 %	3.88 [3.08, 4.68]
Shackford 1983	30	151 (7.6)	28	139 (7.6)		8.1 %	1.56 [0.96, 2.15]
Shackford 1987	26	157 (7.2)	26	140 (7.2)		7.8 %	2.33 [1.61, 3.04]
Younes 1988	18	147 (9)	13	137 (5)		7.7 %	1.28 [0.49, 2.07]
Subtotal (95% CI)	**135**		**126**			**40.8 %**	**3.20 [1.98, 4.42]**
Heterogeneity: Tau² = 1.96; Chi² = 53.42, df = 5 (P<0.00001); I² =91%							
Test for overall effect: Z = 5.14 (P < 0.00001)							
2 Transurethral resection of the prostate							
Baraka 1994	17	138.5 (5)	16	137 (3)		7.9 %	0.35 [-0.34, 1.04]
Kato 1996	20	145 (4.4)	20	139.9 (2.4)		7.9 %	1.41 [0.71, 2.11]
Kimura 1994	7	142 (1)	7	137 (3)		6.2 %	2.09 [0.70, 3.48]
Subtotal (95% CI)	**44**		**43**			**22.0 %**	**1.17 [0.22, 2.11]**
Heterogeneity: Tau² = 0.48; Chi² = 7.09, df = 2 (P = 0.03); I² =72%							
Test for overall effect: Z = 2.42 (P = 0.015)							
3 Other surgery							
Ishikawa 1996	8	144.1 (3.4)	7	139 (3.5)		6.8 %	1.39 [0.22, 2.56]
Jarvela 2000	20	145 (2)	20	140 (2)		7.6 %	2.45 [1.61, 3.29]
Kolsen-Petersen 2004	19	150 (3)	20	141 (3)		7.4 %	2.94 [2.01, 3.87]
Veroli 1992	10	143.7 (1.7)	20	139.95 (1.8)		7.3 %	2.06 [1.12, 3.01]
Wang 1997	30	142 (5)	30	139 (3)		8.2 %	0.72 [0.19, 1.24]
Subtotal (95% CI)	**87**		**97**			**37.2 %**	**1.89 [0.97, 2.81]**
Heterogeneity: Tau² = 0.89; Chi² = 23.84, df = 4 (P = 0.00009); I² =83%							
Test for overall effect: Z = 4.03 (P = 0.000055)							
Total (95% CI)	**266**		**266**			**100.0 %**	**2.24 [1.59, 2.89]**
Heterogeneity: Tau² = 1.28; Chi² = 107.32, df = 13 (P<0.00001); I² =88%							
Test for overall effect: Z = 6.72 (P < 0.00001)							

