Title

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Journal

Anaesthesia, 75(2)

ISSN

0003-2409

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Publication Date

2020-02-01

DOI

10.1111/anae.14857

Peer reviewed

Anaesthesia 2020, 75, 254–265 doi:10.1111/anae.14857

Review Article

Supplemental peri-operative intravenous crystalloids for postoperative nausea and vomiting: an abridged Cochrane systematic review

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Summary

We conducted a Cochrane systematic review on the effectiveness of supplemental intravenous crystalloid administration in preventing postoperative nausea and vomiting. We included randomised controlled trials of patients undergoing surgery under general anaesthesia and given supplemental peri-operative intravenous crystalloid. Our primary outcomes were the risk of postoperative nausea and the risk of postoperative vomiting. We assessed the risk of bias for each included study and applied the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework for the certainty of evidence. We included 41 studies. We found that the intervention probably reduces the overall risk of postoperative nausea, the risk ratio (95%CI) being 0.62 (0.51–0.75) (I^2 = 57%, p < 0.00001, 18 studies; 1766 participants; moderate-certainty evidence). It also probably reduces the risk of postoperative nausea within 6 h of surgery, with a risk ratio (95% CI) of 0.67 (0.58 to 0.78) (I^2 = 9%, p < 0.00001, 20 studies; 2310 participants; moderate-certainty evidence) and by around 24 h, the risk ratio (95%CI) being 0.47 (0.32–0.69) (I^2 = 38%, p = 0.0001, 17 studies; 1682 participants; moderate-certainty evidence). Supplemental intravenous crystalloid probably also reduces the overall risk of postoperative vomiting, with a risk ratio (95%CI) of 0.50 (0.40–0.63) (I^2 = 31%, p < 0.00001, 20 studies; 1970 participants; moderate-certainty evidence). The beneficial effect on vomiting was seen both within 6 h and by around 24 h postoperatively.

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Accepted: 23 August 2019
Keywords: crystalloid; PONV; prophylaxis; systematic review
This article is based on a Cochrane review published in the Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD012212. https://doi.org/10.1002/14651858.cd012212.pub2.
Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database should be consulted for the most recent version of the review.
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Introduction

Postoperative nausea and vomiting (PONV) is a common and unwelcome complication after general anaesthesia, with important implications for patient satisfaction, surgical outcomes and resource utilisation [1]. There are numerous prophylactic treatments for PONV, such as ondansetron, dexamethasone, tropisetron, dolasetron, cyclizine, granisetron and droperidol. Pharmacological interventions are often

used in combination [2], and multimodal prophylaxis is recommended in patients predicted to be at high risk for PONV [3]. The use of regional anaesthesia, or total intravenous (i.v.) anaesthesia with propofol, is comparatively protective against PONV [4–6]. Non-pharmacological methods of PONV prophylaxis have also been described, such as acupuncture [7].

Intravenous crystalloids are widely given peri-operatively. They are inexpensive, have relatively few adverse effects and may offer another non-pharmacological method of preventing PONV. A prior systematic review not only reported that supplemental i.v. crystalloids may be effective in preventing PONV but also suggested the presence of reporting bias [1]. The goal of this review was to systematically assess the effectiveness of supplemental i.v. crystalloid administration in preventing PONV in patients undergoing surgical procedures under general anaesthesia, and also to assess potential harm of this intervention. However, since PONV is inconsistently defined in the literature, we opted to focus on analysis of two related outcomes, postoperative nausea and postoperative vomiting, which are defined more consistently in the literature and are also more commonly reported.

Methods

A prospectively registered protocol for this systematic review [8] and the unabridged Cochrane Review are available elsewhere [9].

We included randomised controlled trials (RCT) examining supplemental peri-operative i.v. crystalloid administration, with participants older than 6 months, undergoing any type of surgical procedure performed under general anaesthesia. For sub-group and sensitivity analyses, we defined 'children' as aged between 6 months and 17 years, and 'adults' as 18 years or older.

Given a lack of agreement in the literature on specific volumes administered, we defined the intervention as an i.v. crystalloid volume larger than that received by a comparator group. We included studies in which the comparator received no supplemental peri-operative i.v. crystalloid. We included studies regardless of the timing of administration, including pre-operative, intra-operative, postoperative or a combination of these. Timing of administration was classified by the point at which administration was initiated. We also included studies that administered dextrose-containing crystalloids but, since i.v. dextrose may independently reduce PONV [10], we planned a sensitivity analysis to explore the effect of including these studies on the meta-analysis. We excluded other routes of crystalloid administration (i.e. oral). We excluded studies that compared only supplemental i.v. colloids with a comparator; however, we included studies that used both colloids and crystalloids, as long as they had an intervention group receiving only supplemental crystalloid, in a volume greater than that received by a comparator group that also received only crystalloid.

Our primary outcomes were: risk of postoperative nausea (defined as the presence of subjective nausea, reported dichotomously or based on a study-defined dichotomous threshold on a continuous scale such as a visual analogue scale); and risk of postoperative vomiting (reported dichotomously by any discrete episodes of vomiting). Although for both primary outcomes our analyses focused on the risk of these outcomes over the overall study period, when the data were available we also analysed the risk of these outcomes occurring at different time periods postoperatively (i.e., 'early' and 'late'). In accordance with the prior systematic review on this topic, we defined the early postoperative period as the time period reporting the highest incidence of nausea or vomiting within 6 h after surgery, and defined the late postoperative period as the time period reporting nausea or vomiting nearest to 24 h after surgery [1]. For the risk of postoperative nausea, when continuous data were reported (i.e. using a visual analogue scale), we also analysed them separately from dichotomous data in order to better characterise the magnitude of effect. Our secondary outcomes were: risk of requiring pharmacological treatment for PONV; risk of unplanned postoperative admission to hospital; and risk of a serious adverse event (i.e. admission to high-dependency unit, postoperative cardiac or respiratory complication, or death).

