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REVIEW ARTICLES

Supplemental intravenous crystalloids for the prevention of postoperative nausea and vomiting: quantitative review

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Editor's key points

- Perioperative i.v. crystalloids are perceived to reduce postoperative nausea and vomiting (PONV).
- A systematic review of 15 studies suggests some benefits.
- More effects seen on later than on early PONV.
- There is still a need for large-scale randomized controlled trials on this subject.

Summary. Hypovolaemia after overnight fasting is believed to exacerbate postoperative nausea and vomiting (PONV). However, data on the efficacy of supplemental i.v. crystalloids for PONV prophylaxis are conflicting. We performed a literature search using CENTRAL, MEDLINE, EMBASE, CINAHL, and Web of Science. We included prospective randomized controlled trials that reported PONV event rates in patients receiving supplemental i.v. crystalloids or a conservative fluid regimen after elective surgery under general anaesthesia. Studies were evaluated with regard to random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data, and selective reporting. We identified 15 trials (n=787 crystalloids; n=783 conservative fluids). Compared with conservative fluids, i.v. crystalloids reduced the risk of early postoperative nausea (PON) (relative risk 0.73, 95% confidence interval 0.59–0.89; P=0.003), late PON (0.41, 0.22–0.76; P=0.004), and overall PON (0.66, 0.46–0.95; P=0.02). I.V. crystalloids did not reduce the risk of early postoperative vomiting (POV) (0.66, 0.37–1.16; P=0.16) or late POV (0.52, 0.25–1.11; P=0.09), but did reduce overall POV (0.48, 0.29–0.79; P=0.004). I.V. crystalloids did not reduce the risk of early PONV (0.74, 0.49–1.12; P=0.16), but did reduce the risk of late PONV (0.27, 0.13–0.54; $P<0.001$) and overall PONV (0.59, 0.42–0.84; P=0.003). I.V. crystalloids reduced the need for antiemetic rescue treatment (0.56, 0.45–0.68; $P<0.001$). In summary, supplemental i.v. crystalloids were associated with a lower incidence of several PONV outcomes. However, a number of PONV outcomes failed to reach statistical significance, perhaps due to the lack of power. Thus, studies sufficiently powered for the less frequent outcomes (e.g. POV) are required.

Keywords: fluid therapy; hypotension/prevention and control; infusions; i.v.; isotonic solutions/administration and dosage; postoperative nausea and vomiting/prevention and control

Postoperative nausea and vomiting (PONV) affects 25–30% of patients after surgery, and the incidence can reach up to 80% in high-risk patients.[1] In addition to causing substantial patient distress and dissatisfaction, PONV can augment healthcare costs by delaying discharge from the post-anaesthesia care unit (PACU) and causing unexpected hospital readmissions.[2] Although there are many antiemetic medications available for PONV prophylaxis, a quantifiable benefit is observed only in a fraction of patients, and the use of some of these drugs may be costly and/or associated with adverse events such as headache, cardiac arrhythmia, or extrapyramidal symptoms.[3]

It has been suggested that preoperative fasting and bowel preparation cause significant dehydration, which may exacerbate PONV.[4] Administration of supplemental fluids has been reported to reduce PONV, presumably by reducing hypovolaemia.[5 6] However, while most studies have concluded that supplemental i.v. crystalloid administration reduced PONV, only a few reported outcomes were positive and reached statistical significance, which raises concerns about a potential selective reporting bias in the literature.[7] Therefore, we conducted an evidence-based review of the efficacy of supplemental i.v. crystalloids for the prevention of PONV.

Methods

We conducted a literature search to identify randomized controlled trials that compared the effects of supplemental i.v. crystalloids with a conservative fluid regimen for the prevention of PONV in adult and adolescent surgical patients of at least 16 yr of age. Paediatric patients were not included as water contributes to a higher percentage of body weight in children, fluid imbalance causes more morbidity and mortality in this surgical population, and accurate reporting of nausea is generally more difficult in younger patients. Without any language restrictions, a search in July 2011 was performed in PubMed, EMBASE, Web of Science, and the Cochrane Library using the following terms: *intravenous infusion; IV; fluid; fluid therapy; fluid therapies; hydration; crystalloid; preoperative; pre-operative; perioperative; perioperative; intraoperative; intra-operative; postoperative; post-operative; postanesthe*; postanaesthe*; post-anesthe*; post-anaesthe*; anesthesia; anaesthesia; surgery; surgical; surgical procedures, operative; PONV; nausea; vomit*; emesis*; and *retch**. Reference lists of identified studies were hand-searched until no further new trials were identified. The last electronic search was performed in July 2011 and a weekly e-mail notification was activated for potentially relevant new trials.

