Aromatherapy for treatment of postoperative nausea and vomiting (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 4

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[Intervention Review]

Aromatherapy for treatment of postoperative nausea and vomiting

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Editorial group: Cochrane Anaesthesia Group.
Publication status and date: New, published in Issue 4, 2012.
Review content assessed as up-to-date: 2 August 2011.

Citation: Hines S, Steels E, Chang A, Gibbons K. Aromatherapy for treatment of postoperative nausea and vomiting. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art. No.: CD007598. DOI: 10.1002/14651858.CD007598.pub2.

ABSTRACT

Background

Postoperative nausea and vomiting is a common and unpleasant phenomenon and current therapies are not always effective for all patients. Aromatherapy has been suggested as a possible addition to the available treatment strategies.

Objectives

This review sought to establish what effect the use of aromatherapy has on the severity and duration of established postoperative nausea and vomiting and whether aromatherapy can be used with safety and clinical effectiveness comparable to standard pharmacological treatments.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3*)*; MEDLINE; EMBASE; CINAHL; CAM on PubMed; Meditext; LILACS; and ISI Web of Science as well as grey literature sources and the reference lists of retrieved articles. We conducted database searches up to August 2011.

Selection criteria

We included all randomized controlled trials (RCTs) and controlled clinical trials (CCTs) where aromatherapy was used to treat postoperative nausea and vomiting. Interventions were all types of aromatherapy. Aromatherapy was defined as the inhalation of the vapours of any substance for the purposes of a therapeutic benefit. Primary outcomes were the severity and duration of postoperative nausea and vomiting. Secondary outcomes were adverse reactions, use of rescue anti-emetics and patient satisfaction with treatment.

Data collection and analysis

Two review authors assessed risk of bias in the included studies and extracted data. As all outcomes analysed were dichotomous, we used a fixed-effect model and calculated relative risk (RR) with associated 95% confidence interval (95% CI).

Main results

The nine included studies comprised six RCTs and three CCTs with a total of 402 participants. The mean age and range data for all participants were not reported for all studies. The method of randomization in four of the six included RCTs was explicitly stated and was adequate. Incomplete reporting of data affected the completeness of the analysis. Compared with placebo, isopropyl alcohol vapour inhalation was effective in reducing the proportion of participants requiring rescue anti-emetics (RR 0.30, 95% CI 0.09 to 1.00, P = 0.05). However, compared with standard anti-emetic treatment, isopropyl alcohol was not effective in reducing the proportion of participants requiring rescue anti-emetics (RR 0.66, 95% CI 0.39 to 1.13, P = 0.13) except when the data from a possibly confounded study were included (RR 0.66, 95% CI 0.45 to 0.98, P = 0.04). Where studies reported data on patient satisfaction with aromatherapy, there were no statistically significant differences between the groups (RR 1.12, 95% CI 0.62 to 2.03, P = 0.71).

Authors' conclusions

Isopropyl alcohol was more effective than saline placebo for reducing postoperative nausea and vomiting but less effective than standard anti-emetic drugs. There is currently no reliable evidence for the use of peppermint oil.

PLAIN LANGUAGE SUMMARY

Aromatherapy for treating postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is a common and unpleasant side effect of surgery, with 20% to 30% of all patients suffering moderate to severe nausea and vomiting following general anaesthesia using volatile agents (inhaled anaesthesia). Nausea is an abdominal discomfort or queasiness that may be accompanied by vomiting (the forceful expulsion of stomach contents through the mouth). Current drug treatments may not always work effectively or they may have unpleasant adverse effects. Aromatherapy is sometimes recommended for treating nausea and vomiting, though currently there is not sufficient evidence that it is effective. Aromatherapy uses inhalation of the vapour of essential oils or other substances to treat or alleviate physical and emotional symptoms. We examined nine studies of aromatherapy for PONV, with a total of 402 participants. Six studies of the brief inhalation of isopropyl alcohol vapours showed that it can have some effect in reducing postoperative nausea and vomiting; however it seems to be less effective than standard drug treatments. There was a moderate risk of bias due to the design of some of the studies. Isopropyl alcohol is also known as rubbing alcohol and is commonly found in the type of 'prep-pad' used to clean skin prior to injection. There is currently no reliable evidence to support the use of other aromatherapies such as peppermint oil to treat postoperative nausea and vomiting. No included studies reported any adverse effects from the aromatherapies used.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Isopropyl alcohol compared to standard treatment for treatment of postoperative nausea and vomiting

Patient or population: patients with treatment of postoperative nausea and vomiting
Settings: Post-anaesthesia Care Areas
Intervention: Isopropyl alcohol
Comparison: Standard treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard treatment	Isopropyl alcohol				
Requirement for rescue anti-emetics	Study population[1]		RR 0.66 (0.45 to 0.98)	215 (4 studies)	⊕⊕◯◯ **low**[2,3]	
	392 per 1000	259 per 1000 (176 to 384)				
	Medium risk population[1]					
	275 per 1000	182 per 1000 (124 to 270)				
Adverse effects[4]	See comment	See comment	Not estimable	0 (0)	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Calculated using control group results.
[2] Study by Merritt (2002) was not adequately randomised.
[3] Total number of events is less than 300.
[4] No data on this outcome.

BACKGROUND

Aromatherapy has been recommended for the treatment of postoperative nausea and vomiting (PONV) (Bone 1990; Maddocks-Jennings 2004). It is known that this therapy is inexpensive, non-invasive and generally has low levels of adverse effects (Price 2007), particularly in comparison to standard pharmacological treatments. What is not known is whether the clinical effectiveness justifies its use.

Nausea is an abdominal discomfort or queasiness that may be accompanied by vomiting (the forceful expulsion of stomach contents through the mouth). Postoperative nausea and vomiting (PONV) is one of the most common adverse reactions to surgery and all types of anaesthesia, with 20% to 30% of all patients suffering moderate to severe nausea and vomiting following general anaesthesia using volatile agents (Watcha 1992).

Aside from the distressing nature of PONV itself, as a result of PONV patients may experience such adverse effects as wound dehiscence, dehydration, electrolyte imbalances or aspiration pneumonia (Kovac 2000). Other adverse effects may include increased patient bed days, unplanned readmissions (particularly in the case of day surgery) (Kovac 2000) and decreased patient satisfaction (Myles 2000). Certain patients are more pre-disposed than others to suffering from PONV and risk factors include being female, a non-smoker, having a history of PONV or perioperative opioid exposure (Koivuranta 1997). Along with postoperative pain, PONV is one of the main concerns of patients facing surgery and one of the main causes of patient dissatisfaction (Myles 2000).

Current treatment involves either the prophylactic or symptomatic administration of anti-emetic drugs such as droperidol, metoclopramide or 5-HT3 receptor antagonists such as ondansetron (White 1999). Despite a wide range of available treatments, some patients will still experience PONV in varying levels of severity (Kazemi-Kjellberg 2001). Clinically, the severity of PONV is generally measured by means of a visual analogue scale (VAS), which provides a visual representation of the patient's condition over a numerical range (for example 0 to 5), or verbal descriptive scales (for example no nausea, some nausea, very nauseated, retching, vomiting) (Boogaerts 2000). The effectiveness of the various drugs for PONV has already been the subject of a Cochrane review (Carlisle 2006), however no existing review has examined the effectiveness of aromatherapy to treat this condition.

The use of aromatherapy oils is recognized as an effective treatment for nausea in general (Chiravalle 2005; Mamaril 2006; Merritt 2002; Tate 1997). Aromatherapy uses the application of essential oils or other substances to any part of the body for the purpose of inhalation of the vapours or absorption of the oil into the skin to treat or alleviate physical and emotional symptoms (Price 2007). Essential oils can be absorbed through the skin and may exert a physiological effect on cellular and organ function, although this is not clinically understood (Ernst 2001). Aromatherapy is well accepted by many health consumers, who find it more pleasant and acceptable than the ingestion or injection of conventional drugs (Eisenberg 1998). A significant number of health consumers already self-prescribe and administer aromatherapy products for various common conditions, or consult qualified or unqualified aromatherapy practitioners for health advice (Eisenberg 1998).

In particular, ginger, fennel and peppermint, as either a topical application (massage or a compress) or via inhalation, are well-known treatments (Price 2007). The effectiveness of the oils may be due to analgesic and anti-emetic properties (with peppermint oil and ginger oil) or anti-spasmodic properties (peppermint oil and fennel oil). Peppermint oil is well recognized for its role in digestion disorders, due principally to the presence of menthols (see Appendix 1 for details). There have been a number of studies conducted using ginger oil, with conflicting results (Arfeen 1995; Bone 1990; Meyer 1995; Phillips 1993). Isopropyl alcohol is said to be a traditional nausea remedy from South America (Anderson 2004; Mamaril 2006; Spencer 2004), however none of the papers citing this provided a primary source for this information. Isopropyl alcohol, also known as rubbing alcohol and commonly found in the type of 'prep-pad' used to clean skin prior to injection, does appear to be widely used in some postanaesthesia care units to treat PONV (Cotton 2007; Merritt 2002; Pellegrini 2009; Spencer 2004; Wang 1999; Winston 2003). It is the subject of several effectiveness studies.

OBJECTIVES

To establish:

- what effect the use of aromatherapy has on the severity of established postoperative nausea and vomiting;
- what effect the use of aromatherapy has on the duration of established postoperative nausea and vomiting;
- whether aromatherapy can be used with safety and clinical effectiveness comparable to standard pharmacological treatments to treat established postoperative nausea and vomiting.