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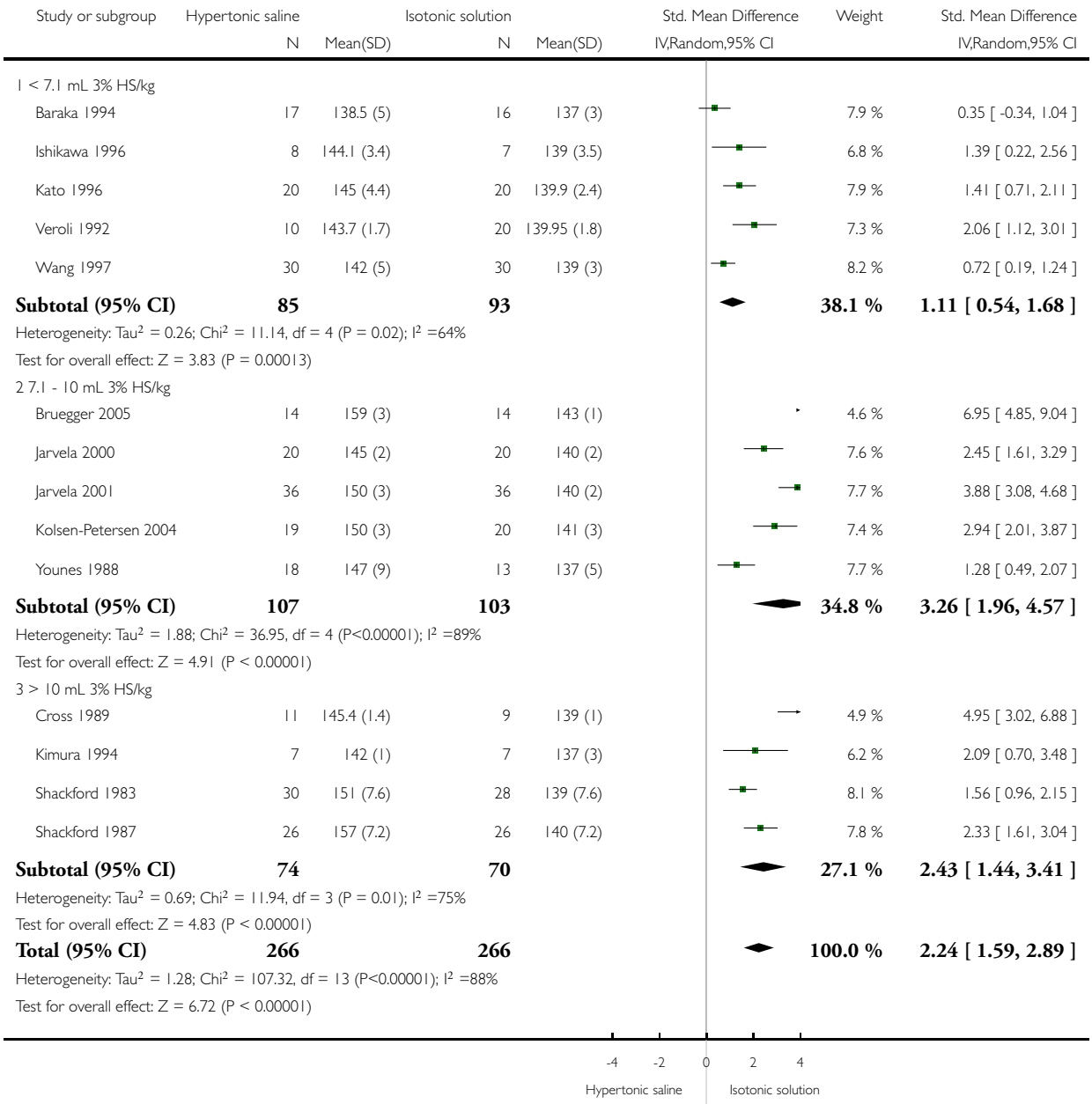
Analysis 6.2. Comparison 6 Peak serum sodium (meq/L), Outcome 2 Peak serum sodium (stratified by dose of HS).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 6 Peak serum sodium (meq/L)

Outcome: 2 Peak serum sodium (stratified by dose of HS)



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Analysis 6.3. Comparison 6 Peak serum sodium (meq/L), Outcome 3 Peak serum sodium (stratified by volume given in control group).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 6 Peak serum sodium (meq/L)

Outcome: 3 Peak serum sodium (stratified by volume given in control group)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 2000 mL/kg							
Jarvela 2000	20	145 (2)	20	140 (2)		11.9 %	2.45 [1.61, 3.29]
Kato 1996	20	145 (4.4)	20	139.9 (2.4)		12.4 %	1.41 [0.71, 2.11]
Veroli 1992	10	143.7 (1.7)	20	139.95 (1.8)		11.5 %	2.06 [1.12, 3.01]
Younes 1988	18	147 (9)	13	137 (5)		12.1 %	1.28 [0.49, 2.07]
Subtotal (95% CI)	**68**		**73**			**48.0 %**	**1.76 [1.22, 2.31]**
Heterogeneity: Tau² = 0.13; Chi² = 5.35, df = 3 (P = 0.15); I² =44%							
Test for overall effect: Z = 6.38 (P < 0.00001)							
2 2000 - 5000 mL							
Bruegger 2005	14	159 (3)	14	143 (1)		7.0 %	6.95 [4.85, 9.04]
Cross 1989	11	145.4 (1.4)	9	139 (1)		7.6 %	4.95 [3.02, 6.88]
Jarvela 2001	36	150 (3)	36	140 (2)		12.1 %	3.88 [3.08, 4.68]
Subtotal (95% CI)	**61**		**59**			**26.8 %**	**5.06 [3.28, 6.84]**
Heterogeneity: Tau² = 1.79; Chi² = 7.59, df = 2 (P = 0.02); I² =74%							
Test for overall effect: Z = 5.58 (P < 0.00001)							
3 > 5000 mL							
Shackford 1983	30	151 (7.6)	28	139 (7.6)		12.8 %	1.56 [0.96, 2.15]
Shackford 1987	26	157 (7.2)	26	140 (7.2)		12.4 %	2.33 [1.61, 3.04]
Subtotal (95% CI)	**56**		**54**			**25.2 %**	**1.91 [1.16, 2.67]**
Heterogeneity: Tau² = 0.18; Chi² = 2.62, df = 1 (P = 0.11); I² =62%							
Test for overall effect: Z = 5.00 (P < 0.00001)							
Total (95% CI)	**185**		**186**			**100.0 %**	**2.69 [1.89, 3.48]**
Heterogeneity: Tau² = 1.20; Chi² = 59.62, df = 8 (P<0.00001); I² =87%							
Test for overall effect: Z = 6.60 (P < 0.00001)							