Two authors (A.M., M.O.-S.) independently reviewed all full reports and abstracts that could potentially meet the inclusion criteria. Dichotomous data on the incidence of postoperative nausea (PON), postoperative vomiting (POV), or both (PONV) from arrival in the PACU up to 72 h after surgery; need for rescue antiemetic medication; and the presence of side-effects were extracted from all trials by two authors (A.M., M.O.-S.) and analysed separately. If data were not clearly stated in the text or in a table, the information was extracted from graphs, if possible. Any discrepancies in the data or disagreements were settled by a third person (C.C.A.).

PON was defined as an unpleasant sensation associated with the urge to vomit. POV was defined as an attempted expulsion of gastric contents (vomiting or retching). PONV was defined as any nausea, vomiting, or both. Antiemetic rescue treatment was defined as any additional intervention provided for the treatment of established PON, POV, or PONV. Side-effects included any kind of associated adverse outcome that was described.

Incidences were evaluated for three time periods: early, late, and overall. The early period was defined as the highest incidence of nausea (PON) or vomiting (POV) within 6 h after surgery. When event rates were reported for several early intervals, we chose the earliest interval (e.g. 0–2 h instead of 0–6 h) in order to increase the chance of detecting a potential difference in the early *vs* late time intervals, unless an outlier was suspected. The late period was defined as the time interval nearest to 24 h reporting PON or POV. The overall period was defined as the longest postoperative period starting after completion of surgery and ending with the time reported nearest to 24 h.

Meta-analyses were conducted with Review Manager 5.1 (Cochrane Collaboration, Oxford, UK). Relative risks (RRs) with associated 95% confidence intervals (CIs) of

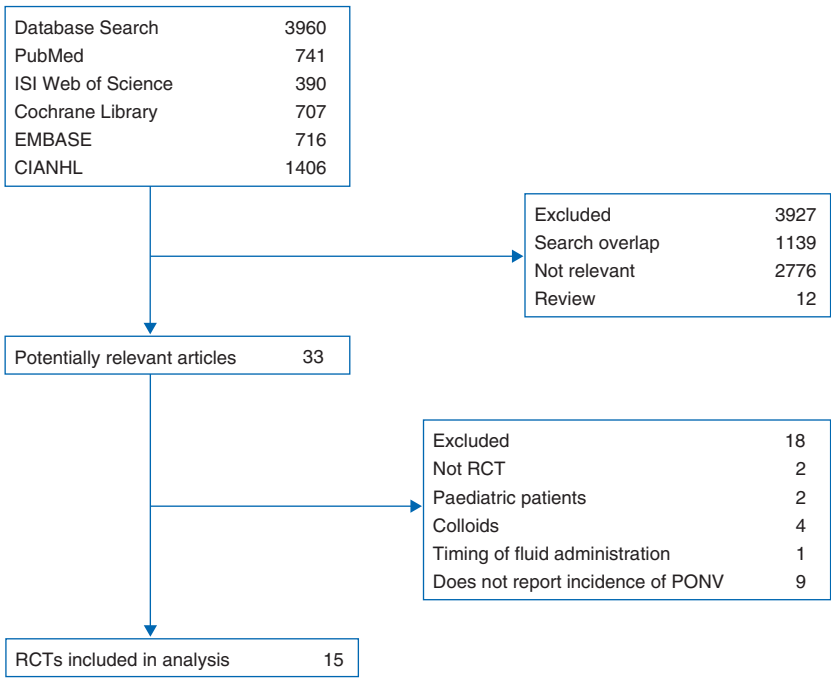


Fig 1 Flow chart detailing the retrieval of included studies. RCT, randomized controlled trial.