METHODS

Criteria for considering studies for this review

Types of studies

We considered any randomized controlled trials (RCTs) or controlled clinical trials (CCTs) that evaluated the effect of aromatherapy on established PONV. In order to obtain the widest range of studies we set no date of publication or language limits.

Types of participants

We considered all studies that included patients (both adult and paediatric, paediatric being children aged less than 18 years of age) having any type of surgical procedure under general anaesthesia, regional anaesthesia or sedation, either as hospital inpatients or in day or ambulatory facilities, who were given aromatherapy treatments for management of existing PONV. For the purposes of this review we considered postoperative to be the period from day of surgery to discharge from hospital or, in the case of day hospital patients, up to the fifth postdischarge day.

We excluded studies of non-surgical patients (medical, oncology). We also excluded studies in which aromatherapy was used solely to prevent postoperative nausea and vomiting.

Types of interventions

Interventions of interest were those where aromatherapy products were used by any delivery method (for example direct inhalation, diffusion, massage or compress) to treat symptoms of established postoperative nausea and vomiting, either in comparison to a placebo or compared with standard anti-emetic treatments. Aromatherapy was defined as the inhalation of the vapours of any substance for the purposes of a therapeutic benefit.

Types of outcome measures

Primary outcomes

- Severity of nausea or vomiting, or both, post-initiation of treatment as measured by a validated scale or medical or nursing observation
- Duration of nausea or vomiting, or both, post-initiation of treatment as measured by patient report or medical or nursing observation

Secondary outcomes

- Use of pharmacological anti-emetics
- Any adverse reactions or events (common reactions to aromatherapy include skin rashes, dyspnoea, headache, cardiac arrhythmias, hypotension, hypertension or dizziness (Price 2007))
- Patient satisfaction with treatment as measured by a validated scale

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3*)*; MEDLINE (via Ovid) (1966 to 2 August 2011); EMBASE (1966 to 2 August 2011); CINAHL (EBSCOhost) (1982 to 2 August 2011); CAM on PubMed (1966 to 2 August 2011); Meditext (1995 to 2 August 2011); LILACS (1982 to 2 August 2011); ISI Web of Science (1985 to 2 August 2011).

We developed a specific strategy for each database. We based each search strategy on that developed for MEDLINE (see Appendix 2 for details). We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy, phases one and two, as contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Searching other resources

We also identified trials by manually searching abstracts of relevant conference proceedings such as the National Association for Holistic Aromatherapy Conference.

We checked the reference lists of relevant articles and attempted to contact relevant trial authors to identify any additional or ongoing studies.

We also searched for relevant trials on specific sites:

1. Current Controlled Trials at http://www.controlled-trials.com;
2. Clinical Study Results at http://www.clinicalstudyresults.org;
3. SIGLE at http://opensigle.inist.fr/ (grey literature);
4. New York Library of Medicine Grey Literature Report at http://www.nyam.org/library/pages/grey_literature_report (grey literature);
5. National Institute of Clinical Studies at http://www.nhmrc.gov.au/nics/index.htm;
6. Science.gov at http://www.science.gov/browse/w_127.htm (grey literature).

We did not apply language or publication date restrictions.

Data collection and analysis

Selection of studies

Two authors (SH and ES) independently scanned the titles and abstracts of reports identified by the described variety of search strategies. We retrieved and evaluated potentially relevant studies, chosen by at least one author, in full-text versions. We retrieved and translated any articles which appeared relevant but were not published in full in English. Two authors (SH and ES) independently assessed the congruence of trials with the review's inclusion criteria using a checklist that was designed in advance for that purpose (Appendix 3). The third author (AC) settled any disagreements.

Data extraction and management

Two authors (SH and ES) independently extracted data using a tool developed and piloted by the authors (Appendix 4). We resolved any disagreements through consultation with the third author (AC).

Assessment of risk of bias in included studies

We assessed the risk of bias using the tool provided in the RevMan 5.1 software, based on the work of The Cochrane Collaboration (Higgins 2011). Any disagreements were adjudicated by the third author (AC). We used the following five criteria to assess risk of bias for each individual study: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

Measures of treatment effect

Because of the subjective nature of nausea, measures of treatment effect were largely limited to patient-reported effects, measured by various scales including visual analogue scales (VAS), verbal numerical rating scales (VRNS) and descriptive ordinal scales (DOS). We included other measures of effect, such as number of vomiting episodes or retching, and the use of pharmacological 'rescue' antiemetics. All outcome measures that were evaluated were dichotomous and, as such, we used relative risk (RR) with 95% confidence interval (95% CI) to measure treatment effect.

Unit of analysis issues

For cross-over trials, a paired t-test was to be used to analyse participant data had sufficient data been available. Had cluster randomized trials been included, effect estimates and standard errors would have been meta-analysed using the generic inverse-variance method in RevMan.

Dealing with missing data

Where necessary, we contacted authors of included studies regarding missing study information. We were able to contact some authors to retrieve missing data, such as details about randomization, statistical detail and standard deviations, however others did not reply or were not contactable. Where data were found to be missing and the authors were not contactable, where possible we calculated missing statistics (such as standard deviations) from other quoted statistics (such as standard errors or CIs). If missing data remained then we performed an available case analysis, excluding data where outcome information was unavailable.

Assessment of heterogeneity

We assessed statistical heterogeneity through the use of the Chi^2 test, as well as by reviewing the I^2 statistic. If either the Chi^2 test resulted in a P value less than 0.10 or the I^2 statistic was greater than 40%, further investigation of the reasons for heterogeneity was carried out. Clinically diverse studies were analysed separately wherever appropriate.

Assessment of reporting biases

Due to the small number of studies included in this review, and the small number that could be included in the meta-analyses, we considered it inappropriate to generate funnel plots to assess reporting biases (Egger 1997). We did consider studies from a wide range of locations, languages and publications, which we believe has reduced the likelihood of reporting biases affecting our findings (Higgins 2011).

Data synthesis

We entered all trials included in the systematic review into Review Manager (RevMan 5.1) and combined data quantitatively, where possible. We presented the main outcomes in this review as dichotomous variables. We calculated pooled estimates using the fixed-effect model with the Mantel-Haenszel method as the studies were homogenous and small numbers of events were observed. We determined the levels of heterogeneity by the I^2 statistic (Higgins 2011). We used a random-effects model when the I^2 was more than 50%.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted where data were available, as described by Deeks et al (Deeks 2001) and as recommended in Section 8.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to compare:

- adults and children;
- different types of surgery (e.g. orthopaedic and gynaecologic surgery);
- types of aromatherapy delivery methods (e.g. inhalation, massage, ingestion);
- trial quality (e.g. RCT, CCT).

Due to the limited data available, we were unable to perform any subgroup analyses.

Sensitivity analysis

Because of considerable concern about the risk of bias due to confounding in Merritt 2002 we performed a sensitivity analysis and have reported findings both with and without the results of this study.

RESULTS

Description of studies

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

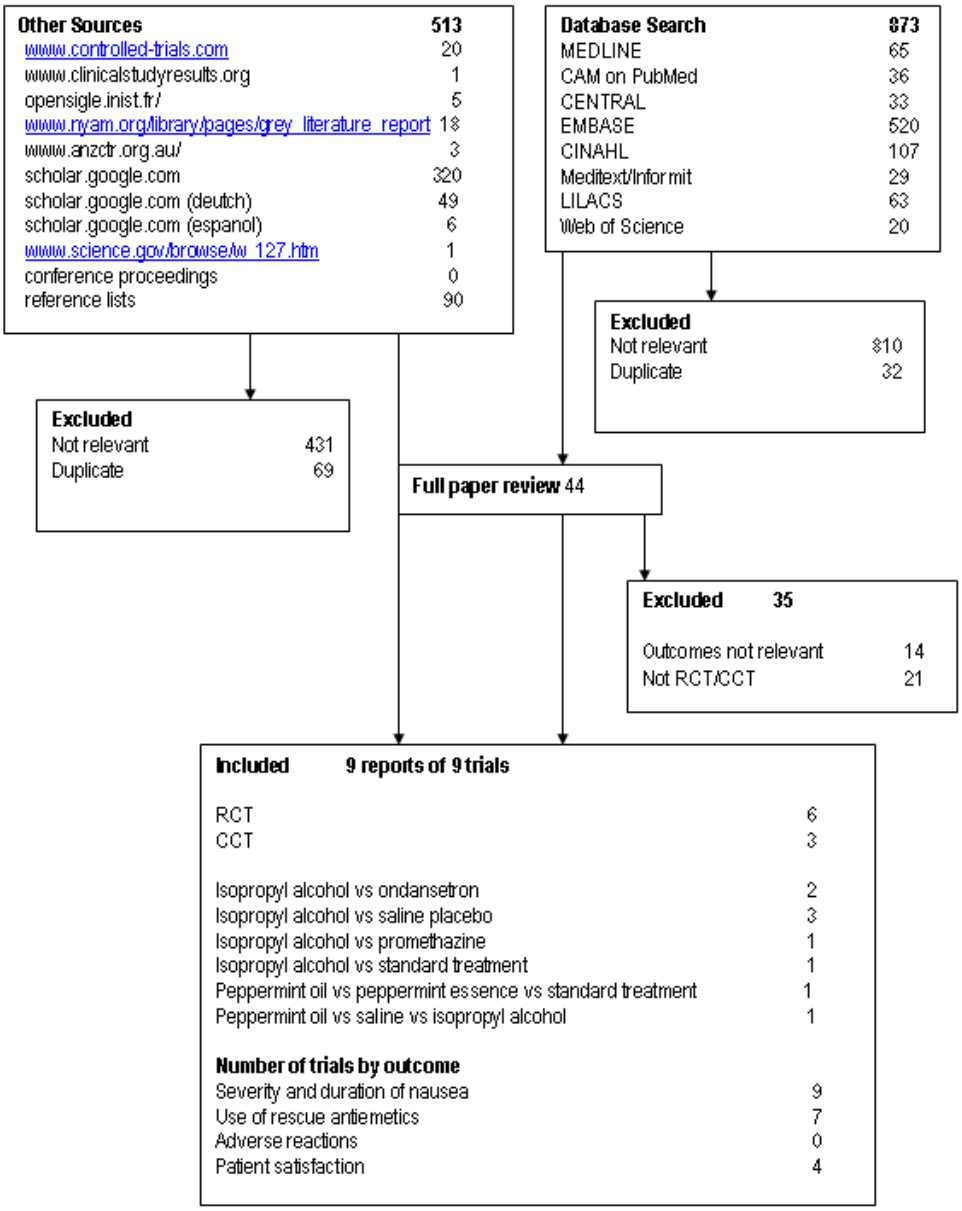
The studies were randomized controlled trials (RCTs) or controlled clinical trials (CCTs) conducted on postoperative adult and paediatric patients in postanaesthesia care units (PACU) and same-day surgery units (SDSU). The intervention groups were given aromatherapy treatments to treat complaints of postoperative nausea and vomiting. The control groups were treated with either a saline placebo or standard anti-emetic drugs.