Our detailed search strategy can be found in the Supporting Information (Appendix S1). We searched the following databases for relevant trials: Cochrane Central Register of Controlled Trials; MEDLINE; Embase; Cumulative Index of Nursing and Allied Health; and also searched the relevant grey literature, and conducted forward and backward searches through our references. When necessary, we attempted to contact trial authors for additional information. Our search was completed on 4 August 2018. We did not exclude any study based on language of publication or publication status.

Two review authors (KJ, MW) read titles and abstracts, removed obviously irrelevant reports and assessed the retained studies using the Cochrane 'Risk of Bias' tool [11, 12]. Disagreements were resolved by discussion with two other authors (RG, SB). Four authors (KJ, MW, RG, SB) examined the full-text reports to determine which met the eligibility criteria, and made final decisions on study inclusion.

We assessed the certainty of the evidence based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [13, 14]. This approach takes into consideration within-study risk of bias (methodological quality), the directness of the evidence, the heterogeneity of the data, the precision of effect estimates and the risk of publication bias. We considered the following standard methodological criteria: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incompleteness of outcome data (attrition bias); selective outcome reporting (reporting bias); and other sources of bias.

We analysed data with Review Manager 5 software [12], using random-effects models for all comparisons, given the anticipated moderate to high amount of heterogeneity across studies [12, 15, 16]. Compared with fixed-effects models, random-effects models are more resistant to finding spurious effects in the face of statistical heterogeneity. We did not treat medians and means as equivalent. When possible, we calculated missing statistics from other quoted statistics. When participant dropout was encountered, we used an intention-to-treat analysis. We presented dichotomous data as risk ratios (RRs) along with their 95%CIs, and continuous data as mean differences (MDs) with 95%CIs.

We considered clinical heterogeneity during manuscript evaluation, before pooling the results. We quantified statistical heterogeneity using the I^2 statistic, judging the amount of heterogeneity as low ($I^2 < 40\%$), moderate ($I^2 = 40–75\%$) or high ($I^2 > 75\%$) [13, 15, 17]. In the event of moderate or high statistical heterogeneity, we started with visual inspection of the forest plots, then proceeded with the following a priori sub-group analyses, namely: volume of supplemental i.v. crystalloid administered (control:intervention volume ratio of less than 1:3 or greater than 1:3); timing of supplemental i.v. crystalloid administration (pre-operative, peri-operative or postoperative); and patient age (6 months to 17 years, 18 years or older). For outcomes that had a moderate or high level of heterogeneity after sub-group analyses, the results of the sub-group analyses are only presented in a narrative manner. For outcomes involving sufficient studies in children, the sub-group results for them are also specifically reported, to elucidate this important source of clinical heterogeneity, and to provide specific guidance for clinicians working with this specific patient population.

We performed sensitivity analyses for outcomes involving studies that used dextrose-containing fluids, as this is an intervention that may independently reduce the risk of PONV [10]. Also, there were different specific volumes of supplemental i.v. crystalloid administered in each study. We therefore conducted sensitivity analyses to determine the effect of including studies that infused larger absolute volumes of supplemental i.v. crystalloid to their respective comparator groups (i.e. 10 $ml.kg^{-1}$ or more). We additionally sought to assess the influence of studies at relatively higher risk of bias. For each outcome involving studies with one or fewer domains at high or unclear risk of bias, we performed a sensitivity analysis using only those studies with low risk of bias. Finally, in order to assess publication bias, we visually inspected funnel plots generated in Review Manager 5 for each outcome [12, 18, 19].

Results

For detailed results, please refer to our original Cochrane review [9]. Study search and selection are shown in Fig. 1. Three studies meeting inclusion criteria did not report data in sufficient detail [20–22]. We were unable to obtain further information from these authors, so we included 38 RCTs in the meta-analysis, using data from 4034 participants.

Details of studies meeting our inclusion criteria are presented in Table 1. All studies enrolled participants undergoing surgery with general anaesthesia, performed on an ambulatory basis or with a short length of stay (i.e. one day). Thirty-one studies only included patients classified as ASA physical status 1 or 2 [20, 23–25, 27–31, 33–38, 40–44, 48–52, 54–58, 60]. One study specifically selected participants at high risk for PONV [27], whereas all other studies were inconsistent in their reporting of baseline risk factors for PONV. Intervention groups were generally administered at least 10 $ml.kg^{-1}$ of i.v. supplemental crystalloid. In a minority of studies, comparator groups were administered an i.v. supplemental crystalloid bolus comparable to this volume [25, 29, 32, 35, 37, 40, 41, 45, 53, 54, 58].

Figure 2 shows the risk of bias for each study. This was generally low to moderate across all included studies, but eight studies were at high risk of bias [20, 21, 42, 43, 47, 48, 56, 59]. Only three studies were at low risk of bias across all domains [24, 40, 41], although nine studies had a single domain at unclear risk of bias but were otherwise at low risk of bias [23, 25, 27, 29, 33, 36, 45, 46, 49].

Thirty-two studies (3268 participants) assessed the risk of postoperative nausea [20, 22–24, 26, 28–32, 34, 36, 37, 39, 41–43, 45–57, 59, 60], but three of them reported data in insufficient detail to be used in any analyses of this outcome [20, 22, 27].