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Analysis 6.4. Comparison 6 Peak serum sodium (meq/L), Outcome 4 Peak serum sodium (sensitivity analysis by study quality).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 6 Peak serum sodium (meq/L)

Outcome: 4 Peak serum sodium (sensitivity analysis by study quality)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Study grade = A							
Jarvela 2000	20	145 (2)	20	140 (2)		7.8 %	5.00 [3.76, 6.24]
Jarvela 2001	36	150 (3)	36	140 (2)		7.8 %	10.00 [8.82, 11.18]
Subtotal (95% CI)	**56**		**56**			**15.5 %**	**7.50 [2.60, 12.40]**
Heterogeneity: Tau² = 12.12; Chi² = 32.85, df = 1 (P<0.00001); I² =97%							
Test for overall effect: Z = 3.00 (P = 0.0027)							
2 Study grade = B							
Baraka 1994	17	138.5 (5)	16	137 (3)		7.0 %	1.50 [-1.29, 4.29]
Bruegger 2005	14	159 (3)	14	143 (1)		7.6 %	16.00 [14.34, 17.66]
Cross 1989	11	145.4 (1.4)	9	139 (1)		7.8 %	6.40 [5.35, 7.45]
Ishikawa 1996	8	144.1 (3.4)	7	139 (3.5)		6.6 %	5.10 [1.60, 8.60]
Kato 1996	20	145 (4.4)	20	139.9 (2.4)		7.3 %	5.10 [2.90, 7.30]
Kimura 1994	7	142 (1)	7	137 (3)		7.3 %	5.00 [2.66, 7.34]
Kolsen-Petersen 2004	19	150 (3)	20	141 (3)		7.5 %	9.00 [7.12, 10.88]
Shackford 1987	26	157 (7.2)	26	140 (7.2)		6.3 %	17.00 [13.09, 20.91]
Veroli 1992	10	143.7 (1.7)	20	139.95 (1.8)		7.7 %	3.75 [2.43, 5.07]
Wang 1997	30	142 (5)	30	139 (3)		7.4 %	3.00 [0.91, 5.09]
Younes 1988	18	147 (9)	13	137 (5)		5.6 %	10.00 [5.03, 14.97]
Subtotal (95% CI)	**180**		**182**			**78.2 %**	**7.33 [4.59, 10.08]**
Heterogeneity: Tau² = 19.76; Chi² = 204.53, df = 10 (P<0.00001); I² =95%							
Test for overall effect: Z = 5.23 (P < 0.00001)							
3 Study grade = D							
Shackford 1983	30	151 (7.6)	28	139 (7.6)		6.3 %	12.00 [8.09, 15.91]
Subtotal (95% CI)	**30**		**28**			**6.3 %**	**12.00 [8.09, 15.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.01 (P < 0.00001)							
Total (95% CI)	**266**		**266**			**100.0 %**	**7.64 [5.47, 9.80]**
Heterogeneity: Tau² = 15.32; Chi² = 245.24, df = 13 (P<0.00001); I² =95%							
Test for overall effect: Z = 6.92 (P < 0.00001)							

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Analysis 7.1. Comparison 7 Final serum sodium (meq/L), Outcome 1 Final serum sodium (all studies).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 7 Final serum sodium (meq/L)

