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High initial concentration versus low initial concentration sevoflurane for inhalational induction of anaesthesia (Review)

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(Review)

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[Intervention Review]

High initial concentration versus low initial concentration sevoflurane for inhalational induction of anaesthesia

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ABSTRACT

Background

Sevoflurane induction for general anaesthesia has been reported to be safe, reliable and well accepted by patients. Sevoflurane induction uses either low or high initial concentrations. The low initial concentration technique involves initially administering a low concentration of sevoflurane and gradually increasing the concentration of the dose until the patient is anaesthetized. The high initial concentration technique involves administering high concentrations from the beginning, then continuing with those high doses until the patient is anaesthetized. This review was originally published in 2013 and has been updated in 2016.

Objectives

We aimed to compare induction times and complication rates between high and low initial concentration sevoflurane anaesthetic induction techniques in adults and children who received inhalational induction for general anaesthesia. We defined 'high' as greater than or equal to and 'low' as less than a 4% initial concentration.

Search methods

For the updated review, we searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2), MEDLINE (1950 to February 2016), EMBASE (1980 to February 2016), Latin American Caribbean Health Sciences Literature (LILACS) (1982 to February 2016) and the Institute for Scientific Information (ISI) Web of Science (1946 to February 2016). We also searched the reference lists of relevant articles and conference proceedings and contacted the authors of included trials. The original search was run in September 2011.

Selection criteria

We sought all published and unpublished, randomized controlled trials comparing high versus low initial sevoflurane concentration inhalational induction. Our primary outcomes included two measures of anaesthesia (time to loss of the eyelash reflex (LOER) and time until a weighted object held in the patient's hand was dropped), time to successful insertion of a laryngeal mask airway (LMA) and time to endotracheal intubation. Other outcomes were complications of the technique.

Data collection and analysis

We used standardized methods for conducting a systematic review as described in the *Cochrane Handbook for Systematic Reviews of Interventions*. Two review authors independently extracted details of trial methods and outcome data from reports of all trials considered eligible for inclusion. We conducted all analyses on an intention-to-treat basis, when possible. We estimated overall treatment effects by

using a fixed-effect model when we found no substantial heterogeneity, whereas we applied the random-effects model in the presence of considerable heterogeneity.

Main results

We reran the searches and included one new study (100 participants) in this updated review. In total, we included 11 studies with 829 participants, although most analyses were based on data from fewer participants and evidence of low quality. We noted substantial heterogeneity in the included trials. Thus, our results should be read with caution. It was not possible to combine trials for the primary outcome (LOER), but individual trials reported faster induction times (typically 24 to 82 seconds faster, 41 seconds (31.37 to 50.62)) with high initial concentration sevoflurane (six studies, 443 participants, low-quality evidence). Apnoea appeared to be more common in the high initial concentration sevoflurane group (risk ratio (RR) 3.14, 95% confidence interval (CI) 1.72 to 5.7, two studies, 160 participants, low-quality evidence). We found no evidence of differences between the two groups in the incidence of cough (odds ratio (OR) 1.23, 95% CI 0.53 to 2.81, eight studies, 589 participants, low-quality evidence), laryngospasm (OR 1.59, 95% CI 0.16 to 15.9, seven studies, 588 participants, low-quality evidence), breath holding (OR 1.16, 95% CI 0.47 to 2.83, five studies, 389 participants, low-quality evidence), patient movement (RR 1.14, 95% CI 0.69 to 1.89, five studies, 445 participants, low-quality evidence) or bradycardia (OR 0.8, 95% CI 0.22 to 2.88, three studies, 199 participants, low-quality evidence), and the overall incidence of complications was low.

Authors' conclusions

A high initial concentration sevoflurane technique probably offers more rapid induction of anaesthesia and a similar rate of complications, except for apnoea, which may be more common with a high initial concentration. However, this conclusion is not definitive because the included studies provided evidence of low quality.

PLAIN LANGUAGE SUMMARY

High initial concentration versus low initial concentration sevoflurane for inhalational induction of anaesthesia

Review question

We reviewed the evidence from randomized controlled trials comparing high initial concentrations of sevoflurane with low initial concentrations to see whether the evidence supports use of high initial concentrations to reduce induction times and complications for inhalational induction of anaesthesia. This update of a review first published in 2013 is current to February 2016.