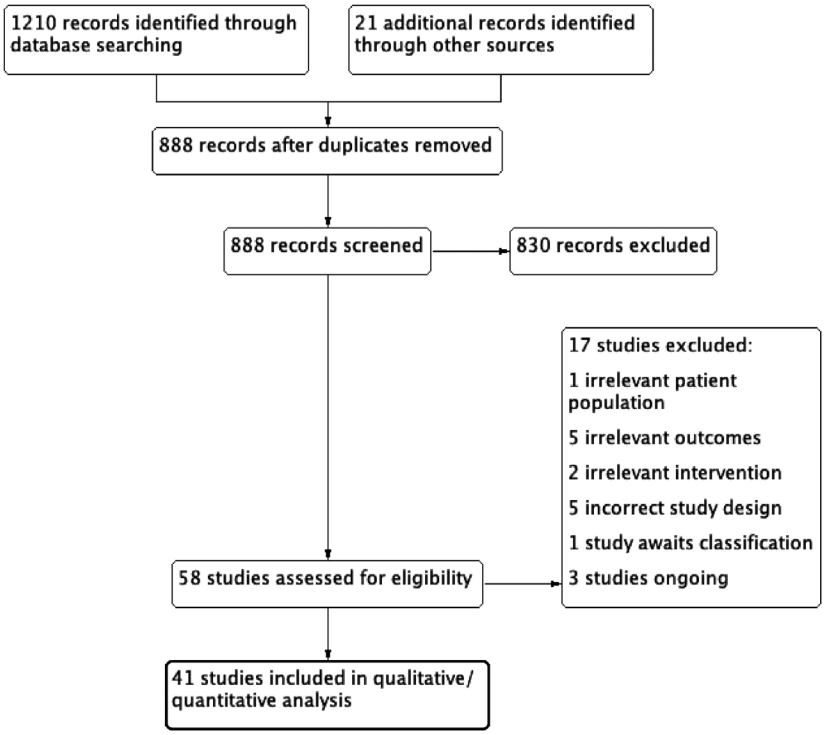

Figure 1 PRISMA flow diagram of study screening for inclusion.

Eighteen studies (1766 participants) reported dichotomous data for risk of nausea during the overall study period [23, 24, 26, 29, 32, 36, 39, 41, 43, 45, 46, 48–52, 54, 60]. Supplemental i.v. crystalloid decreased the risk of nausea during the overall study period, with a risk ratio (95% CI) of 0.62 (0.51–0.75; I^2 = 57%, p < 0.00001, Fig. 3). The moderate statistical heterogeneity could not be reduced by our planned sub-group analyses. We downgraded the certainty of this evidence to 'moderate' due to risk of publication bias, as indicated by funnel plot inspection. One study (30 participants) used a dextrose-containing solution in the intervention group [52], and a sensitivity analysis found that inclusion of this study did not substantially affect the risk ratio or the statistical heterogeneity. Additional planned sensitivity analyses of studies at low risk of bias [23, 24, 29, 36, 41, 46, 49], and of studies administering comparator groups at least 10 $ml.kg^{-1}$ of supplemental i.v. crystalloid [29, 32, 41, 45, 54] also did not substantially affect the risk ratio.

Details of results for dichotomous data during specific time periods and for continuous data across all time periods, as well as their respective sensitivity analyses, are all available in the full Cochrane review [9]. In summary, supplemental peri-operative i.v. crystalloids decreased the risk of nausea during both early and late time periods. The risk ratio (95%CI) for early nausea was 0.67 (0.58–0.78; I^2 = 9%, p < 0.00001), and the risk ratio (95%CI) for late nausea was 0.47 (0.32–0.69; I^2 = 38%, p = 0.0001). For both time periods, we downgraded the certainty of evidence to 'moderate' due to risk of publication bias, as indicated by funnel plot inspection. There were no studies reporting continuous data for overall postoperative nausea; however, the mean difference (95%CI) for early nausea was −16.38 (−21.81 to −10.96; I^2 = 47%, p < 0.00001), and for late nausea was −9.62 (−14.91 to −4.32; I^2 = 71%, p = 0.0004).

Thirty-one studies (3105 participants) evaluated postoperative vomiting [22–34, 36–39, 41, 45–51, 53–55, 57, 58, 60]; however, one study did not report sufficiently detailed data to be included in our analyses [22]. Four studies (500 participants) reported vomiting in children, aged 6 months to 18 years [25, 33, 39, 58].

Twenty studies (1970 participants) provided data for vomiting across all time points [23–28, 32, 33, 36, 38, 39, 41, 45, 48–51, 54, 58, 60]. Supplemental i.v. crystalloids decreased the risk of vomiting over the overall study period, with a risk ratio (95%CI) of 0.50 (0.40–0.63; I^2 = 31%, p < 0.00001, Fig. 4). We downgraded the certainty of this evidence to 'moderate' due to risk of publication bias, as indicated by funnel plot inspection. For children specifically, the intervention also reduced the overall risk of vomiting,

Table 1 Details of studies meeting inclusion criteria.