Results of the search

We conducted searches in a wide range of databases and sources: MEDLINE; CAM on PubMed; CENTRAL; EMBASE; CINAHL; Meditext; LILACS; Web of Science; Current Controlled Trials; Clinical Study Results; SIGLE; New York Library of Medicine Grey Literature Report; National Institute of Clinical Studies; Google Scholar (English, German, Spanish); Science.gov (grey literature); Conference Proceedings of the National Association for Holistic Aromatherapy; and reference lists.

Of the 1386 articles we identified, 44 were deemed relevant enough to be retrieved for further evaluation. After appraisal of the full version of each study, nine studies were found to meet the criteria for inclusion in the review. For further details see Figure 1.

Figure 1. Results of searches



Included studies

We included nine studies, comprised of six RCTs (Anderson 2004; Cotton 2007; Kamalipour 2002; Pellegrini 2009; Wang 1999; Winston 2003) and three CCTs (Langevin 1997; Merritt 2002; Tate 1997) with a total of 402 participants. The mean age and range data for all participants were not available for all studies. See Characteristics of included studies for further details.

Excluded studies

We excluded 35 studies for not meeting the inclusion criteria, either by study design (not RCT or CCT) or by study outcomes (prevention of PONV not treatment). See Characteristics of excluded studies for details.

Risk of bias in included studies

We assessed the risk of bias in terms of allocation sequence generation, blinding, incomplete reporting of outcome data, and selective reporting. Risk of bias was found to be moderate to high across all included studies. For details of the risk of bias assessment, see Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

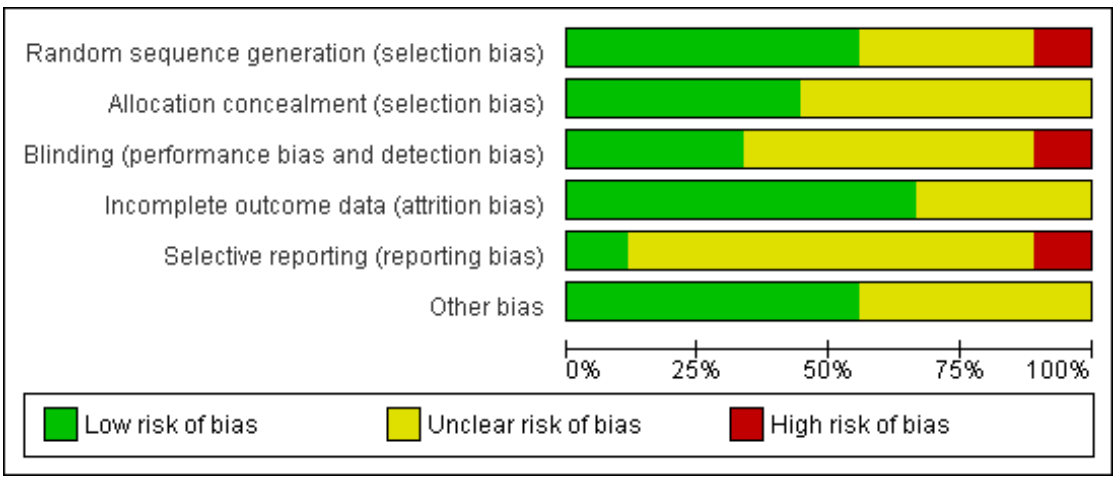
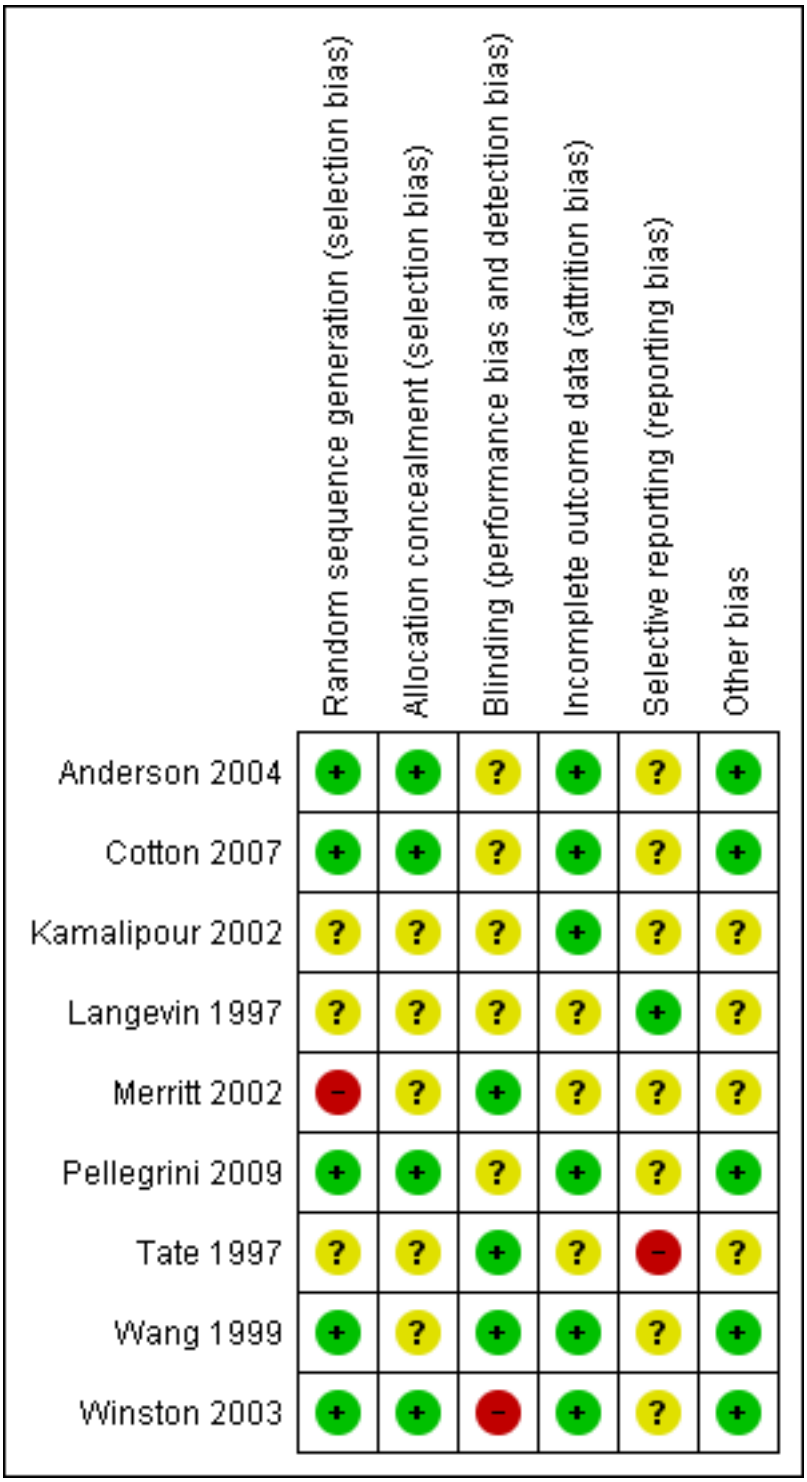


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Methods of allocation varied across the included studies. In four studies the method of randomization was explicitly stated: Wang 1999 utilized a 'random number table'; Cotton 2007 and Pellegrini 2009 utilized a 'computer generated random numbers table'; and Anderson 2004 used a 'random number generator'. For Kamalipour 2002 the treatment and control groups were "randomly selected" but the authors did not state what method of randomization was used. Similarly, in Winston 2003 participants were "randomly assigned" to receive either the treatment or control but the method of sequence generation was not stated. In Langevin 1997, which used a cross-over clinical trial design, the test agents were administered in a "random sequence" but again the method of randomization was not stated. The study by Merritt 2002 was a CCT and participants were not randomly allocated, rather assignment to the treatment and control groups was alternated by day. The participants in Tate 1997 were "randomly allocated" to wards which had been assigned to the separate treatments, the control and placebo arms of the study.