Background

General anaesthesia for surgery can be induced by having patients breathe a mixture of sevoflurane (a sweet-smelling inhaled anaesthetic vapour or drug) and oxygen through a mask. This technique has been reported to be safe, reliable and well accepted by patients. The initial concentration of sevoflurane used for induction can be low or high. The low initial concentration technique involves administering a low concentration of sevoflurane (less than 4%), then gradually increasing the concentration until the patient is anaesthetized. The high initial concentration technique involves administering high concentrations of sevoflurane (from 4% to 8%) from the beginning, then continuing until the patient is anaesthetized. Immediately following loss of consciousness and before anaesthesia is deep enough to allow surgery, patients can go through a stage where they cough, their breathing and heart rate become irregular and they may hold their breath and make uncontrolled movements. A high concentration might shorten this stage.

Study characteristics

We included in our review 11 randomized controlled trials (829 participants). These trials were conducted between 1997 and 2014 and differed with regard to participants (adults vs children), concentrations of sevoflurane used, addition of nitrous oxide and opioids and other factors. Some elements of the methods suggested low-quality evidence would be obtained. The studies could not always be combined, and study results cannot be stated with certainty.

Key results

The high initial concentration technique shortened induction time (six studies, 443 participants, low-quality evidence) and led to similar rates of cough (eight studies, 589 participants, low-quality evidence), sudden sustained closure of the vocal cords that prevented breathing (seven studies, 588 participants, low-quality evidence), breath holding (five studies, 389 participants, low-quality evidence), sudden movements (five studies, 445 participants, low-quality evidence) and slow heart rate (three studies, 199 participants, low-quality evidence). The high initial concentration technique showed greater suspension of breathing when compared with the low initial concentration technique (two studies, 160 participants, low-quality evidence).

Quality of the evidence

The included studies provided low-quality evidence, and study results should be interpreted with caution. More studies are needed to enable firm conclusions.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. High initial concentration versus low initial concentration for inhalational induction of anaesthesia

High initial concentration versus low initial concentration for inhalational induction of anaesthesia

Patient or population: patients with inhalational induction of anaesthesia

Settings: patients undergoing various surgical procedures in operating rooms in Asia, Europe, North America

Intervention: high initial concentration versus low initial concentration

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	High initial concentration vs low initial concentration				
Time to loss of eyelash reflex	Mean time to loss of eyelash reflex in control groups was 112.9 seconds	Mean time to loss of eyelash reflex in intervention groups was 41 lower (31.37 to 50.62 lower)		443 (6 studies)	⊕⊕⊕⊕ low ^a	
Cough	38 per 1000	47 per 1000 (21 to 101)	OR 1.23 (0.53 to 2.81)	589 (8 studies)	⊕⊕⊕⊕ low ^b	
Laryngospasm	5 per 1000	7 per 1000 (1 to 68)	OR 1.59 (0.16 to 15.92)	588 (7 studies)	⊕⊕⊕⊕ low ^c	
Breath holding	56 per 1000	64 per 1000 (27 to 144)	OR 1.16 (0.47 to 2.83)	389 (5 studies)	⊕⊕⊕⊕ low ^d	
Apnoea	141 per 1000	442 per 1000 (242 to 802)	RR 3.14 (1.72 to 5.7)	160 (2 studies)	⊕⊕⊕⊕ low ^e	
Patient movement	163 per 1000	186 per 1000 (113 to 309)	RR 1.14 (0.69 to 1.89)	445 (5 studies)	⊕⊕⊕⊕ low ^f	
Bradycardia	66 per 1000	53 per 1000 (15 to 169)	OR 0.8 (0.22 to 2.88)	199 (3 studies)	⊕⊕⊕⊕ low ^g	

*The basis for the **assumed risk** (e.g. 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; **OR:** odds ratio; **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

^aDowngraded two levels because of serious concerns about selection bias, allocation concealment and blinding

^bDowngraded two levels because of serious concerns about allocation concealment and blinding

^cDowngraded two levels because of serious concerns about selection bias, allocation concealment and blinding

^dDowngraded two levels because of serious concerns about selection bias, allocation concealment and blinding