	Participant characteristics			Intervention characteristics	
Study	**Age**	**Procedure type**	**Timing**	**Comparator group**	**Intervention group(s)**
Ali et al. [23]	Adult	Various	Pre-operative	RL 2 $ml.kg^{-1}$	RL 15 $ml.kg^{-1}$
Amireh et al. [24]	Adult	Laparoscopic cholecystectomy	Pre-operative	No crystalloid bolus	RL 10 $ml.kg^{-1}$
Ashok et al. [25]	Child	Various	Intra-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Behdad et al. [26]	Adult	Otorhinolaryngological surgery	Intra-operative	RL 4 $ml.kg^{-1}$	RL 10 $ml.kg^{-1}$
			Intra-operative	—	RL 20 $ml.kg^{-1}$
Bennett et al. [20]	Adult	Dental extractions	Pre-operative	NS 1–2 $ml.kg^{-1}$	NS 15 $ml.kg^{-1}$
Bhukal et al. [27]	Adult	Various	Intra-operative	NS 4 $ml.kg^{-1}$	NS 10 $ml.kg^{-1}$
Chaudhary et al. [28]	Adult	Open cholecystectomy	Pre-operative	RL 2 $ml.kg^{-1}$	RL 12 $ml.kg^{-1}$
Chauhan et al. [29]	Adult	Laparoscopic gynaecological surgery	Pre-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Chohedri et al. [30]	Adult	Various	Pre-operative	NS 2 $ml.kg^{-1}$	NS 20 $ml.kg^{-1}$
Cook et al. [31]	Adult	Laparoscopic surgery	Pre-operative	No crystalloid bolus	RL 20 $ml.kg^{-1}$
			Pre-operative	—	RL 20 $ml.kg^{-1}$ with 1 $g.kg^{-1}$ dextrose
Dagher et al. [32]	Adult	Otorhinolaryngological surgery	Pre-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Egeli et al. [21]	Child	Otorhinolaryngological surgery	Postoperative	No crystalloid bolus	D5RL 60–120 $ml.h^{-1}$
Elgueta et al. [33]	Child	Otorhinolaryngological surgery	Intra-operative	RL 10 $ml.kg^{-1}.h^{-1}$	RL 30 $ml.kg^{-1}.h^{-1}$
Elhakim et al. [34]	Adult	Therapeutic abortion	Intra-operative	No crystalloid bolus	RL 1000 ml
Goodarzi et al. [35]	Child	Strabismus repair	Intra-operative	RL 10 $ml.kg^{-1}.h^{-1}$	RL 30 $ml.kg^{-1}.h^{-1}$
Gwak et al. [36]	Adult	Various	Intra-operative	RL 6 $ml.kg^{-1}.h^{-1}$	RL 18 $ml.kg^{-1}.h^{-1}$
Hashish et al. [37]	Adult	Laparoscopic gynaecological surgery	Pre-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Heidari et al. [38]	Adult	Orthopaedic surgery	Pre-operative	No crystalloid bolus	RL 10 $ml.kg^{-1}$
Heshmati et al. [39]	Child	Otorhinolaryngological surgery	Intra-operative	No crystalloid bolus	RL 4 $ml.kg^{-1}.h^{-1}$
Holte et al. [40]	Adult	Laparoscopic cholecystectomy	Pre-operative	RL 15 $ml.kg^{-1}$	RL 40 $ml.kg^{-1}$
Ismail et al. [41]	Adult	Laparoscopic cholecystectomy	Intra-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Keane et al. [42]	Adult	Various	Mixed	No crystalloid bolus	Intra-operative RL 1000 ml then postoperative D5W 1000 ml
Lambert et al. [43]	Adult	Laparoscopic gynaecological surgery	Pre-operative	No crystalloid bolus	RL 900–1000 ml
Lee et al. [44]	Adult	Laparoscopic cholecystectomy	Pre-operative	RL 5 $ml.kg^{-1}.h^{-1}$	RL 30 $ml.kg^{-1}.h^{-1}$
Magner et al. [45]	Adult	Laparoscopic gynaecological surgery	Pre-operative	RL 10 $ml.kg^{-1}$	RL 30 $ml.kg^{-1}$
Maharaj et al. [46]	Adult	Laparoscopic gynaecologic surgery	Pre-operative	RL 2 $ml.kg^{-1}$ per hour fasted	RL 3 $ml.kg^{-1}$ per hour fasted
McCaul et al. [47]	Adult	Laparoscopic gynaecological surgery	Intra-operative	No crystalloid bolus	RL 1.5 $ml.kg^{-1}$ per hour fasted
			Intra-operative	—	D5RL 1.5 $ml.kg^{-1}$ per hour fasted

(continued)

Table 1 (*continued*)