Outcome: 1 Final serum sodium (all studies)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bruegger 2005	6	143 (5.3)	6	140 (4)		7.4 %	0.59 [-0.58, 1.76]
Cross 1989	11	144 (2)	9	139.5 (1)		6.8 %	2.64 [1.37, 3.91]
Jarvela 2000	20	145 (2)	20	140 (2)		9.5 %	2.45 [1.61, 3.29]
Jarvela 2001	20	141 (1)	20	139 (1)		10.0 %	1.96 [1.19, 2.73]
Kato 1996	20	140.6 (2.6)	20	138.6 (2.4)		10.8 %	0.78 [0.14, 1.43]
Kolsen-Petersen 2004	19	139 (2)	20	138 (1)		10.8 %	0.62 [-0.02, 1.27]
Shackford 1983	30	146 (7.6)	28	136 (15.2)		11.5 %	0.83 [0.29, 1.37]
Shackford 1987	26	145 (7.2)	26	139 (7.2)		11.3 %	0.82 [0.25, 1.39]
Wang 1997	30	142 (5)	30	138 (3)		11.5 %	0.96 [0.42, 1.49]
Younes 1988	18	136 (7)	13	138 (6)		10.3 %	-0.29 [-1.01, 0.42]
Total (95% CI)	**200**		**192**			**100.0 %**	**1.07 [0.60, 1.54]**

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 39.29$, df = 9 (P = 0.00001); $I^2 = 77\%$

Test for overall effect: Z = 4.48 (P < 0.00001)

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Analysis 7.2. Comparison 7 Final serum sodium (meq/L), Outcome 2 Final serum sodium (stratified by dose of HS given).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 7 Final serum sodium (meq/L)

Outcome: 2 Final serum sodium (stratified by dose of HS given)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 7.1 mL 3% HS/kg							
Kato 1996	20	140.6 (2.6)	20	138.6 (2.4)		10.8 %	0.78 [0.14, 1.43]
Wang 1997	30	142 (5)	30	138 (3)		11.5 %	0.96 [0.42, 1.49]
Subtotal (95% CI)	**50**		**50**			**22.4 %**	**0.89 [0.47, 1.30]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.21 (P = 0.000025)							
2 7.1 - 10 mL 3% HS/kg							
Bruegger 2005	6	143 (5.3)	6	140 (4)		7.4 %	0.59 [-0.58, 1.76]
Jarvela 2000	20	145 (2)	20	140 (2)		9.5 %	2.45 [1.61, 3.29]
Jarvela 2001	20	141 (1)	20	139 (1)		10.0 %	1.96 [1.19, 2.73]
Kolsen-Petersen 2004	19	139 (2)	20	138 (1)		10.8 %	0.62 [-0.02, 1.27]
Younes 1988	18	136 (7)	13	138 (6)		10.3 %	-0.29 [-1.01, 0.42]
Subtotal (95% CI)	**83**		**79**			**48.0 %**	**1.07 [0.06, 2.07]**
Heterogeneity: $Tau^2 = 1.13$; $Chi^2 = 31.78$, df = 4 (P<0.00001); $I^2 = 87\%$							
Test for overall effect: Z = 2.08 (P = 0.038)							
3 > 10 mL 3% HS/kg							
Cross 1989	11	144 (2)	9	139.5 (1)		6.8 %	2.64 [1.37, 3.91]
Shackford 1983	30	146 (7.6)	28	136 (15.2)		11.5 %	0.83 [0.29, 1.37]
Shackford 1987	26	145 (7.2)	26	139 (7.2)		11.3 %	0.82 [0.25, 1.39]
Subtotal (95% CI)	**67**		**63**			**29.7 %**	**1.21 [0.43, 2.00]**
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 7.17$, df = 2 (P = 0.03); $I^2 = 72\%$							
Test for overall effect: Z = 3.04 (P = 0.0024)							
Total (95% CI)	**200**		**192**			**100.0 %**	**1.07 [0.60, 1.54]**
Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 39.29$, df = 9 (P = 0.00001); $I^2 = 77\%$							
Test for overall effect: Z = 4.48 (P < 0.00001)							

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Analysis 7.3. Comparison 7 Final serum sodium (meq/L), Outcome 3 Final serum sodium (stratified by volume given in control group).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 7 Final serum sodium (meq/L)