^eDowngraded two levels because of serious concerns about allocation concealment and blinding

^fDowngraded two levels because of serious concerns about allocation concealment and blinding

^gDowngraded two levels because of serious concerns about allocation concealment

BACKGROUND

Description of the condition

General anaesthesia (GA) may be induced by receiving an intravenous injection (IV induction) or by breathing in through a mask an anaesthetic vapour mixed with oxygen (inhalational induction). Inhalational anaesthetic induction may be the preferred method in children and in some adult patients who refuse intravenous cannulation (Eger 2003; Goresky 1996) or who have poor venous access or potentially difficult airways. One of the volatile anaesthetic agents commonly used for inhalational induction of anaesthesia is sevoflurane (Ultane[®], Sevorane[®], Sojourn[™]). Sevoflurane (2,2,2-trifluoro-1-[trifluoromethyl] ethyl fluoromethyl ether) was first introduced into clinical practice in Japan in 1990; it is sweet-smelling, non-flammable and less irritating to mucous membranes than other agents.

Induction of anaesthesia with sevoflurane has been reported to be safe, reliable and well accepted by patients (De Hert 2015; van den Berg 2005). Its characteristics include inherent stability; low flammability; non-pungent odour; limited irritation to airways; low blood or gas anaesthetic solubility, which allows rapid induction of and emergence from anaesthesia; minimal cardiovascular and respiratory side effects; and minimal end-organ effects (Delgado-Herrera 2001). The muscle relaxant properties of sevoflurane allow insertion of a laryngeal mask airway (LMA) or endotracheal tube (Aantaa 2001) without a muscle relaxant, provided adequate concentrations of anaesthetic are given.

Description of the intervention

Inhalational induction of anaesthesia with sevoflurane involves the use of a low or a high initial concentration of sevoflurane. The low initial concentration technique involves initially administering a low concentration of sevoflurane, then gradually increasing the concentration until the patient is anaesthetized (Eger 2003). The high initial concentration technique involves administering high concentrations of sevoflurane (from 4% to 8%) from the beginning, then continuing until the patient is anaesthetized (Eger 2003). Both techniques can be carried out by using different breathing patterns - vital capacity or tidal volume breathing. The vital capacity method consists of breathing out the residual volume, then taking a maximal breath and holding it as long as is comfortable, followed by spontaneous respiration; the tidal volume method involves normal breathing and respiratory rates.

Other interventions or medications can be used to improve the quality of induction of anaesthesia, for example, inspiratory pressure support at 15 cm H₂O via an anaesthetic ventilator (Banchereau 2005); priming of the breathing circuit with high concentration sevoflurane in oxygen, with or without prior nitrous oxide induction of anaesthesia (Yurino 1995); use of nitrous oxide with sevoflurane and oxygen (Dubois 1999; O'Shea 2001); and use of sufentanil (Meaudre 2004), midazolam (Nishiyama 2002), clonidine (Watanabe 2006) or dexmedetomidine (Mizrak 2013; Yao 2015) before induction of anaesthesia. Induction time- time to loss of the eyelash reflex (LOER) - is measured to compare the efficacy of different methods. However, complications during induction of anaesthesia such as coughing, salivation, failed induction at the first attempt, laryngospasm, breath holding, apnoea, severe movement or panic reaction, hypotension, an epileptiform electroencephalogram (EEG) and bradycardia can

increase morbidity (Epstein 1998; Kaisti 1999; Martin-Larrauri 2004; Merquiol 2006; Roodman 2003; Vakkuri 2001; Yurino 1995).

How the intervention might work

High concentration volatile anaesthetic induction has been reported to result in a shorter (faster) induction time (Epstein 1998; Martin-Larrauri 2004). A high inspired sevoflurane concentration could increase sevoflurane concentration in alveoli and in the brain, so the action of sevoflurane is more rapid than with a low inspired sevoflurane concentration. A high concentration might shorten the second stage of anaesthesia, reducing the time during which coughing and breath holding may occur. On the other hand, a high initial concentration might cause increased irritation to the patient's airways.