Table 1 Characteristics of included studies

Study	No. of patients	Participants: ASA status; type of surgery	Intervention(s)	Main findings	Other
Ali and colleagues[5]	80	ASA I–II, aged 18–70; laparoscopic cholecystectomy or gynaecological surgery	15 ml kg^{-1} RL *vs* 2 ml kg^{-1} RL	Prevalence of PONV was significantly reduced with supplemental crystalloids	
Chaudhary and colleagues[26]	60	ASA I–II, aged 18–60; open cholecystectomy	12 ml kg^{-1} RL *vs* 2 ml kg^{-1} RL	Prevalence and severity of PONV was reduced with supplemental crystalloids, significantly at 4 h after operation. Need for a rescue antiemetic was also significantly reduced	
Chohedri and colleagues[27]	200	ASA I–II, aged 17–60; general, orthopaedic, or gynaecological surgery	20 ml kg^{-1} 0.9% NaCl *vs* 2 ml kg^{-1} 0.9% NaCl	Prevalence of POV was significantly reduced with supplemental crystalloids. PON was reduced, but not significantly. Thirst was also significantly reduced	
Cook and colleagues[28]	75	ASA I–II, aged 18–40; gynaecological laparoscopy	20 ml kg^{-1} RL *vs* no i.v. fluid	Prevalence of PONV was not significantly reduced with supplemental fluids	
Dagher and colleagues[29]	100	Thyroidectomy	30 ml kg^{-1} RL *vs* 10 ml kg^{-1} RL	Prevalence of PONV was not significantly reduced with supplemental fluids	
Elhakim and colleagues[30]	100	ASA I–II; termination of pregnancy	1000 ml RL *vs* no i.v. fluid	Prevalence and severity of PONV was significantly reduced with supplemental crystalloids	
Keane and Murray[4]	212	ASA I–II, aged 18–50; breast biopsy, varicose vein ligation, dilatation and curettage, or inguinal hernia repair	1000 ml RL *vs* no i.v. fluid	Prevalence of PON was not significantly reduced with supplemental crystalloids Prevalence of drowsiness, thirst, headache, and dizziness were all reduced with supplemental crystalloids	
Lambert and colleagues[31]	46	ASA I–II, aged 18–72; gynaecological laparoscopy	Up to 1000 ml RL (4-2-1 rule) *vs* the routine amount of RL	Prevalence of PONV was significantly reduced with supplemental crystalloids	
Magner and colleagues[32]	141	ASA I; gynaecological laparoscopy	30 ml kg^{-1} RL *vs* 10 ml kg^{-1} RL	Prevalence of PONV and antiemetic rescue medication use were both reduced with supplemental crystalloids	
Maharaj and colleagues[6]	80	ASA I–III, aged 18–50; gynaecological laparoscopy	2 ml kg^{-1} RL per hour of fasting time *vs* 3 ml kg^{-1} RL	Prevalence and severity of PONV and antiemetic rescue requirement were both significantly reduced with supplemental crystalloids. Postoperative pain scores and analgesic requirements were also reduced	
McCaul and colleagues[33]	108	ASA I; gynaecological laparoscopy	1.5 ml kg^{-1} RL per hour of fasting time *vs* no i.v. fluid	Prevalence of PONV was not significantly reduced with supplemental crystalloids	
Monti and Pokorny[34]	90	ASA I–II, aged 18–55; gynaecological laparoscopy	1000 ml normal saline *vs* standard fluid regimen	Prevalence of PONV was significantly reduced with supplemental crystalloids. Need for rescue antiemetic medication was not significantly reduced	

Continued

Table 1 *Continued*

Study	No. of patients	Participants: ASA status; type of surgery	Intervention(s)	Main findings	Other
Sharma and colleagues[35]	90	ASA I–II, aged 18–60; laparoscopic cholecystectomy	30 ml kg^{-1} RL *vs* 10 ml kg^{-1} RL	Prevalence and severity of PONV and antiemetic rescue requirements were both significantly reduced with supplemental crystalloids. Prevalence of thirst and dizziness were also reduced	
Spencer[36]	100	ASA I–II, aged 18–50; minor gynaecological surgery	1000 ml RL *vs* no i.v. fluid	Prevalence of PONV was not significantly reduced with supplemental crystalloids. Dizziness was significantly reduced	
Yogendran and colleagues[37]	200	ASA I–III, aged 18–55; ambulatory gynaecological, laparoscopic, orthopaedic, and general surgical operations	20 ml kg^{-1} Plasmalyte 148 isotonic solution *vs* 2 ml kg^{-1} Plasmalyte 148 isotonic solution	Prevalence of late PON was significantly reduced with supplemental crystalloids; POV was not different between groups. Prevalence of thirst, drowsiness, and dizziness were also significantly reduced	15% of patients complained of pain along the arm of infusions

supplemental crystalloid compared with conventional fluid therapy were calculated using a random-effects model. An RR <1 indicates a potentially beneficial effect, while an RR >1 indicates a potentially adverse effect for the administration of supplemental i.v. crystalloids. $P<0.05$ was considered statistically significant.