Outcome: 3 Final serum sodium (stratified by volume given in control group)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 < 2000 mL							
Jarvela 2000	20	145 (2)	20	140 (2)		12.3 %	2.45 [1.61, 3.29]
Kato 1996	20	140.6 (2.6)	20	138.6 (2.4)		13.6 %	0.78 [0.14, 1.43]
Younes 1988	18	136 (7)	13	138 (6)		13.1 %	-0.29 [-1.01, 0.42]
Subtotal (95% CI)	**58**		**53**			**39.1 %**	**0.96 [-0.49, 2.42]**
Heterogeneity: Tau^2 = 1.51; Chi^2 = 23.78, df = 2 (P<0.00001); I^2 =92%							
Test for overall effect: Z = 1.30 (P = 0.19)							
2 2000 - 5000 mL							
Bruegger 2005	6	143 (5.3)	6	140 (4)		10.2 %	0.59 [-0.58, 1.76]
Cross 1989	11	144 (2)	9	139.5 (1)		9.6 %	2.64 [1.37, 3.91]
Jarvela 2001	20	141 (1)	20	139 (1)		12.8 %	1.96 [1.19, 2.73]
Subtotal (95% CI)	**37**		**35**			**32.6 %**	**1.73 [0.68, 2.78]**
Heterogeneity: Tau^2 = 0.57; Chi^2 = 5.96, df = 2 (P = 0.05); I^2 =66%							
Test for overall effect: Z = 3.22 (P = 0.0013)							
3 > 5000 mL							
Shackford 1983	30	146 (7.6)	28	136 (15.2)		14.3 %	0.83 [0.29, 1.37]
Shackford 1987	26	145 (7.2)	26	139 (7.2)		14.1 %	0.82 [0.25, 1.39]
Subtotal (95% CI)	**56**		**54**			**28.3 %**	**0.83 [0.43, 1.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.98); I^2 =0.0%							
Test for overall effect: Z = 4.14 (P = 0.000034)							
Total (95% CI)	**151**		**142**			**100.0 %**	**1.17 [0.55, 1.79]**
Heterogeneity: Tau^2 = 0.62; Chi^2 = 38.07, df = 7 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 3.70 (P = 0.00022)							

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Analysis 7.4. Comparison 7 Final serum sodium (meq/L), Outcome 4 Final serum sodium (stratified by type of surgery).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 7 Final serum sodium (meq/L)

Outcome: 4 Final serum sodium (stratified by type of surgery)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Cardiovascular surgery							
Bruegger 2005	6	143 (5.3)	6	140 (4)		7.4 %	0.59 [-0.58, 1.76]
Cross 1989	11	144 (2)	9	139.5 (1)		6.8 %	2.64 [1.37, 3.91]
Jarvela 2001	20	141 (1)	20	139 (1)		10.0 %	1.96 [1.19, 2.73]
Shackford 1983	30	146 (7.6)	28	136 (15.2)		11.5 %	0.83 [0.29, 1.37]
Shackford 1987	26	145 (7.2)	26	139 (7.2)		11.3 %	0.82 [0.25, 1.39]
Subtotal (95% CI)	**93**		**89**			**47.0 %**	**1.28 [0.65, 1.91]**
Heterogeneity: Tau² = 0.34; Chi² = 13.09, df = 4 (P = 0.01); I² =69%							
Test for overall effect: Z = 3.96 (P = 0.000075)							
2 Transurethral resection of prostate							
Kato 1996	20	140.6 (2.6)	20	138.6 (2.4)		10.8 %	0.78 [0.14, 1.43]
Subtotal (95% CI)	**20**		**20**			**10.8 %**	**0.78 [0.14, 1.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.38 (P = 0.017)							
3 Other surgery							
Jarvela 2000	20	145 (2)	20	140 (2)		9.5 %	2.45 [1.61, 3.29]
Kolsen-Petersen 2004	19	139 (2)	20	138 (1)		10.8 %	0.62 [-0.02, 1.27]
Wang 1997	30	142 (5)	30	138 (3)		11.5 %	0.96 [0.42, 1.49]
Younes 1988	18	136 (7)	13	138 (6)		10.3 %	-0.29 [-1.01, 0.42]
Subtotal (95% CI)	**87**		**83**			**42.1 %**	**0.91 [-0.04, 1.87]**
Heterogeneity: Tau² = 0.83; Chi² = 24.37, df = 3 (P = 0.00002); I² =88%							
Test for overall effect: Z = 1.87 (P = 0.061)							
Total (95% CI)	**200**		**192**			**100.0 %**	**1.07 [0.60, 1.54]**
Heterogeneity: Tau² = 0.42; Chi² = 39.29, df = 9 (P = 0.00001); I² =77%							
Test for overall effect: Z = 4.48 (P < 0.00001)							

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Analysis 7.5. Comparison 7 Final serum sodium (meq/L), Outcome 5 Final serum sodium (sensitivity analysis by study quality).