Allocation concealment appeared to have been undertaken for four studies (Anderson 2004; Cotton 2007; Pellegrini 2009; Winston 2003). The remaining five studies did not report data on whether allocation was concealed.

Blinding

Five included studies (Anderson 2004; Langevin 1997; Merritt 2002; Tate 1997; Wang 1999) appeared to have undertaken at least some blinding of participants and assessors; published details were unclear for two (Kamalipour 2002; Pellegrini 2009) and for two studies (Cotton 2007; Winston 2003) blinding was explicitly not done. Three included studies (Anderson 2004; Langevin 1997; Wang 1999) explicitly blinded assessors.

Incomplete outcome data

Data appeared to have been reported for all participants and outcomes in seven studies (Anderson 2004; Cotton 2007; Kamalipour 2002; Pellegrini 2009; Tate 1997; Wang 1999; Winston 2003), however it was unclear whether this had occurred in the remaining two studies (Langevin 1997; Merritt 2002).

Selective reporting

For seven studies (Anderson 2004; Cotton 2007; Kamalipour 2002; Langevin 1997; Merritt 2002; Pellegrini 2009; Wang 1999) it was unclear whether there was any degree of selective reporting, and for two studies it appeared that a degree of selective reporting had taken place (Tate 1997; Winston 2003).

Other potential sources of bias

Other potential sources of bias were evident in two studies. Due to the design of the study by Tate 1997, it was possible there was some demand characteristic effect (an effect where participants interpret the purpose of the study and modify their behaviour or reporting accordingly (Orne 1962)) on patient self-reporting of results. The authors of Merritt 2002 reported that their study was probably confounded by the aggressive preoperative anti-emetic prophylaxis given to 104 out of the 111 participants enrolled into the study. Four studies appeared free of other potential sources of bias (Cotton 2007; Pellegrini 2009; Wang 1999; Winston 2003). It was unclear from the minimal data reported in Langevin 1997 and Kamalipour 2002 whether there were any other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Isopropyl alcohol compared to standard treatment for treatment of postoperative nausea and vomiting; **Summary of findings 2** Isopropyl alcohol compared to saline for treatment of postoperative nausea and vomiting

Seven studies examined the effectiveness of isopropyl alcohol (IPA) as an anti-emetic and two studies investigated the effectiveness of peppermint oil (one study trialled both interventions). All included studies measured nausea as a chief outcome. Five studies also reported data on the number of participants requiring rescue anti-emetics for unresolved nausea. All analyses resulted in significance values for heterogeneity testing of greater than 0.10 and I^2 values less than 40%, indicating that statistical heterogeneity was not present.

Primary outcome: severity and duration of nausea

The only studies able to be compared for this outcome, with compatible drug administration times, were the Langevin 1997 and Kamalipour 2002 studies. However, the primary outcome analysis could not be performed on these two studies. The only measure of nausea for the Kamalipour study was percentage of patients who responded to the treatment, and this measure could not be compared with the Langevin study as there was ambiguity in the paper's definition of response.

The Anderson 2004 study could not be compared with the Langevin and Kamalipour studies for this outcome as the times for drug administration were: reporting nausea, two minutes later, then three minutes later; which is different to the drug administration times for the two other studies.

The two studies examining isopropyl alcohol versus standard drug treatment also could not be compared as the number of applications of isopropyl alcohol differed between the studies. For the

Cotton 2007 study, the maximum number of isopropyl alcohol applications was three whereas for the Winston 2003 study the maximum number of applications was two.

Finally, the two studies which looked at peppermint aromatherapy (Anderson 2004; Tate 1997) could not be compared due to differing drug administration times and units of measurement.

The single paediatric study that was included (Wang 1999) compared isopropyl alcohol and saline in a population of 39 children having elective outpatient surgery under general anesthesia. This study found that while isopropyl alcohol did have an effect on postoperative nausea at 20 minutes post-treatment (P = 0.05), this effect could not be sustained at 60 minutes (RR 2.85, 95% CI 0.32 to 25.07, P = 0.35). No effect on postoperative vomiting was demonstrated at 20 minutes or 60 minutes (RR 1.27, 95% CI 0.33 to 4.93).

Primary outcome: duration of nausea

Findings for studies measuring time to relief of nausea, which could not be combined statistically, are presented in Table 1.

Primary outcome: severity of nausea

Studies measuring severity of nausea by nausea scale measurements, which could not be combined statistically, are presented in Table 2.

Secondary outcome: use of rescue anti-emetics

Four studies with a total of 215 participants compared isopropyl alcohol to standard treatment (ondansetron or promethazine) and reported the number of participants in each group who required rescue anti-emetics. The studies by Cotton 2007, Merritt 2002, Pellegrini 2009 and Winston 2003 were able to be combined in a meta-analysis which showed a statistically significant effect (RR 0.66, 95% CI 0.45 to 0.98, P = 0.04) (Analysis 1.1). However, due to the likely confounding of the study by Merritt 2002, from the administration of preoperative prophylactic anti-emetics to 94 out of the 111 original participants, a sensitivity analysis was performed. Without the Merritt data there was no statistically significant evidence of an effect (RR 0.66, 95% CI 0.39 to 1.13, P = 0.13) (Analysis 2.1). These findings are summarized in Summary of findings for the main comparison.

Separating out results for participants with nausea only, as reported in Cotton 2007, Winston 2003 and Pellegrini 2009, we found that the proportion requiring rescue anti-emetics was not significantly different between the experimental and control groups (RR 0.66, 95% CI 0.39 to 1.13, P = 0.13) (Analysis 2.1).

Three studies of adult patients (Anderson 2004; Kamalipour 2002; Langevin 1997), with a total of 135 participants, compared isopropyl alcohol and saline and measured the number of participants who required rescue anti-emetics. These studies were combined. Meta-analysis showed a trend toward evidence of an effect (RR 0.30, 95% CI 0.09 to 1.00, P = 0.05) (Analysis 4.1). These findings are summarized in Summary of findings 2.

One study of 39 paediatric patients having day surgical procedures (Wang 1999) also compared isopropyl alcohol and saline and measured the number of participants requiring rescue anti-emetics. For participants with nausea only, 60% of those in the placebo (saline) group required rescue anti-emetics compared to 9% of those in the isopropyl alcohol group (RR 0.15, 95% CI 0.02 to 1.05). For participants with vomiting, 89% of the saline group required rescue anti-emetics compared to 67% of the isopropyl alcohol group (RR 0.75, 95% CI 0.23 to 1.12).

One RCT (Anderson 2004) trialled a comparison of isopropyl alcohol, peppermint oil and saline inhalations. This study randomized 33 participants to receive either isopropyl alcohol, peppermint oil or saline to treat reported nausea in a postoperative care unit. Of the participants receiving isopropyl alcohol 45% required rescue anti-emetics, while 60% of participants in the peppermint oil group and 50% of the control (saline) group required rescue anti-emetics. This study found no significant difference between the treatment and control groups (no significance value reported).

Secondary outcome: adverse reactions

No data on adverse reactions to the experimental substances were reported by any of the included studies.

Secondary outcome: patient satisfaction with treatment

Four studies measured patient satisfaction with treatment.

Cotton 2007 (comparing isopropyl alcohol to ondansetron) used a four-point ordinal scale on which the participants were asked to rate their postoperative experience as poor, fair, good or excellent; participants in both the treatment and control groups reported their experience as good or excellent, resulting in no statistically significant difference between the groups (P > 0.05).

Winston 2003 also measured patient satisfaction using a four-point ordinal scale (0 = poor; 1 = fair; 2 = good and 3 = excellent). For the ondansetron group: 0 = 1 participant (3%); 1 = 2 participants (6%); 2 = 17 participants (52%); and 3 = 13 participants (39%). For the isopropyl alcohol group, the satisfaction numbers were: 0 = 0 participants; 1 = 0 participants; 2 = 18 participants (47%), and 3 = 20 participants (53%). The authors stated that although these findings were not statistically significant, they nonetheless regarded them as clinically significant (unreported data supplied via email). Results from Cotton 2007 and Winston 2003 were collapsed into binary data (good or excellent interpreted as satisfied) and combined in Analysis 5.1.

Patients also reported high levels of satisfaction with their treatment regardless of allocation in Pellegrini 2009, with a median score of 4 on a 5-point ordinal scale (1, totally dissatisfied; 2, somewhat dissatisfied; 3, somewhat satisfied; 4, satisfied; 5, totally satisfied).

Anderson 2004 measured patient satisfaction on a VAS (0 mm

extremely dissatisfied, 100 mm fully satisfied). Participants across all three groups reported high levels of satisfaction with their treatment: isopropyl alcohol 90.3 (SD 14.9); peppermint oil 86.3 (SD 32.3); saline 83.7 (SD 25.6).