Results

The search identified 33 potentially relevant studies, of which 15 studies met the eligibility criteria for inclusion (Fig. 1). Eighteen of the 33 potentially relevant trials were excluded for various reasons: the trial did not report the incidence of PONV,[8–16] studied a paediatric surgical population,[17 18] compared crystalloids with colloids[19–21] or examined supplemental colloids,[22] was not a randomized controlled trial,[23 24] or compared crystalloids administered before operation against intraoperatively.[25]

Of a total of 1570 patients, 787 patients received supplemental crystalloids and 783 received a conservative fluid regimen (Table 1).[4–6 26–37] All trials recruited healthy (ASA I–III) adults of at least 16 yr of age undergoing elective surgery under general anaesthesia. Although the amount of fluid administered as part of the restricted and supplementary regimens varied across the 15 included studies, the majority of studies defined a 'restricted regimen' as 0–2 ml kg^{-1} fluid and a 'supplementary i.v. fluid regimen' as 15–30 ml kg^{-1} fluid. All but three studies reported the incidence of PONV and the remaining three studies reported either PON or POV.

Postoperative nausea

In only one of the 10 studies did supplemental crystalloids show a significant reduction in early PON, but by grouping and weighing the effects of the individual studies, the cumulative effect of supplemental crystalloids on early PON shows a significant reduction (RR 0.73, 95% CI 0.59–0.89; $P=0.003$) (Table 2). The effect size for late PON may be even larger with three statistically significant studies out of seven and a cumulative effect of 0.41 (0.22–0.76; $P=0.004$). However, we did not conduct a formal statistical test comparing the effect sizes of early and late PON. The cumulative effect of overall PON was in a similar range, that is, an RR of 0.66 (0.46–0.95; $P=0.02$).

Postoperative vomiting

Supplemental i.v. crystalloids did not reduce the risk of early POV (0.66, 0.37–1.16; $P=0.15$) or late POV (0.52, 0.25–1.11; $P=0.09$), but did reduce overall POV (0.48, 0.29–0.79; $P=0.004$) (Table 3). The 0.66 RR for early POV is similar to the 0.73 RR for early PON, just as the 0.52 RR for late POV is similar to the 0.41 RR for late PON.

Postoperative nausea and vomiting

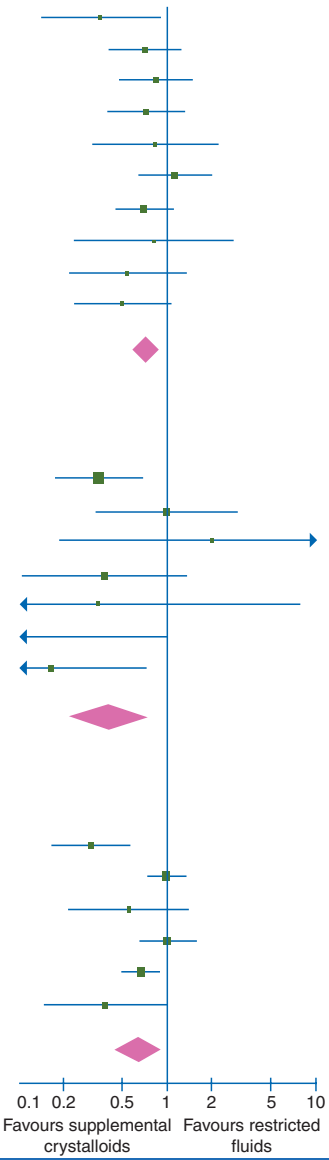
I.V. crystalloids did not reduce the risk of early PONV (0.74, 0.49–1.12; $P=0.16$), but did reduce the risk for late PONV (0.27, 0.13–0.54; $P<0.001$) and overall PONV (0.59, 0.42–0.84; $P=0.003$). With an RR for overall PONV of 0.59, the RR for PONV was reduced by 41% (1–0.59=0.41). For example, in a patient with a 40% risk, supplemental crystalloids would reduce this risk to 23.6% (40%×0.59=23.6%), that is, the absolute risk would decrease by 16.4%.

Rescue antiemetic medication

Supplemental i.v. crystalloids reduced the risk of need for antiemetic rescue treatment (RR 0.56, 95% CI 0.45–0.68; $P<0.001$).