	Participant characteristics			Intervention characteristics	
Study	**Age**	**Procedure type**	**Timing**	**Comparator group**	**Intervention group(s)**
Monti et al. [48]	Adult	Laparoscopic gynaecological surgery	Pre-operative	No crystalloid bolus	RL 1000 ml
Murshed et al. [49]	Adult	Laparoscopic surgery	Pre-operative	RL 1.5 $ml.kg^{-1}$ per hour fasted	RL 15 $ml.kg^{-1}$
Najafianaraki [50]	Adult	Cervical cerclage	Pre-operative	RL 2 $ml.kg^{-1}$ per hour fasted	RL 2 $ml.kg^{-1}$ per hour fasted then RL 10 $ml.kg^{-1}$
Onyando [51]	Adult	Various	Pre-operative	No crystalloid bolus	RL 'maintenance' rate per hour fasted (maximum 1000 ml)
Ooi et al. [52]	Adult	Therapeutic abortion	Pre-operative	No crystalloid bolus	4% dextrose/0.18% saline solution 20 $ml.kg^{-1}$
Paganelli [53]	Adult	Laparoscopic cholecystectomy	Intra-operative	NS 10 $ml.kg^{-1}.h^{-1}$	NS 1000 ml bolus then 10 $ml.kg^{-1}.h^{-1}$
Sharma et al. [54]	Adult	Laparoscopic cholecystectomy	Pre-operative	RL 10 $ml.kg^{-1}$	RL 20 $ml.kg^{-1}$
			Pre-operative	—	RL 30 $ml.kg^{-1}$
Shin et al. [55]	Mixed	Various	Pre-operative	RL 2 $ml.kg^{-1}$	RL 20 $ml.kg^{-1}$
Singh et al. [22]	Adult	Various	Pre-operative	No crystalloid bolus	RL 30 $ml.kg^{-1}$
Soleimani et al. [56]	Adult	Breast cancer surgery	Pre-operative	NS 1.5 $ml.kg^{-1}.h^{-1}$	NS 1.5 $ml.kg^{-1}.h^{-1}$ then RL 5 $ml.kg^{-1}$
			Intra-operative	—	NS 1.5 $ml.kg^{-1}.h^{-1}$ then RL 5 $ml.kg^{-1}$
Spencer [57]	Adult	Various	Intra-operative	No crystalloid bolus	RL 1000 mL
Yilmaz [58]	Child	Otorhinolaryngological surgery	Intra-operative	NS 10 $ml.kg^{-1}.h^{-1}$	NS 20 $ml.kg^{-1}.h^{-1}$
Yogendran et al. [59]	Adult	Various	Pre-operative	Plasmalyte 2 $ml.kg^{-1}$	Plasmalyte 20 $ml.kg^{-1}$
Yoon et al. [60]	Adult	Various	Intra-operative	RL 2 $ml.kg^{-1}$	RL 18 $ml.kg^{-1}$

D5RL, dextrose 5% in Ringer's Lactate; D5W, dextrose 5% in water; NS, normal saline; RL, Ringer's lactate.

albeit to a lesser degree, with a risk ratio (95%CI) of 0.69 (0.57–0.85; I^2 = 0%, p = 0.0004). There were insufficient studies to conduct sensitivity analyses for dextrose-containing solutions. Neither sensitivity analysis for studies at low risk of bias [23–25, 27, 33, 36, 41, 45, 49] nor for studies administering comparator groups at least 10 $ml.kg^{-1}$ of supplemental i.v. crystalloid substantially affected the risk ratio.

Details of results for specific time periods are available in the full Cochrane review [9]. In summary, the intervention decreased the risk of postoperative vomiting in both early and late time periods. The risk ratio (95%CI) for early vomiting was 0.56 (0.41–0.76; I^2 = 0, p = 0.0003), and the risk ratio (95%CI) for late vomiting was 0.48 (0.29–0.79; I^2 = 0%, p = 0.004).

Twenty-three studies (2416 participants) contributed to our analysis of the risk of requiring pharmacological treatment for PONV [23, 25–29, 31–36, 40, 41, 45, 46, 48, 49, 51, 54, 56, 59, 60]. Supplemental i.v. crystalloids decreased the risk of requiring pharmacological treatment for PONV, with a risk ratio (95%CI) of 0.62 (0.51–0.76; I^2 = 40%, p < 0.00001, Fig. 5). We downgraded the certainty of this evidence to 'moderate' due to risk of publication bias, as indicated by funnel plot inspection. Due to moderate statistical heterogeneity, we carried out our planned sub-group analyses, but the risk ratio was not affected in any of them. Inclusion of dextrose-containing solutions did not substantially affect the ratio or statistical heterogeneity.

For children specifically, supplemental i.v. crystalloid administration did not reduce the risk of requiring pharmacological treatment for PONV, with a risk ratio (95% CI) of 0.81 (0.50–1.30; I^2 = 0%, p = 0.38). Neither inclusion of studies administering comparator groups at least 10 $ml.kg^{-1}$ of supplemental i.v. crystalloid [25, 29, 32, 33, 35, 40, 41, 45, 54], nor of studies at low risk of bias [23, 25, 27, 29, 33, 36, 40, 41, 45, 46, 49] substantially affected the risk ratio.

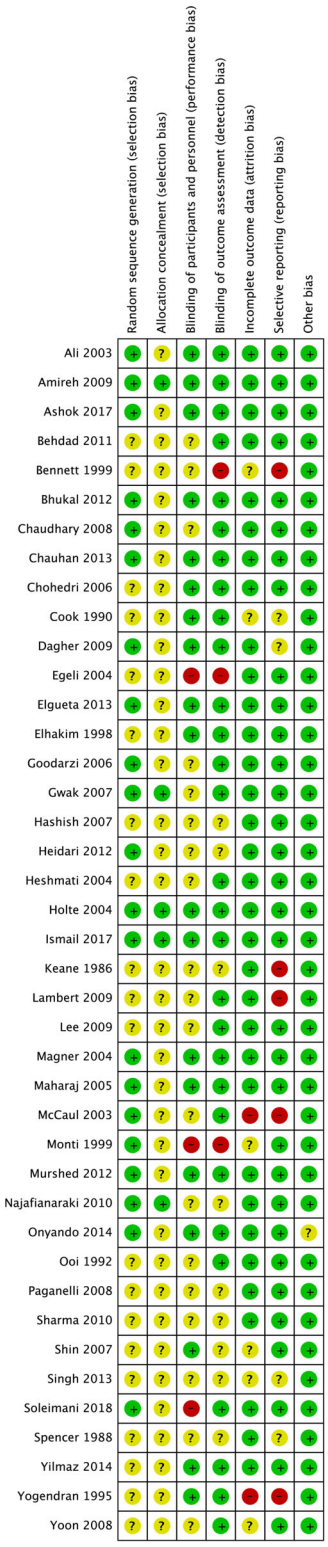

Figure 2 Risk of bias of included studies. Green: low risk of bias; red: high risk of bias; yellow: risk of bias uncertain from trial report.