Review: Hypertonic saline for peri-operative fluid management

Comparison: 7 Final serum sodium (meq/L)

Outcome: 5 Final serum sodium (sensitivity analysis by study quality)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Study grade = A							
Jarvela 2000	20	145 (2)	20	140 (2)		13.8 %	5.00 [3.76, 6.24]
Jarvela 2001	20	141 (1)	20	139 (1)		15.3 %	2.00 [1.38, 2.62]
Subtotal (95% CI)	**40**		**40**			**29.2 %**	**3.45 [0.51, 6.39]**
Heterogeneity: Tau^2 = 4.25; Chi^2 = 18.00, df = 1 (P = 0.00002); I^2 =94%							
Test for overall effect: Z = 2.30 (P = 0.021)							
2 Study grade = B							
Bruegger 2005	6	143 (5.3)	6	140 (4)		4.2 %	3.00 [-2.31, 8.31]
Cross 1989	11	144 (2)	9	139.5 (1)		13.5 %	4.50 [3.15, 5.85]
Kato 1996	20	140.6 (2.6)	20	138.6 (2.4)		12.9 %	2.00 [0.45, 3.55]
Kolsen-Petersen 2004	19	139 (2)	20	138 (1)		14.5 %	1.00 [0.00, 2.00]
Shackford 1987	26	145 (7.2)	26	139 (7.2)		6.3 %	6.00 [2.09, 9.91]
Wang 1997	30	142 (5)	30	138 (3)		11.1 %	4.00 [1.91, 6.09]
Younes 1988	18	136 (7)	13	138 (6)		5.1 %	-2.00 [-6.59, 2.59]
Subtotal (95% CI)	**130**		**124**			**67.6 %**	**2.74 [1.11, 4.38]**
Heterogeneity: Tau^2 = 3.11; Chi^2 = 26.15, df = 6 (P = 0.00021); I^2 =77%							
Test for overall effect: Z = 3.28 (P = 0.0010)							
3 Study grade = D							
Shackford 1983	30	146 (7.6)	28	136 (15.2)		3.3 %	10.00 [3.75, 16.25]
Subtotal (95% CI)	**30**		**28**			**3.3 %**	**10.00 [3.75, 16.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.13 (P = 0.0017)							
Total (95% CI)	**200**		**192**			**100.0 %**	**3.18 [1.91, 4.44]**
Heterogeneity: Tau^2 = 2.61; Chi^2 = 49.84, df = 9 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 4.92 (P < 0.00001)							

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Analysis 12.1. Comparison 12 Other outcomes of interest, Outcome 1 Maximum intraoperative serum osmolarity (mOsm/kg H2O).

Review: Hypertonic saline for peri-operative fluid management

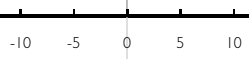
Comparison: 12 Other outcomes of interest

Outcome: 1 Maximum intraoperative serum osmolarity (mOsm/kg H2O)

Study or subgroup	Hypertonic saline		Isotonic solution		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Ishikawa 1996	8	295.8 (4.4)	7	281.5 (10.2)		10.8 %	1.76 [0.51, 3.01]
Jarvela 2000	20	302 (5)	20	292 (3)		12.0 %	2.38 [1.55, 3.20]
Jarvela 2001	20	313 (6)	20	290 (4)		11.0 %	4.42 [3.23, 5.61]
Kato 1996	20	298.2 (6.1)	20	284.3 (3.5)		11.8 %	2.74 [1.85, 3.62]
Kimura 1994	7	296 (4)	7	287 (7)		10.9 %	1.48 [0.25, 2.71]
Kolsen-Petersen 2004	19	302 (2)	20	285 (0.5)		6.4 %	11.56 [8.78, 14.34]
Shackford 1983	30	301 (15.2)	28	284 (7.6)		12.5 %	1.38 [0.80, 1.96]
Shackford 1987	26	309 (14.4)	26	284 (7.2)		12.3 %	2.16 [1.47, 2.86]
Younes 1988	18	327 (11)	13	320 (8)		12.2 %	0.69 [-0.05, 1.43]
Total (95% CI)	**168**		**161**			**100.0 %**	**2.72 [1.73, 3.71]**

Heterogeneity: $Tau^2 = 1.95$; $Chi^2 = 82.38$, df = 8 (P<0.00001); $I^2 = 90\%$

Test for overall effect: Z = 5.38 (P < 0.00001)



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Analysis 12.2. Comparison 12 Other outcomes of interest, Outcome 2 Maximum intraoperative pulmonary artery wedge pressure (mm Hg).