The results from all studies reporting on this outcome are collated in Table 3.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Isopropyl alcohol compared to saline for treatment of postoperative nausea and vomiting

Patient or population: patients with treatment of postoperative nausea and vomiting
Settings: Post-anaesthesia Care Areas
Intervention: Isopropyl alcohol
Comparison: saline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	saline	Isopropyl alcohol				
Requirement for rescue anti-emetics[1,2] count	**Study population**[3]		**RR 0.23** (0.14 to 0.38)	135 (3 studies)	⊕⊕◯◯ **low**[4,5]	
	868 per 1000	**200 per 1000** (122 to 330)				
	Low risk population[3]					
	100 per 1000	**23 per 1000** (14 to 38)				
Adverse effects[6]	See comment	See comment	Not estimable	0 (0)	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Participants enrolled into study on complaint of nausea and/or vomiting.
[2] Calculated using control group results.
[3] Risk calculations based on: Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. Canadian Journal of Anesthesia / Journal Canadien d'Anesthesie. 2002;49(3):237-42.
[4] Study by Langevin (1997) is controlled clinical trial and not randomised.
[5] Total number of events is less than 300.
[6] No data on this outcome.

DISCUSSION

Summary of main results

This review was able to include studies of isopropyl alcohol and peppermint oil aromatherapy compared to a saline placebo, ondansetron, promethazine, or other unspecified 'standard antiemetic' treatments. All aromatherapy was delivered via direct inhalation. There were 311 adult and 91 paediatric patients in the included studies. The majority of patients were women. Studies were conducted in both inpatient and day surgery settings. Outcomes measured were time to reduction in nausea, severity of nausea, number of nausea and vomiting events, the use of 'rescue' antiemetics, patient satisfaction, recurrence of symptoms, and cost of treatment.

Isopropyl alcohol (IPA) has been tested in several studies, both against standard pharmacological treatments and against other aromatherapies and placebo, in both adults and children. In comparison to saline placebo, IPA appears effective in reducing the number of patients requiring rescue anti-emetics (Kamalipour 2002; Langevin 1997) and in providing short-term relief of symptoms in children (Wang 1999). In two studies (Cotton 2007; Winston 2003) IPA provided a faster time to 50% relief of symptoms than ondansetron and promethazine (Pellegrini 2009); however, when meta-analysed, there was no statistically significant difference in the number of participants requiring rescue anti-emetics in the combined results of these three studies.

Peppermint oil inhalations are often recommended for PONV (Chiravalle 2005; Pompeo 2007; Price 2007) however this review was unable to find sufficient evidence to support this. Two studies examined the use of peppermint as a treatment for PONV (Anderson 2004; Tate 1997) but only Anderson 2004 was adequately randomized and blinded. Tate 1997 reported evidence of an effect however methodological concerns mean that these results should be viewed with caution. Anderson 2004 found that the effect of peppermint oil inhalation was not statistically different from the effect of inhalations of isopropyl alcohol or saline.

No adverse reactions were reported by any of the included studies. Patient satisfaction with aromatherapy treatment appeared high in studies that measured this outcome (Anderson 2004; Cotton 2007; Pellegrini 2009; Winston 2003), with patients reporting high levels of satisfaction with their experience. However it should be noted that all participants in these studies (treatment and comparison groups) reported high levels of satisfaction.

Overall completeness and applicability of evidence

It seems likely that further studies of isopropyl alcohol to treat postoperative nausea and vomiting could provide different results from those described here. Well-conducted studies of peppermint oil or other aromatherapies may provide definitive evidence for the effectiveness of these therapies. The evidence base for aromatherapy to treat PONV is currently incomplete, with only one study of children meeting the inclusion criteria and many aromatherapy treatments incompletely investigated or tested. While there appears to be no evidence of adverse reactions from the use of the included interventions, it is unclear from the included studies whether data were collected on any possible adverse reactions experienced by participants. In the context of current postoperative practice, there is a place for adjunct therapies to treat PONV and while isopropyl alcohol vapour inhalation is a simple and inexpensive treatment that seems to be more effective than placebo, there is currently no evidence to suggest that it can replace pharmacological anti-emetics.

Of additional concern are the early time points utilised by all included studies except Tate 1997, which did measure PONV at 24 and 48 hours but only reported average daily scores for each group. Apfel 2002 recommends that study authors measure PONV for early (greater than two hours) and late (to 24 hours) outcomes. The data able to be included in this review are incomplete for effects longer than 60 minutes.

Due to the many risk factors for and influences on PONV, such as type of anaesthesia, narcotic medication intake, sex, and type of surgery, it was a concern that there were differences between groups that might account for some of the effect. Examination of the demographic and procedural data, however, shows that control and experimental groups were very similar and that confounding due to risk factors was unlikely.

It should be remembered that we have not included any evidence of effectiveness for aromatherapy in the prevention of PONV and that all results apply only to treatment of an existing complaint.

Quality of the evidence

The included studies were comprised of six RCTs and three CCTs, with total of 402 participants. The overall quality of the retrieved evidence was low, with incomplete reporting and unavailable data hampering the comparison of most studies. Due to the age of several studies, further data were either not available or the authors were not contactable. The nine included studies measured the effectiveness of only two aromatherapy treatments for postoperative nausea and vomiting, neither of which were shown to be effective in comparison to standard pharmacological anti-emetics, although isopropyl alcohol appears to be more effective than placebo.

Agreements and disagreements with other studies or reviews

A recent systematic review of the effectiveness of noninvasive complementary therapies for reducing PONV in women having abdominal laparoscopic hysterectomy (Hewitt 2009) found, similarly to this review, that there was no strong evidence to support

the use of aromatherapy for PONV. We have been unable to find any other systematic reviews of aromatherapy for treating PONV.

AUTHORS' CONCLUSIONS

Implications for practice

From the evidence of this review, it seems that using isopropyl alcohol vapour inhalation as an adjunct therapy for PONV is unlikely to be harmful and may reduce nausea for some adult patients. It may provide a useful therapeutic option, particularly when the alternative is no treatment at all. As an inexpensive, readily available therapy (in the form of injection site 'prep-pads'), isopropyl alcohol vapour inhalation could be considered for use in situations where standard pharmacological anti-emetics are unavailable, refused by patients, or contra-indicated.

Included studies that examined this intervention used one prep-pad or isopropyl alcohol-soaked cotton ball or gauze pad per treatment and most asked the patient to take two or three deep breaths while the pad was held close to their nose without touching. Treatments were repeated up to three times without any adverse effects being reported.

There is currently no evidence to show that using peppermint oil aromatherapy reduces PONV, however there is no evidence of its use being harmful.

Implications for research

It is important that future trials fully report their methodology, demography and findings. Full descriptions of the results of interventions would enable clinicians to make more informed decisions about the uptake of these therapies in their clinical setting. Improved reporting would also benefit future updates of this review. There is an absence of large, well-reported trials in this area, particularly of therapies other than isopropyl alcohol. Further studies in paediatric populations are needed before aromatherapy can be recommended for treatment of PONV in children. Future trials should include measures for longer time intervals (two to 24 hours) and report discrete data on both postoperative nausea and postoperative vomiting.

ACKNOWLEDGEMENTS

We thank Mathew Zacharias, Jung T Kim, NL Pace, Peter Kranke and Anne Lyddiatt for their help and advice during the preparation of the systematic review.

We also thank Mathew Zacharias, Katrina Farber, Milli Reddy, Jung T Kim and Janet Wale for their help and editorial advice during the preparation of the protocol for the systematic review.

The authors wish to acknowledge Kathy Hibberd (Librarian, University of Queensland Medical Library) for her invaluable assistance in preparing and conducting the searches for this review, and Leandra Blake for her comments on the protocol and review. We also thank Kate Kynoch and Lisa Brown for assisting with the testing of the data extraction tool.

Thanks to Marie Kristensson for the Swedish translations, Abbas Breesem for the Farsi translation, and Laurie Bay at the Institute of Modern Languages at the University of Queensland for the French translation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anderson 2004

Methods	Randomized controlled trial of peppermint oil, isopropyl alcohol or normal saline aromatherapy to treat postoperative nausea and vomiting Setting: Postanaesthesia care unit (PACU) acute hospital, USA
Participants	33 patients aged 18 years+ having surgery under general or regional anaesthesia, or deep IV sedation, who reported nausea in postanaesthesia care unit. Treatment groups did not differ in the percentage having general anaesthesia, the type of surgery, age or gender distribution Exclusions: patients who were unable to give informed consent; patients who did not require anaesthesia services
Interventions	On the patient's spontaneous report of postoperative nausea, they were instructed to take three slow deep breaths to inhale the vapours from a pre-prepared gauze pad soaked with either peppermint oil, isopropyl alcohol or normal saline placebo held directly under their nostrils. After 2 minutes the patient was asked to rate their nausea by VAS and given the choice to continue aromatherapy or have standard IV anti-emetics. At 5 minutes post the initial treatment, the patient was again asked to rate their nausea and if they would like to continue aromatherapy or have standard IV anti-emetics
Outcomes	1. Severity of nausea as measured on 100 mm VAS at 2 minutes and 5 minutes after treatment. Visual analogue scale from 'no nausea' to 'worst possible nausea' 2. Choosing to use 'rescue' anti-emetics. 3. Satisfaction with management of nausea, as measured by 100 mm VAS with range from 0 = extremely dissatisfied to 100 = fully satisfied
Notes	Possible lack of accuracy with some participants self-recording data in PACU if they had poor or blurred vision. Authors Lynn Anderson and Dr Jeffrey Gross emailed to request further information on group sizes, which was supplied by Dr Gross

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"group assignments were made in a randomized, double-blind fashion" Comment: probably done. Nurses administering treatment were unaware of contents of each package of treatment materials. Patients who had consented to participate entered study when they spontaneously reported nausea

Anderson 2004 (*Continued*)

Allocation concealment (selection bias)	Low risk	"A random number generator determined the contents of each serially numbered bag. " "...prepared by an individual not otherwise involved in the study..." Data "analysed by investigator unaware of treatment allocation" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Staff administering treatment blinded by use of "lightly scented" surgical masks. However patients were self-reporting subjective assessment of nausea and were not blinded Comment: Due to the strong aroma of the peppermint oil, it would be impossible to blind the patients receiving this to their allocation once treatment commenced. Probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes reported for all participants.
Selective reporting (reporting bias)	Unclear risk	Comment: results reported for all stated outcomes, however original study protocol not available
Other bias	Low risk	Comment: study appears to be free of other sources of bias.