Three studies (235 participants) reported the rate of unplanned admission to hospital after ambulatory surgery [23, 31, 46]. The intervention did not affect this outcome, where the risk ratio (95%CI) was 1.05 (0.77–1.43; I^2 = 0%, p = 0.77). We downgraded the certainty of this evidence to 'low' due to imprecision and inconsistency of the results. There were insufficient studies for sensitivity analyses.

No studies reported risks of serious adverse events.

Discussion

In summary, we found 41 trials (4224 participants) that met our inclusion criteria, of which 38 trials (4034 participants) contributed to our meta-analysis. We found that supplemental peri-operative i.v. crystalloid administration probably reduces the risk of both nausea and vomiting in the overall postoperative period, as well as during early and late time periods. The certainty of the evidence for postoperative nausea and postoperative vomiting outcomes, assessed using GRADE, is rated as 'moderate'. Additionally, moderate-certainty evidence suggests that the intervention probably reduces the risk of needing treatment with anti-emetic rescue medication. There is low certainty evidence suggesting the intervention does not influence the risk of unintended postoperative hospital admission after ambulatory surgery. No studies reported serious adverse events with this intervention (i.e. admission to high-dependency unit, postoperative cardiac or respiratory complication, or death).

Before this meta-analysis, the most comprehensive review of supplemental i.v. crystalloid administration for PONV prophylaxis included 15 RCTs [1]. The results of that review demonstrated statistically significant decreases in early, late and overall postoperative nausea, overall postoperative vomiting, late and overall PONV and postoperative antiemetic administration. Pooled effect sizes for early and late vomiting, and early PONV, had suggested a risk reduction but 95%CIs could not rule out a type-1 error. Our meta-analysis furthers the work undertaken in that review. By identifying new publications and completing a thorough grey literature search up to August 2018, we have included 26 additional studies, more than doubling the number of participants. This allowed for a more highly powered analysis with greater precision than the previous meta-analysis. Improved power also likely explains why some outcomes, specifically early and late vomiting, were found to have significant risk reductions, when this was not the case in the prior analysis [1].

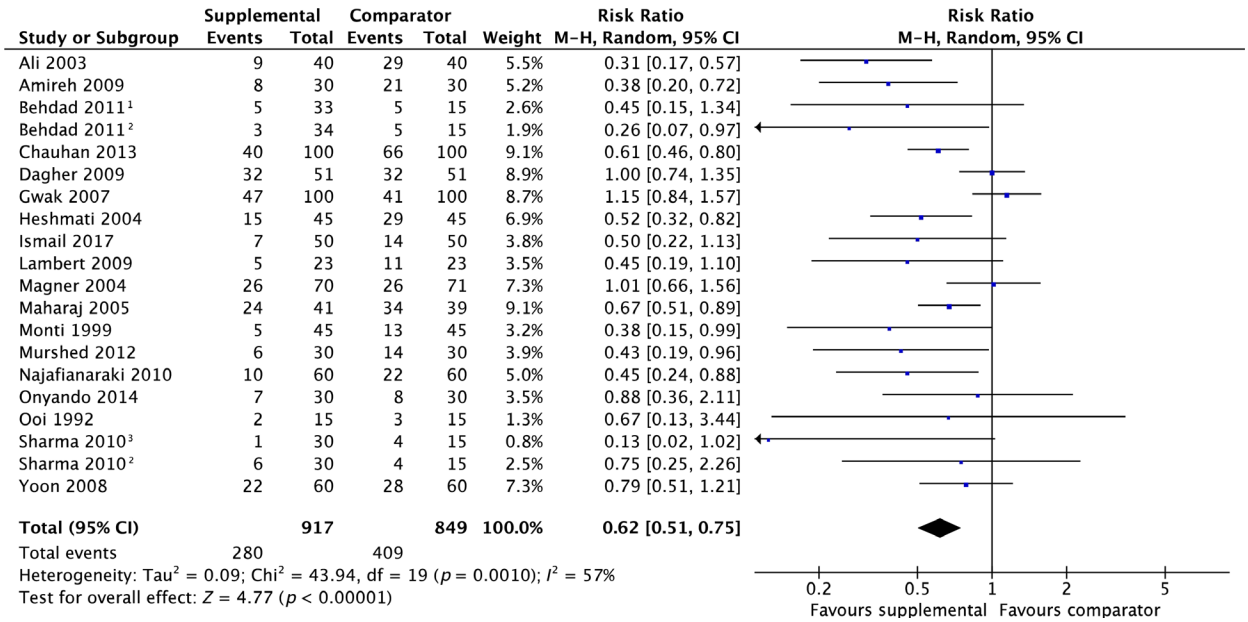

Figure 3 Forest plot of effect of supplemental peri-operative intravenous crystalloids on risk of postoperative nausea, during overall postoperative period. [1]10 mg.kg^{-1} intervention. [2]20 mg.kg^{-1} intervention. [3]30 mg.kg^{-1} intervention. M-H, Mantel–Haenszel.