Table 2 Efficacy of supplemental crystalloids in the prevention of PON in the early (0–6 h), late (6–24 h), and overall (0–24 h) postoperative periods

Study	Supplemental crystalloids		Conservative fluids		Weight (%)	Risk ratio, random (95% CI)
	Events	Total	Events	Total		
Early PON						
Ali *et al.*[5]	5	40	14	40	5.1	0.36 (0.14–0.90)
Chohedri *et al.*[27]	17	100	24	100	14.0	0.71 (0.41–1.24)
Cook *et al.*[28]	11	24	13	24	13.3	0.85 (0.48–1.50)
Dagher *et al.*[29]	13	50	18	50	12.2	0.72 (0.40–1.31)
Keane and Murray[4]	7	108	8	104	4.5	0.84 (0.32–2.24)
Magner *et al.*[32]	19	70	17	71	13.6	1.13 (0.64–1.99)
Maharaj *et al.*[6]	17	41	23	39	21.6	0.70 (0.45–1.10)
McCaul *et al.*[33]	4	36	5	37	2.9	0.82 (0.24–2.82)
Spencer[36]	6	50	11	50	5.2	0.55 (0.22–1.36)
Yogendran *et al.*[37]	9	100	18	100	7.7	0.50 (0.24–1.06)
Total events	108	619	151	615	100.0	0.73 (0.59–0.89)
Heterogeneity	χ^2=6.47, df=9		P=0.69		I^2=0%	
Overall effect	Z=3.01		P=0.003			
Late PON						
Ali *et al.*[5]	8	40	23	40	34.9	0.35 (0.18–0.68)
Cook *et al.*[28]	5	24	5	24	20.6	1.00 (0.33–3.01)
Dagher *et al.*[29]	2	50	1	50	6.1	2.00 (0.19–21.4)
Magner *et al.*[32]	3	70	8	71	16.7	0.38 (0.11–1.38)
McCaul *et al.*[33]	0	36	1	37	3.6	0.34 (0.01–8.14)
Spencer[36]	0	50	8	50	4.4	0.06 (0.00–0.99)
Yogendran *et al.*[37]	2	92	12	92	13.7	0.17 (0.04–0.72)
Total events	20	362	58	364	100.0	0.41 (0.22–0.76)
Heterogeneity	χ^2=8.00, df=6		P=0.24		I^2=26%	
Overall effect	z=2.84		P=0.004			
Overall PON						
Ali *et al.*[5]	9	40	29	40	15.4	0.31 (0.17–0.57)
Dagher *et al.*[29]	32	50	32	50	22.8	1.00 (0.75–1.34)
Lambert *et al.*[31]	5	23	9	23	9.8	0.56 (0.22–1.41)
Magner *et al.*[32]	26	70	26	71	19.5	1.01 (0.66–1.56)
Maharaj *et al.*[6]	24	41	34	39	23.0	0.67 (0.51–0.89)
Monti *et al.*[34]	5	45	13	45	9.5	0.38 (0.15–0.99)
Total events	101	269	143	268	100.0	0.66 (0.46–0.95)
Heterogeneity	χ^2=17.27, df=5		P=0.004		I^2=71%	
Overall effect	z=2.25		P=0.02			



Adverse side-effects

No studies reported adverse events associated with supplemental fluid administration, such as pulmonary oedema or wound dehiscence, when comparing a liberal i.v. crystalloid regimen with a restricted fluid regimen. However, one study did report that 15% of patients in the i.v. crystalloid group complained of pain along the infusion arm.[37]

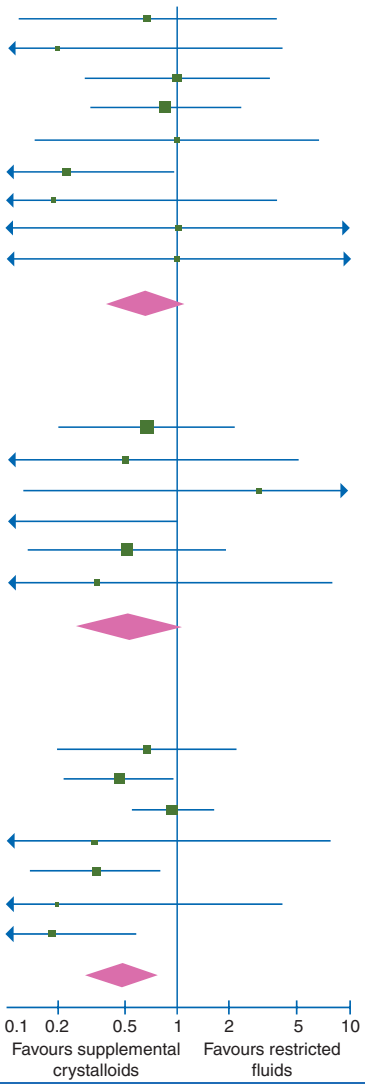
Discussion

This systematic review of the efficacy of supplemental i.v. crystalloids for the prevention of PONV suggests that i.v. crystalloids reduce the incidence of several but not all PONV outcomes. Specifically, i.v. crystalloids significantly reduced early, late, and overall PON, overall POV, and late and overall PONV. The effect of i.v. crystalloids was not statistically significant for early and late POV and early PONV. Supplemental i.v. crystalloids reduced overall PONV and the need for rescue treatment as effectively as many prophylactic antiemetic drugs.[38 39]