Cotton 2007

Methods	Prospective randomized study of isopropyl alcohol inhalation as compared to IV ondansetron for PONV. Replication of study: Winston 2003. Setting: PACU/same day surgery unit, USA.
Participants	100 women aged 18-65 who were scheduled for laparoscopic same-day surgery (ASA physical status I, II or III) Exclusions: patients who had recent upper respiratory tract infections, inability or impaired ability to breathe through the nose, or history of hypersensitivity to IPA, 5HT3 antagonists, promethazine or any other anaesthesia protocol medication, had used an anti-emetic within 24 hours of surgery, were pregnant or breastfeeding, had history of inner ear pathology, motion sickness or migraine headaches or were taking disulfram, cefoperazone, or metronidazole
Interventions	Comparison of inhaled isopropyl alcohol to intravenous ondansetron for treatment of PONV Ondansetron (control) group: nausea treated with ondansetron 4mg IV every 15 minutes to a maximum 8mg dose. Time, dose and VNRS score recorded

	IPA (experimental) group: nausea treated by holding a folded alcohol pad approximately 1/2 inch from the participant's nares and instructing them to take 3 deep breaths in and out through the nose. Treatments given every 5 minutes up to a total of 3 administrations Breakthrough PONV was treated with promethazine suppositories for both groups Participants were also given supplies of IPA and promethazine to use as needed at home after discharge and asked to record any occurrences of PONV with a data collection tool provided by the researchers
Outcomes	Time to reduction in nausea score as measured by Verbal Numeric Rating Scale (VRNS) (range 0-10 where 0 = no nausea and 10 = worst imaginable nausea). Collected for baseline at preop, then immediately postop in PACU and at any time the participant complained of nausea. Additionally, participants who complained of nausea were assessed every 5 minutes following treatment for 30 minutes and then every 15 minutes until discharge from PACU Participants also reported data on PONV for the 24 hours post-discharge as well rating their anaesthesia experience overall
Notes	Author, Joseph Pellegrini contacted for further data. Some was provided however due to data corruption problems not all requested data was available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patient was randomly assigned to the control group or the experimental group by using a computer-generated random numbers program." Comment: done.
Allocation concealment (selection bias)	Low risk	"Block randomization was used for all of the studies using a computer generated randomization program done by an independent party (myself) who was not involved in the data collection" (emailed author response) Comment: done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information given regarding blinding. Does not appear to have been done
Incomplete outcome data (attrition bias) All outcomes	Low risk	28 participants "disenrolled due to protocol violations": 12 from control group who were given IPA postoperatively; 6 from experimental group given other anti-emetics in PACU before IPA; and 10 who lost their IPA or promethazine following discharge to home

Cotton 2007 (*Continued*)

		Comment: probably done.
Selective reporting (reporting bias)	Unclear risk	Comment: original study protocol unavailable. Results reported for all stated outcomes
Other bias	Low risk	Comment: study appears to be free of other sources of bias.

Kamalipour 2002

Methods	Randomized controlled trial of ISO versus normal saline placebo for treatment of PONV Setting: postoperative care unit, acute hospital, Iran.
Participants	82 consecutive patients randomized into experimental and control groups. No age data or demographic except 48 female/34 male
Interventions	2 sniffs of ISO (treatment) or 2 sniffs normal saline (control) (on reporting symptoms) and re-treated at 5 minutes if necessary. Patients who did not respond the 2nd time received metoclopramide injection
Outcomes	Response to treatment/cessation of symptoms, recurrence of symptoms, use of rescue anti-emetics
Notes	Attempted to contact author, Dr H Kamalipour, via email however no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly divided into two groups." Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: no data.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data reported for all stated outcomes.
Selective reporting (reporting bias)	Unclear risk	Comment: brief report with little detail.
Other bias	Unclear risk	Comment: unable to ascertain from details reported.

Langevin 1997

Methods	Double-blinded cross-over clinical trial/pilot study. Setting: acute hospital, USA.
Participants	15 consecutive patients in PACU who complained of nausea or vomiting after elective surgery
Interventions	Either 0.5 ml saline or 0.5 ml isopropyl alcohol on a cotton ball (according to random sequence) was held under participants' noses and the participant was instructed to sniff twice. If symptoms recurred, the test agents were re-administered in random sequence. When neither test agent was effective, standard anti-emetics were given and the PONV assessed every 5 minutes until participant left PACU
Outcomes	Severity of PONV as assessed with VAS. VAS range from 0 = none to 10 = vomiting Treatment failure attributed to the last agent given.
Notes	No demographic data supplied in brief report. Letter sent to author, Dr Paul Langevin, to ask for more data, no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"the test agents were readministered in the randomized sequence" Comment: no information on how this sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported on who conducted the allocation and how
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"We designed a randomized double-blinded study..." "Nurses who administered the test therapy were blinded to group assignment by applying an ISO-soaked Band-Aid under their noses while another person applied the test agent to a cotton ball, which was attached to a sponge stick. " Comment: participants would not have been blinded to the treatment due to the distinctive odour of the isopropyl alcohol. Unclear where the 'double-blinding' occurred
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: original study protocol not available.
Selective reporting (reporting bias)	Low risk	Comment: data reported for all participants, no apparent losses to follow-up

Langevin 1997 (*Continued*)

Other bias	Unclear risk	Comment: minimal data reported in this publication.

Merritt 2002

Methods	Controlled clinical trial of isopropyl alcohol inhalation for treatment of PONV Setting: acute hospital, USA.
Participants	111 adults having surgery (40 with nausea were evaluated for study). Age range: 19-80 years; mean age = 43. Types of surgery included intra-abdominal (29.7%), orthopaedic/ extremity (23.4%), perineal (19.8%) neuro-skeletal (10.8%), extra-thoracic (6.3%) eyes/ ears/nose/throat (6.3%), neck (3.6%) Of 40 patients evaluated for study, 21 received IPA and 18 were controls. 1 patient entered into the study had their PONV resolve spontaneously Inclusion criteria were (a) requirements for general anaesthesia, (b) ability to breathe through nose before and after procedure, (c) minimum of 18 years of age, (d) American Society of Anesthesiologists (ASA) physical status of I, II, or III, and (e) ability to read and write English Exclusion criteria were (a) allergy to IPA, (b) alcohol abuse, (c) no recent history of nausea or vomiting within the last 8 hours, (d) no recent intake of cefoperazone, Antabuse, or metronidazole, (e) ability to communicate in recovery room, (f) regional anaesthesia, and (g) monitored anaesthesia care.
Interventions	Isopropyl alcohol inhalation for treatment of PONV. "If nausea or vomiting was present in control participants, an appropriate anti-emetic was given. Experimental participants were given IPA via nasal inhalation using standard hospital alcohol pads. The participant was instructed to take three deep sniffs with the pad one inch from the nose. This was repeated every five minutes for three doses or until nausea and vomiting was relieved. If nausea and vomiting continued after three doses of IPA, then an intravenous drug was given."
Outcomes	Severity of PONV as measured by a descriptive ordinal scale (DOS) from "0 to 10, with 0 being no nausea or vomiting and 10 being the worst nausea and vomiting they could imagine." Cost of treatment in USD.
Notes	Anti-emetic prophylaxis was given to patients in both groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Group assignment was alternated by day: experimental one day and control the next. " Comment: study is controlled clinical trial.

Merritt 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: allocators and caregivers appear to have been aware of the allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants were blinded to which treatment they were to receive." Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: original study protocol unavailable. Stated outcomes were all addressed in report
Selective reporting (reporting bias)	Unclear risk	Comment: no apparent loss to follow-up. No P values reported for main findings of pre and post-test DOS, though P value for cost differences reported
Other bias	Unclear risk	"Only 40 of the 111 participants recruited had PONV. This is explained by aggressive prophylactic treatment at the study facility where only 7 (6.3%) of 111 participants did not receive prophylactic medication and none of these 7 participants had PONV. Additionally, the researchers speculate that pain may have been a confounding factor in accurate assessment on the DOS. " Comment: several possible confounders.