Review: Hypertonic saline for peri-operative fluid management

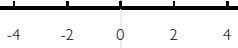
Comparison: 12 Other outcomes of interest

Outcome: 2 Maximum intraoperative pulmonary artery wedge pressure (mm Hg)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Jarvela 2001	20	9.1 (3.5)	20	8.4 (4.5)		26.6 %	0.17 [-0.45, 0.79]
Shackford 1983	30	10 (7.6)	28	11 (7.6)		38.6 %	-0.13 [-0.65, 0.39]
Shackford 1987	26	11 (7.2)	26	11 (7.2)		34.7 %	0.0 [-0.54, 0.54]
Total (95% CI)	**76**		**74**			**100.0 %**	**0.00 [-0.33, 0.32]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.53$, df = 2 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 0.03 (P = 0.98)



Analysis 12.3. Comparison 12 Other outcomes of interest, Outcome 3 Maximum intraoperative cardiac index (L/min/M2).

Review: Hypertonic saline for peri-operative fluid management

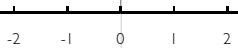
Comparison: 12 Other outcomes of interest

Outcome: 3 Maximum intraoperative cardiac index (L/min/M2)

Study or subgroup	Hypertonic saline N	Mean(SD)	Isotonic solution N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Cross 1989	11	3.1 (0.3)	9	2.65 (0.3)		12.6 %	1.44 [0.43, 2.45]
Jarvela 2000	20	3.19 (0.5)	20	3.02 (0.65)		20.9 %	0.29 [-0.34, 0.91]
Jarvela 2001	20	3.2 (1)	20	2.3 (0.5)		19.6 %	1.12 [0.44, 1.79]
Shackford 1983	30	3.1 (0.8)	28	3 (0.8)		23.9 %	0.12 [-0.39, 0.64]
Shackford 1987	26	3.7 (1.2)	26	3.4 (1.2)		23.0 %	0.25 [-0.30, 0.79]
Total (95% CI)	**107**		**103**			**100.0 %**	**0.55 [0.10, 1.00]**

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 9.77$, df = 4 (P = 0.04); $I^2 = 59\%$

Test for overall effect: Z = 2.38 (P = 0.017)



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APPENDICES

Appendix 1. MEDLINE (1966 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)

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#49 #22 or #38 or #48
#50 #13 and #49

Appendix 2. EMBASE (1980 to 2007 week 18)

#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

Appendix 3. CINAHL (1982 to April week 1, 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*

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#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

Appendix 4. LILACS (1982 to April 2007)

"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]

Appendix 5. CENTRAL, (*The Cochrane Library, 2007* Issue 1)

#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)

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#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

Appendix 6. Search update: April 2007 to August 2009

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

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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)

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Conceiving the review: T. Znajda (TZ), K. Burns (KB), V. McAlister (VM)

Co-ordinating the review: VM

Undertaking manual searches: TZ, K.B, VM

Screening search results: TZ, KB, VM, BC

Organizing retrieval of papers: TZ, VM

Screening retrieved papers against inclusion criteria: TZ, KB, VM

Appraising quality of papers: TZ, KB, VM

Abstracting data from papers: TZ, KB, VM, BC

Writing to authors of papers for additional information: VM

Obtaining and screening data on unpublished studies: TZ, KB, VM

Data management for the review: TZ, KB, VM

Entering data into Review Manager (RevMan 5.0): VM, KB

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RevMan statistical data: VM, KB

Other statistical analysis not using RevMan: KB

Double entry of data: (data entered by person one: VM ; data entered by person two: KB)

Interpretation of data: TZ, KB, VM

Statistical analysis: TZ, KB, VM

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

DECLARATIONS OF INTEREST

None.

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