The mechanism by which i.v. hydration reduces PONV is unclear, although several hypotheses have been proposed. It has previously been believed that surgical patients become hypovolaemic after overnight fasting, and this was

Table 3 Efficacy of supplemental crystalloids in the prevention of POV in the early (0–6 h), late (6–24 h), and overall (0–24 h) postoperative periods

Study	Supplemental crystalloids		Conservative fluids		Weight (%)	Risk ratio, random (95% CI)
	Events	Total	Events	Total		
Early POV						
Ali *et al.*[5]	2	40	3	40	10.6	0.67 (0.12–3.78)
Chohedri *et al.*[27]	0	100	2	100	3.5	0.20 (0.01–4.11)
Cook *et al.*[28]	4	24	4	24	20.0	1.00 (0.28–3.54)
Dagher *et al.*[29]	6	50	7	50	30.9	0.86 (0.31–2.37)
Elhakim *et al.*[30]	2	50	2	50	8.7	1.00 (0.15–6.82)
Magner *et al.*[32]	2	70	9	71	14.3	0.23 (0.05–1.01)
Maharaj *et al.*[6]	0	41	2	39	3.5	0.19 (0.01–3.85)
McCaul *et al.*[33]	1	36	1	37	4.3	1.03 (0.07–15.82)
Spencer[36]	1	50	1	50	4.2	1.00 (0.06–15.55)
Total events	18	461	31	461	100.0	0.66 (0.37–1.16)
Heterogeneity	χ^2=4.40, df=8		P=0.82		I^2=0%	
Overall effect	z=1.45		P=0.15			
Late POV						
Ali *et al.*[5]	4	40	6	40	40.1	0.67 (0.20–2.18)
Cook *et al.*[28]	1	24	2	24	10.4	0.50 (0.05–5.15)
Dagher *et al.*[29]	1	50	0	50	5.6	3.00 (0.13–71.92)
Elhakim *et al.*[30]	0	50	8	50	7.1	0.06 (0.00–0.99)
Magner *et al.*[32]	3	70	6	71	31.2	0.51 (0.13–1.95)
McCaul *et al.*[33]	0	36	1	37	5.6	0.34 (0.01–8.14)
Total events	9	270	23	272	100.0	0.52 (0.25–1.11)
Heterogeneity	χ^2=3.95, df=5		P=0.56		I^2=0%	
Overall effect	z=1.68		P=0.09			
Overall POV						
Ali *et al.*[5]	4	40	6	40	12.5	0.67 (0.20–2.18)
Chaudhary *et al.*[26]	6	20	13	20	22.1	0.46 (0.22–0.97)
Dagher *et al.*[29]	16	50	17	50	28.0	0.94 (0.54–1.65)
Lambert *et al.*[31]	0	23	1	23	2.4	0.33 (0.01–7.78)
Magner *et al.*[32]	6	70	18	71	18.9	0.34 (0.14–0.80)
Monti and Pokorny[34]	0	45	2	45	2.6	0.20 (0.01–4.05)
Sharma *et al.*[35]	3	30	16	30	13.5	0.19 (0.06–0.58)
Total events	35	278	73	279	100.0	0.48 (0.29–0.79)
Heterogeneity	χ^2=9.46, df=6		P=0.15		I^2=37%	
Overall effect	z=2.90		P=0.004			



thought to lead to organ hypoperfusion, specifically cerebral and intestinal hypoperfusion, which would trigger PONV. I.V. crystalloids were assumed to prevent PONV by maintaining blood volume, mean arterial pressure, and hence organ perfusion. However, a study using the indocyanine green dilution method established that ASA I–III patients undergoing hysterectomy under general anaesthesia remain normovolaemic even after 10 h of fasting.[40] Irrespective of fluid balance, overnight fasting is not typically associated with nausea or vomiting in otherwise healthy individuals.