Pellegrini 2009

Methods	Randomized controlled trial comparing 70% isopropyl alcohol inhalation to promethazine to treat breakthrough nausea in surgical patients at high risk of PONV Setting: day hospital, USA.
Participants	85 surgical patients scheduled for general anaesthesia of more than 60 minutes' duration and having 2 of the 4 individual risk factors for PONV, (female gender, nonsmoker, history of PONV or motion sickness) (IPA group, 42; promethazine group, 43) Excluded: recent upper respiratory infection; documented allergy to IPA, ondansetron, promethazine, or metoclopramide; anti-emetic or psychoactive drug use within 24 hours; inability to breathe through the nose; pregnancy; history of inner ear pathology; and/or taking disulfiram, cefoperazone, or metronidazole
Interventions	Control group: 12.5 to 25 mg IV promethazine for complaints of PONV in the postanaesthesia care unit (PACU) and same-day surgery unit (SDSU) and by promethazine suppository self-administration following discharge to home Experimental group: administration of inhaled 70% IPA.

Pellegrini 2009 (*Continued*)

Outcomes	Nausea, measured by Verbal Numeric Rating Scale (VNRS) (0-10, 0 = no nausea 10 = worst imaginable nausea) Incidence of nausea events in PACU, SDSU or at home (number) Doses of promethazine required as rescue anti-emetic (number) Promethazine requirements in PACU, SDSU or at home (mg). Time in minutes to 50% reduction of nausea scores. Participant satisfaction.
Notes	All participants received anti-emetic prophylaxis prior to surgery. Author J Pellegrini emailed to request numeric data for results published in graph form. Data received. Other clarifications requested and some were received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All subjects were then randomly assigned using a computer-generated random numbers process into a control or an experimental group." Comment: probably done.
Allocation concealment (selection bias)	Low risk	"Block randomization was used for all of the studies using a computer generated randomization program done by an independent party (myself) who was not involved in the data collection." (emailed author response) Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no data on blinding. It appears that participants and assessors were aware of group allocations during study
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A total of 96 subjects were enrolled, but 11 subjects were withdrawn, leaving a total of 85 subjects (IPA group, 42; promethazine group, 43) whose data would be included in the final analysis. Reasons for withdrawal included 4 subjects who received additional anti-emetics intraoperatively (2 in each group), 1 subject inadvertently enrolled despite being scheduled for a nasal surgical procedure (IPA group), and 6 subjects who required postoperative inpatient hospitalization for reasons unrelated to PONV (3 in each group)." Comment: probably done.

Selective reporting (reporting bias)	Unclear risk	Comment: all outcomes stated in the article have data reported, however original study protocol is not available
Other bias	Low risk	Comment: no other sources of bias apparent.

Tate 1997

Methods	Three-arm controlled clinical trial of peppermint oil inhalations, peppermint essence inhalations (placebo) and no treatment (control) to treat PONV in women Setting: acute hospital, UK.
Participants	18 women undergoing major gynaecological surgery. Mean weight group 1: 152lb; group 2: 139.5lb; group 3: 144.2lb. Mean height group 1: 64.2in; group 2: 62.5in; group 3: 64.3in. Mean age group 1: 54 years; group 2: 43.2 years; group 3: 45.5 years. Participants were assessed as having no significant differences in personal characteristics, past medical history or preoperative anxiety levels. There were no statistically significant differences in preoperative fasting times, anaesthetic and recovery times or postoperative fasting times. Five of the experimental group had intra-abdominal surgery, compared with three in each of the other two groups
Interventions	Participants were given bottles of their assigned substance postoperatively and instructed to inhale the vapours from the bottle whenever they felt nauseous
Outcomes	Self-reported nausea as measured by VAS of 0-4 where 0 = "not experiencing any nausea" and 4 = "about to vomit" reported as the average score per person per day Cost of treatment in GBP. Patient satisfaction with treatment, reported narratively.
Notes	Participants may or may not have received standard anti-emetics in PACU. Author Sylvina Tate supplied some extra data on group allocation methods

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The subjects were assigned to one of three groups." Comment: author states that participants were "randomly assigned" to ward areas
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported regarding concealment.
Blinding (performance bias and detection bias)	Low risk	Comment: use of peppermint essence as placebo blinded experimental and placebo

Tate 1997 (*Continued*)

All outcomes		group patients to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mention of patients lost to follow-up, however group numbers are not reported. (Group numbers clarified by author via email)
Selective reporting (reporting bias)	High risk	Comment: trialists did not provide measure of statistical significance or measures of variance for daily average nausea scores, even though they state 'statistically significant difference in the amount of self-reported nausea between the placebo and experimental groups
Other bias	Unclear risk	Comment: due to study design, entirely possible there was some demand-characteristic effect on patient self-reporting of results. However, experimental group received 'on average, slightly less' postoperative anti-emetics and more postoperative opioids than placebo group, which would tend to indicate evidence of an effect

Wang 1999

Methods	Double-blind randomized controlled study of isopropyl alcohol as a treatment for PONV. "When any episode of vomiting or nausea occurred, patients were randomized, using a random number table to receive a cotton ball soaked with ISO or saline placed under the patient's nose by the nursing staff. The patient was instructed to sniff twice by a nurse who was blind to group assignment. It should be emphasized that the nursing staffs were instructed not to smell the content of cotton ball and to hold it away from themselves when administering to patient If the severity of nausea or vomiting improved after a single treatment, a VAS assessment of nausea was obtained every 5 minutes until the patient was discharged or PONV symptoms recurred. Improvement of nausea was defined as a decrease of at least 40% in initial VAS score, and improvement of vomiting was defined as no further episodes of vomiting. If, after treatment, severity of nausea did not improve or retching/vomiting persisted, a second treatment with the same agent was given. Treatment sequences were repeated for a maximum of three times in a 15-minute period. When severity of either nausea or vomiting failed to improve despite three treatments, intravenous (IV) ondansetron 0.1 mg/kg (maximum 4 mg) was administered. If symptoms persisted, a second dose of ondansetron was administered. For patients who failed to improved after two ondansetron doses (maximum dose: 8mg), other IV ant-emetic medications (i.e., 200 mg/kg of metoclopramide; 10 mg/kg droperidol) were given." Setting: acute paediatric day surgery centre.

Wang 1999 (*Continued*)

Participants	91 children aged 6-16 years having surgery under general anaesthesia. ASA physical status I and II. Of these, 39 developed PONV and were enrolled into treatment or control groups. Treament n = 20. Control n = 19. No significant differences in demographic data across groups Exclusions: children with a history of chronic illness or developmental delay
Interventions	Inhalations of isopropyl alcohol or saline placebo. Intervention repeated up to three times. IV ondansetron was used as 'rescue therapy' if PONV continued
Outcomes	1. Severity of nausea and vomiting as measured by 100 mm VAS with a range of 0 = no nausea to 100 = extreme nausea 2. Use of rescue anti-emetics as measured by drug and number of doses
Notes	Study author, Dr Shu-Ming Wang contacted for any further data, however due to the age of the study there was none available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"If any episode of vomiting or nausea occurred, patients were randomized, using a random number table to receive a cotton ball soaked with ISO or saline placed under the patient's nose by the nursing staff." Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: no data on who conducted the allocation and any degree of separation from the conduct of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	"The patient was instructed to sniff twice by a nurse who was blind to group assignment. It should be emphasized that the nursing staffs were instructed not to smell the content of cotton ball and to hold it away from themselves when administering to patient." Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data reported for all participants. No apparent losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Comment: original study protocol not available. All stated outcomes reported

Wang 1999 (*Continued*)

Other bias	Low risk	Comment: no other sources of bias apparent.

Winston 2003

Methods	Randomized controlled trial of isopropyl alcohol for treatment of PONV. Participants were randomized to receive either isopropyl alcohol inhalations, or 4mg ondansetron Setting: same day surgery centre, USA.
Participants	100 women aged 18-65 years who were scheduled for diagnostic laparoscopy, operative laparoscopy or laparoscopic bilateral tubal occlusion (ASA physical status I, II or III) in a day surgery unit Exclusions: inability or impaired ability to breathe through the nose, or history of sensitivity to IPA or ondansetron, had used an anti-emetic within 24 hours of surgery, pregnant or breastfeeding, reported existing nausea, history of significant PONV resistant to anti-emetics, using disulfram or had a history of alcoholism
Interventions	Comparison of inhaled 70% isopropyl alcohol to ondansetron for treatment of PONV Ondansetron (control) group: at first request for treatment participants in this group received IV ondansetron 4mg, repeated once in 15 minutes if required 70% IPA (experimental) group: a standard alcohol prep pad was held under the participant's nose and she was instructed to take 3 consecutive deep breaths through the nose Nausea score collected for baseline at preop, then immediately postop in PACU and at any time the participant complained of nausea. Additionally, participants who complained of nausea were assessed every 5 minutes following treatment for 30 minutes and then every 15 minutes until discharge from PACU
Outcomes	1. Nausea score as measured by Verbal Numeric Rating Scale (VRNS) (range 0-10 where 0 = no nausea and 10 = worst imaginable nausea) 2. Number of emetic events, defined as episodes of nausea or vomiting more than one minute apart 3. Time to reduction of PONV in minutes. 4. Cost. 5. Patient satisfaction with anaesthesia care.
Notes	This study was replicated by Cotton 2007 with the number and frequency of IPA inhalations increased. Author J Pellegrini provided additional data via email

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"subjects were randomly assigned to receive inhaled 70% IPA (experimental group) or IV ondansetron (control group) for the treatment of PON" "despite the use of block randomization" Comment: author states via email that ran-

		domization was conducted using a computer generated random numbers table
Allocation concealment (selection bias)	Low risk	"Block randomization was used for all of the studies using a computer generated randomization program done by an independent party (myself) who was not involved in the data collection." Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	High risk	"...this did not allow us to blind the study intervention." Comment: it appears that no blinding of participants or caregivers was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears that data was reported for all participants, no evidence of exclusions or attrition
Selective reporting (reporting bias)	Unclear risk	Comment: original study protocol unavailable. Despite stating collection of data on patient satisfaction with anaesthetic experience, no results for this were reported, however this data was made available by an author via email
Other bias	Low risk	Comment: no other sources of bias apparent.