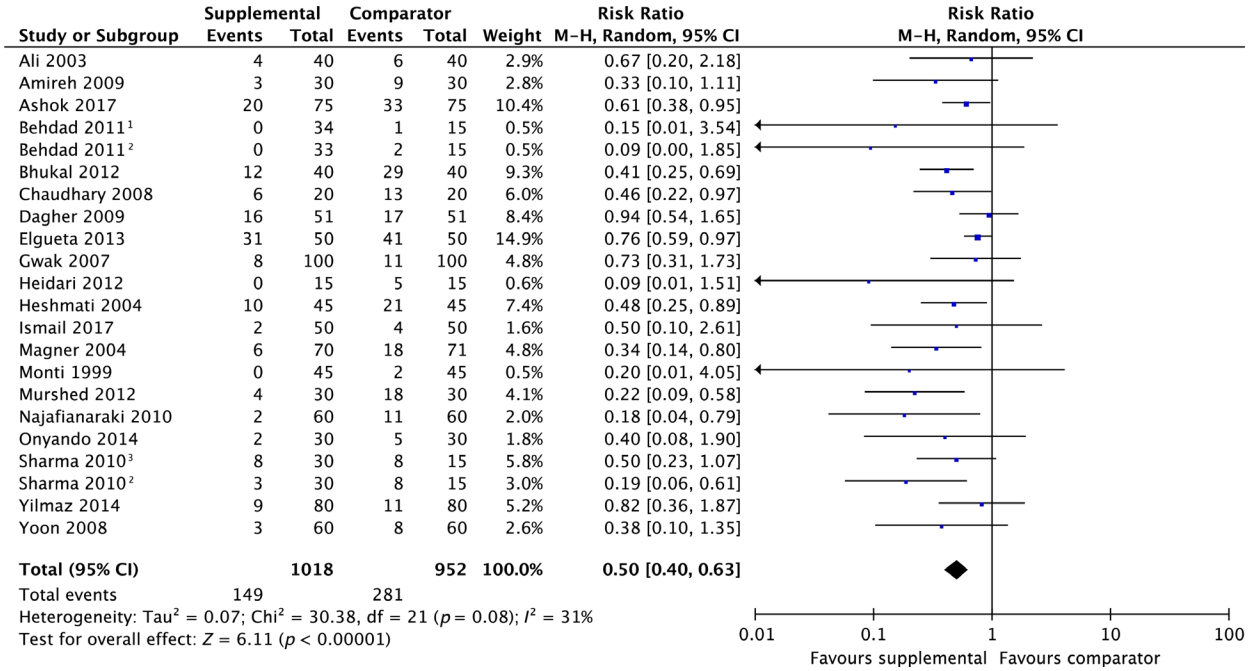

Figure 4 Forest plot of effect of supplemental peri-operative intravenous crystalloids on risk of postoperative vomiting, during overall postoperative period. [1]10 mg.kg^{-1} intervention. [2]20 mg.kg^{-1} intervention. [3]30 mg.kg^{-1} intervention; M-H, Mantel–Haenszel.

Most trials enrolled only ASA physical status 1 and 2 patients, for ambulatory or short length of stay procedures (i.e. one day). Otherwise, there was significant diversity among the included studies. Trials took place in a number of countries across the developed, emerging and developing world. Participants underwent a wide range of surgical procedures. Anaesthetic technique was varied, including induction and maintenance agents, use of muscle relaxants