We believe that the effect of supplemental crystalloids on PONV may be mediated by antidiuretic hormone (arginine vasopressin, AVP). Although there is no preoperative hypovolaemia, anaesthetics can induce a relative hypovolaemia through vasodilation with reduced venous return and preload.[41] This leads to reduced central venous pressure with reduced negative feedback of the right atrial stretch receptors, leading to increased AVP release from the posterior pituitary. AVP is strongly associated with nausea and vomiting. A previous study reported that plasma AVP levels are increased right at the onset of surgery and are significantly higher in patients who experience PONV than in those who do not.[42] Other models of nausea and vomiting corroborate these observations. For example, plasma AVP concentrations have been shown to rapidly increase in people who experienced nausea, emesis, or both in response

to circular vection,[43 44] apomorphine,[45] and cisplatin.[46 47] AVP was found to be released concurrently with gastric dysrhythmias and reports of nausea in study participants who experienced motion sickness, while no AVP release or slow wave gastric rhythm disruption occurred in participants who did not.[43] Dogs and humans react to i.v. AVP infusions with nausea, retching, and vomiting.[48] Exogenous AVP infusion caused both motion sickness-susceptible and -resistant participants to experience nausea.[43] Vasopressin V_1 receptor antagonists have been shown to prevent the induction of motion sickness in animal models.[49 50] Given that opioid administration is a strong predictor of PONV,[51] it is also interesting to note that morphine administration has been shown to raise plasma AVP levels in ferrets[52] and humans.[53]

It is interesting that i.v. hydration seems to have a greater effect on late than on early PONV, considering that crystalloid infusions are redistributed in the body within 90 min.[54] One possible explanation is that rehydration induces long-lasting effects by replacing extracellular fluid and/or by dampening the secretion of emetic stress response hormones, whose plasma levels take time to diminish once elevated.[42] This may be of clinical interest because some antiemetics are short-acting and are therefore most effective in the early postoperative period.[55 56]

Other outcomes

Although not systematically reported in this review, supplemental crystalloids were also noted to reduce the prevalence of other minor morbidities such as postoperative thirst,[4 27 35 37] dizziness,[4 35–37] drowsiness,[4 37] and headache.[4] Pain scores and analgesic requirements were also significantly reduced by supplemental fluid administration in one study.[6] In the setting of elective minor or moderate surgery, supplemental i.v. crystalloids had virtually no side-effects with the exception of pain reported in the infusion arm in one trial.[37] However, for larger procedures such as major intra-abdominal operations, where fluid accumulation is more likely, there is some evidence that supplemental fluids interfere with wound healing and recovery.[9 57 58]

A limitation of our study is that nearly half of the studies included had sample sizes of <50 patients per treatment group, and, given a realistic RR reduction of about 30% (e.g. from 40% to 28%), a 50-patient sample size has only 20% power to detect such a difference at a two-sided *P*-value of 0.05.[38 59] This may explain, in part, why not all PONV outcomes reached statistical significance, even when the effect size was in the expected range.

A further limitation is that the trials included in our meta-analysis studied a wide range of supplemental fluid volumes, from 2 to 30 ml kg^{-1}, and also fluids given during both the preoperative and the intraoperative periods. While this review was not designed to evaluate the relative efficacy of different supplemental fluid volumes or timing, our results may suggest that providing supplemental fluids improved PONV outcomes compared with a restricted fluid regimen, regardless of the definition of 'supplemental' and 'restricted' regimens (Fig. 2). This is further supported by the fact that the tests for heterogeneity were not statistically significant in the majority of cases, that is, irrespective of the specific amounts and