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

Study	Reason for exclusion
Apariman 2006	Prevention of PONV, not treatment.
Apfel 2001	Not RCT/CCT. Not aromatherapy.
Arfeen 1995	Prevention of PONV, not treatment.
Betz 2005	Not RCT/CCT.
Bone 1990	Prevention of PONV, not treatment.
Buckle 1999	Not RCT/CCT.
Chaiyakunapruk 2006	Prevention of PONV, not treatment.

(*Continued*)

Chiravalle 2005	Not RCT/CCT.
Chrubasik 2005	Not RCT/CCT.
Couture 2006	Prevention of PONV, not treatment.
DePradier 2006	Not RCT/CCT.
Eberhart 2003	Prevention of PONV, not treatment.
Eberhart 2006	Not RCT/CCT.
Ekenberg 2007	Not RCT/CCT.
Ernst 2000	Not RCT/CCT.
Fujii 2008	Not RCT/CCT.
Geiger 2005	Not RCT/CCT.
Golembiewski 2005	Not RCT/CCT.
Keifer 2007	Not RCT/CCT.
Kim 2006	Not PONV.
Kim 2007	Not PONV.
King 2009	Not RCT/CCT.
Koretz 2004	Not RCT/CCT.
Mamaril 2006	Not RCT/CCT.
Morin 2004	Not RCT/CCT.
Nale 2007	Prevention of PONV, not treatment.
Nanthakomon 2006	Prevention of PONV, not treatment.
Phillips 1993	Prevention of PONV, not treatment.
Pompeo 2007	Not RCT/CCT.
Pongrojpaw 2003	Prevention of PONV, not treatment.
Rosén 2006	Not RCT/CCT.
Spencer 2004	Not RCT/CCT.

(*Continued*)

Tavlan 2006	Prevention of PONV, not treatment.
Tramer 2001	Not RCT/CCT.
Visaylaputra 1998	Prevention of PONV, not treatment.

DATA AND ANALYSES

Comparison 1. Isopropyl alcohol versus standard treatment for PONV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion requiring rescue antiemetics	4	215	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.45, 0.98]

Comparison 2. Isopropyl alcohol versus standard treatment for PON: sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion requiring rescue antiemetics	3	176	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.39, 1.13]

Comparison 3. Isopropyl alcohol versus standard treatment for PON

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion requiring rescue antiemetics	3	176	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.39, 1.13]

Comparison 4. Isopropyl alcohol versus saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion requiring rescue antiemetics	3	135	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 1.00]

Comparison 5. Aromatherapy versus standard anti-emetics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient satisfaction	2	172	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.62, 2.03]

ADDITIONAL TABLES

Table 1. Table 1. Studies measuring time to relief of nausea

Study	Design	Intervention/Control	Outcome	Findings
Cotton 2007	RCT	IPA/ondansetron	Time to 50% reduction in nausea (VNRS[1])	IPA: mean 15.00 (SD:10.6mins) Ondansetron: mean 33.88 (SD: 23.2mins)
Kamalipour 2002	RCT	IPA/saline	Percentage "response"[2] to treatment within 5 minutes	IPA: 78% Saline: 7.3%
Langevin 1997	CCT	IPA/saline	Percent with complete relief of nausea in 5 minutes	IPA: 80% Saline: 0%
Pellegrini 2009	RCT	IPA/Promethazine	Mean time to 50% reduction in nausea scores (VNRS[1])	IPA: (mean +/- SD) PACU[3]: 6.43 +/- 3.78 minutes SDSU[4]: 8.33 +/- 4.82 minutes HOME[5]: 16.58 +/- 6.9 minutes Promethazine: (mean +/- SD) PACU[3]: 20.5 +/- 18.236 minutes SDSU[4]: 23.3 +/- 18.86 minutes HOME[5]: 26.67 +/- 12.5 minutes
Winston 2003	RCT	IPA/ondansetron	Mean time to 50% reduction of VNRS[1]	IPA: 6.3 minutes Ondansetron: 27.7 minutes

[1]VRNS: Verbal Numeric Rating Scale.
[2]Meaning of response not defined by study authors.
[3]PACU: Postanaesthesia Care Unit.
[4]SDSU: Same Day Surgery Unit.
[5]Home: Participant's residence post-discharge.

Table 2. Table 2. Studies measuring a decrease in nausea scores

Study	Design	Intervention/Control	Outcome	Findings
Merritt 2002	CCT	IPA/standard anti-emetics	Decrease in mean nausea score (DOS[1]) 0-10 (0 = no nausea, 10 = worst nausea and vomiting imaginable)	IPA: Mean DOS[1] score Pre-treatment: 5.71 Post-treatment: 2.7 Standard treatment: Pre-treatment: 6.11 Post-treatment: 1.94
Tate 1997	CCT	Peppermint oil/peppermint essence/standard treatment	Mean daily nausea scores (DOS[1]) 0-4 (0 = no nausea, 4 = about to vomit)	Standard treatment: mean daily nausea score = 0.975 Peppermint essence mean daily nausea score (placebo): 1.61 Peppermint oil mean daily nausea score: 0.5
Wang 1999	RCT	IPA/saline	Percentage of participants with decrease in nausea after 3 treatments (VAS) 0-100 (0 = no nausea, 100 = extreme nausea)	IPA: 91% Saline: 40%

[1]DOS: Descriptive Ordinal Scale.

Table 3. Patient satisfaction

Study	Design	Intervention/Comparison	Measure	Satisfied
Cotton 2007	RCT	IPA/ondansetron	4-point DOS (poor, fair, good, excellent)	Good or excellent: Intervention: 38/38 Comparison: 34/34
Winston 2003	RCT	IPA/ondansetron	4-point DOS (poor, fair, good, excellent)	Good or excellent: Intervention: 38/50 Comparison: 30/50
Pellegrini 2009	RCT	IPA/Promethazine	5-point DOS (1 = totally unsatisfied, 5 = totally satisfied)	Both groups report median score 4
Anderson 2004	RCT	IPA/Saline/Peppermint	100mm VAS (0 mm extremely dissatisfied; 100 mm fully satisfied)	IPA: 90.3 (SD: 14.9) peppermint: 86.3 (SD: 32.3) saline: 83.7 (SD: 25.6)

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 4, 2012

Date	Event	Description
15 March 2010	Amended	Change in author's name: Kristen Gibbons was previously known as Kristen Gilshenan. Previous citation read: Hines S, Steels E, Chang A, Gilshenan K

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Sonia Hines (SH)

Designing the review: SH

Co-ordinating the review: SH

Undertaking manual searches: SH

Screening search results: SH, Elizabeth Steels (ES)

Organizing retrieval of papers: SH

Screening retrieved papers against inclusion criteria: SH, ES

Appraising quality of papers: SH, ES, Anne Chang (AC)

Abstracting data from papers: SH, ES, Kirsten Gibbons (KG)

Writing to authors of papers for additional information: SH

Providing additional data about papers: SH, AC

Obtaining and screening data from unpublished studies: SH, ES

Data management for the review: SH

Entering data into Review Manager (RevMan 5.1): SH, KG

Analysis of data: SH, ES, KG

Interpretation of data: SH, ES, AC, KG

Writing the review: SH, AC, KG

Securing funding for the review: SH

Performing previous work that was the foundation of the present study: SH

Guarantor for the review (one author): SH

Statistical analysis: KG, AC

DECLARATIONS OF INTEREST

Sonia Hines: Queensland Health Nursing and Midwifery Research Grant received by Sonia Hines to assist with the conduct of the review (AUD 5906). The granting body had no influence on the findings of this review.

All other authors: no conflict of interest is known.

SOURCES OF SUPPORT

Internal sources

- Nursing Research Centre, Mater Health Services, Australia.

Time and facilities.

External sources

- Queensland Health, Australia.

Nursing and Midwifery Research Grant ($5906) awarded to Sonia Hines

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol stated "We will judge the study quality using a validated critical appraisal checklist developed by the Joanna Briggs Institute and based on the work of The Cochrane Collaboration and the Centre for Reviews and Dissemination (Figure 2). This checklist assesses selection, allocation, treatment, and attrition biases". Due to changes in the Cochrane requirements, we have used the Cochrane risk of bias assessment instead.

We had originally planned to search the website http://www.nhmrc.gov.au/nics/asp/index.asp, however this no longer exists and http://www.nhmrc.gov.au/nics/index.htm was searched instead.

INDEX TERMS

Medical Subject Headings (MeSH)

2-Propanol [*administration & dosage]; Administration, Inhalation; Antiemetics [*administration & dosage]; Aromatherapy [*methods]; Controlled Clinical Trials as Topic; Plant Oils [*administration & dosage]; Postoperative Nausea and Vomiting [*therapy]; Salvage Therapy [methods]

MeSH check words

Humans