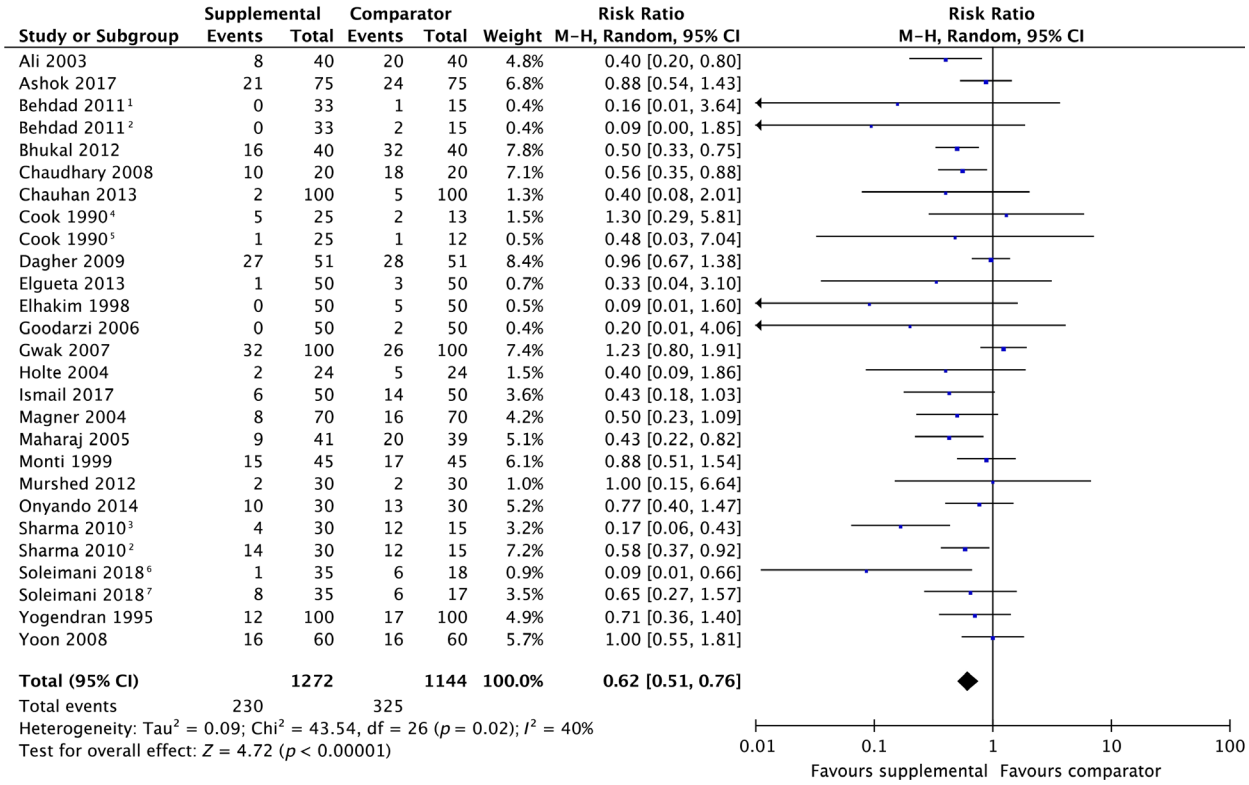

Figure 5 Forest plot of effect of supplemental peri-operative intravenous crystalloids on risk of pharmacological treatment of PONV, during overall postoperative period. [1]10 mg.kg^{-1} intervention. [2]20 mg.kg^{-1} intervention. [3]30 mg.kg^{-1} intervention. [4]Ringer's lactate/dextrose intervention. [5]Ringer's lactate intervention. [6]pre-operative intervention. [7]postoperative intervention; M-H, Mantel–Haenszel.

and reversal agents, opioid administration and pharmacological PONV prophylaxis. Participants' baseline risk of PONV probably varied between studies, but this information was insufficiently reported for us to confirm. Although such variation probably introduced heterogeneity into the results, it also suggests that our conclusions are generalisable to a sizeable scope of ambulatory surgical populations.

We found that PONV was very inconsistently defined across studies. This challenge led us to focus instead on the related outcomes of postoperative nausea and postoperative vomiting, which are more precisely and consistently defined. Most trials included in this review reported on one of our primary outcomes (i.e. risk of nausea, or risk of vomiting). There were few studies reporting continuous data for risk of postoperative nausea, so far fewer studies and patients were pooled for these data, but we were still able to assess how nausea severity was affected by supplemental i.v. crystalloid administration.

Very few studies examined potential harm that patients may experience from vigorous administration of i.v. fluid. For instance, no studies examined the risk of serious adverse events, or the risk of prolonged length of stay in the recovery area. This is clearly a deficiency in the existing literature, as also demonstrated in prior systematic reviews, [61] and warrants further investigation. Due to differences in the way that studies defined and reported the volume of supplemental i.v. crystalloid that was administered to patients, it was difficult to compare absolute volume administered across studies. Where applicable, we conducted sub-group analyses of relative supplemental i.v. crystalloid volume administered in comparator and intervention groups, and we did not find this variable to be influential. Moreover, we conducted sensitivity analyses omitting studies where comparator groups received a volume of i.v. supplemental crystalloid comparable to most studies' intervention groups (i.e. at least 10 ml.kg^{-1}), and this appeared to have negligible influence on the effect of the intervention. Optimal dosing and timing for supplemental peri-operative i.v. crystalloid administration remains unclear, and this presents an obvious avenue for further clarification.

Most studies reported a consistent direction of effect, with overlap of confidence intervals, whereas pooled

participant numbers exceeded optimal effect size calculations, so we did not downgrade any primary outcome for imprecision [62]. Assessment of population, interventions and outcomes of all included studies discovered no risk of indirectness. We also completed a thorough grey literature search; nonetheless, funnel plots for both primary outcomes as well as risk of requiring pharmacological treatment for PONV suggested a risk of publication bias.

There were some common pitfalls affecting the risk of bias in this literature. For the majority of included studies, there was insufficient description of measures to ensure random sequence generation and allocation concealment. Similarly, the nature of the intervention and its timing made it possible in many instances that blinding of participants and personnel could have been compromised. However, we performed sensitivity analyses of studies at low risk of bias where possible, and it was reassuring that the inclusion of studies at relatively higher risk of bias did not appear to affect our estimate of risk in any outcome.

Despite these limitations, there are sufficient data to suggest that supplemental i.v. crystalloid administration may be helpful to reduce the risk of PONV. The varied settings do provide a degree of generalisability, albeit in an ambulatory setting with generally healthy patients. These results may not be easily generalised to sicker patients, or more extensive operations where hospital length of stay is expected to exceed one or two days.

Acknowledgements

We thank M. Bennett (content editor), V. E. Horstmann (statistical editor), L. Eberhart, D. M. Franco, B. Mesgarpour (peer reviewers), M. Kakhu (consumer referee) and A. Smith (Co-ordinating Editor) for their help and editorial advice during the preparation of our Cochrane Review. We acknowledge J. Hayden, for her advice in the development of this review, and J. Scott for her contribution to the review protocol [8]. In the completion of the review, her role was assumed by M. Wong. We offer many thanks to D. Sayyad for translating our Persian studies. Finally, we recognise J. Cracknell (Managing Editor, Cochrane Anesthesia) for her patient guidance and correction of various drafts of this review. AH received research support from Acacia Pharma, Pacira Biosciences, BioQ Pharma, Avanos Medical Inc. and Trevana Inc. He was an advisory board member for Mylan, Trevana and Baxter. None of those entities produce the intervention of interest except for Baxter, which manufactures i.v. fluids. Acacia and Baxter are pharmaceutical companies that manufacture anti-emetics for the management of PONV, but anti-emetic medications are not the intervention of interest in this review. The advisory board relationship with Baxter was not related to i.v. fluids. No other competing interests declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Systematic review search strategy.