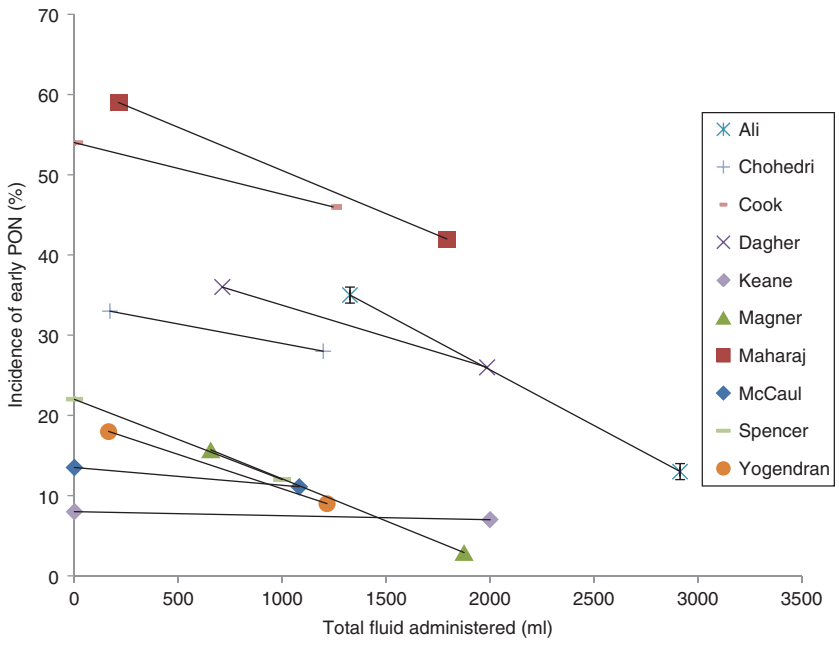


Fig 2 Total fluid administered and incidence of PON in the early period ($n=1234$). For each study, the percentage of patients who experienced PON is plotted with the corresponding mean amount of fluid administered to the control group and the supplemental i.v. crystalloids group. The trend line shows the change in incidence with treatment.

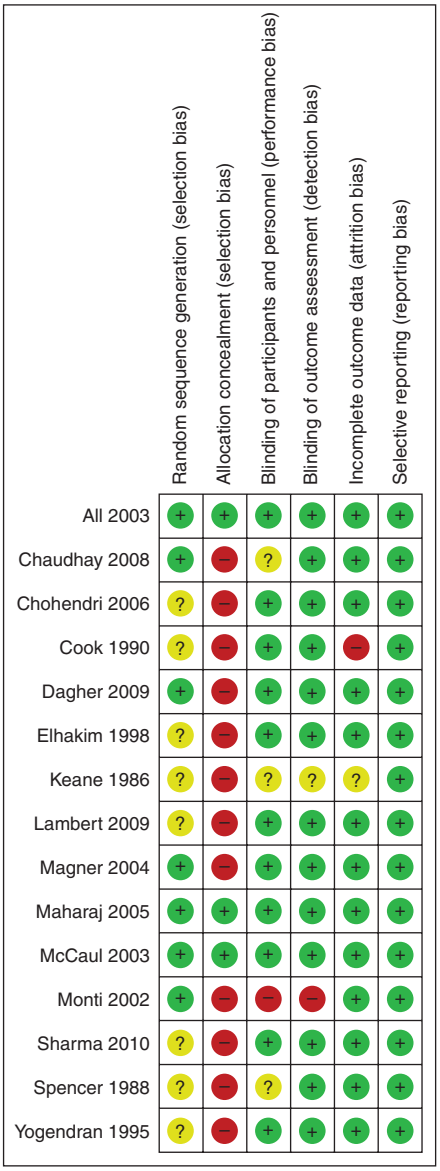


Fig 3 Risk of bias of included studies.

timing used in the individual studies. However, the findings of some previous meta-analyses of relatively small studies have been refuted by subsequent large, well-designed trials.[60 61] Therefore, despite these promising results, a well-powered study will be required to definitively determine whether supplemental i.v. crystalloids reduce a range of PONV outcomes.

Several trials showed a possible or high risk of bias on one or more components of methodological quality (Fig. 3). We used the Cochrane risk of bias scale to assess study quality.[62] Inclusion of studies of poor methodological quality may over- or under-estimate the overall effect.[63] However, it may be a problem to exclude a trial entirely based on a quality threshold, especially if the study is adequately randomized and blinded, and the use of quality assessment in reviews is not universally recommended.[64] Sensitivity analysis would clarify whether inclusion of lower quality studies biased our results. However, the limited number of studies included in the analysis, and their small size, did not allow us to perform such analysis.

Another limitation of meta-analyses may be publication bias, which can lead to the overestimation of the treatment effect. Specifically, negative studies (i.e. no treatment effect) are less likely to be submitted and published than positive studies, especially when studies are small, unless the study is well powered and the negative result is of exceptionally high relevance. A funnel plot analysis of our results showed moderate heterogeneity, but found no significant discrepancies suggestive of publication bias. As the number and size of the studies in this meta-analysis are small, and since other methods to detect publication bias have other limitations, we did not use any additional formal testing.

Our review of the available evidence suggests that supplemental i.v. crystalloids may reduce several PONV outcomes. However, due to the limited number of trials and the small size of the trials themselves, well-powered studies, ideally including endocrine and autonomic data, are still needed.

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Declaration of interest

None declared.

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