Why it is important to do this review

A shorter induction time is usually desirable, but this may be accompanied by several complications such as breath holding, laryngospasm, severe movement, salivation and hypotension (Dubois 1999; Epstein 1998; Martin-Larrauri 2004). More frequent apnoea of longer duration (Pancaró 2005) has been reported after induction with a high concentration of sevoflurane, as have a higher incidence of bradycardia (Green 2000) and an epileptiform electroencephalogram (EEG) (Constant 2005; Vakkuri 2001).

OBJECTIVES

We aimed to compare induction times and complication rates between high and low initial concentration sevoflurane anaesthetic induction techniques in adults and children who received inhalational induction for general anaesthesia. We defined 'high' as greater than or equal to and 'low' as less than a 4% initial concentration.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include all published and unpublished randomized controlled trials (RCTs) comparing high ($\geq 4\%$) versus low ($< 4\%$) initial concentration inhalational induction.

Types of participants

We included participants of all ages who received a sevoflurane induction technique for general anaesthesia.

Types of interventions

We included two sevoflurane induction techniques for general anaesthesia.

1. High initial concentration sevoflurane (control) - equal to or greater than a 4% concentration of sevoflurane, including vital capacity and tidal volume breath induction.
2. Low initial concentration sevoflurane induction (intervention) - starting concentration less than 4% sevoflurane.

Types of outcome measures

Primary outcomes

1. Induction time (time to loss of eyelash reflex (LOER), assessed in seconds (beginning from inhalation of gas until LOER); or time to drop a weighted object, assessed in seconds (beginning from inhalation of gas until weighted object, for example, a weighted syringe, dropped); or time to successfully insert laryngeal mask.

Secondary outcomes

1. Patient satisfaction (numerical rating scale).
2. Failed inhalational induction, from any cause, at the first attempt (yes or no).
3. Complications.

We defined complications as follows.

1. Major complications.
 - a. Cough during induction period.
 - b. Laryngospasm.
 - c. Breath holding.
 - d. Apnoea.
 - e. Severe patient movement or physical reaction such as grabbing the mask, trying to move off the operating table, etc.
2. Minor complications.
 - a. Hypotension (drop of more than 20% of baseline blood pressure).
 - b. Salivation.
 - c. Epileptiform EEG.
 - d. Bradycardia (fall of heart rate to below 20% of baseline value).

Search methods for identification of studies

Electronic searches

In this updated review, we searched the following databases for relevant trials in February 2016: the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2); MEDLINE SilverPlatter (1950 to February 2016), EMBASE SilverPlatter (1980 to February 2016), Latin American Caribbean Health Sciences Literature (LILACS) (1982 to February 2016) and the Institute for Scientific Information (ISI) Web of Science (1946 to February 2016).

We developed a specific search strategy for each database. We based each search strategy on search developed for MEDLINE ([Appendix 1](#)). Please see [Appendix 2](#) (CENTRAL); [Appendix 3](#) (EMBASE); [Appendix 4](#) (LILACS); and [Appendix 5](#) (ISI Web of Science).

Searching other resources

We searched the following for relevant trials in February 2016.

1. Specialist journals such as *Anesthesia and Analgesia*; *Anesthesiology*; *Anaesthesia*; *Acta Anaesthesiologica Scandinavica*; *British Journal of Anaesthesia*; *Canadian Journal of Anaesthesia*; and *European Journal of Anaesthesiology*.
2. Conference proceedings and abstracts (American Society of Anesthesiologists (ASA); International Anaesthesia Research Society (IARS)).
3. European Society of Anaesthesiologists (ESA).

4. The grey literature (System for Information on Grey Literature in Europe (SIGLE)).
5. Reference lists of relevant articles.

We also contacted known trialists, experts and medical or pharmaceutical companies to ask about unpublished trials.

We applied no language restriction.

Data collection and analysis

Selection of studies

Two review authors (PB and SB) independently scanned the titles and abstracts of reports identified by searching electronic databases and by handsearching journals. We obtained and assessed the full articles of any possibly or definitely relevant trials according to definitions provided in the criteria for considering studies for this review. We (PB and SB) resolved disagreements by consensus or, if necessary, by consulting a third review author (PP).

Data extraction and management

We used a data extraction form to obtain data from individual studies ([Appendix 6](#)). Two review authors (PB and SB) extracted the data. We used five studies previously chosen as fulfilling the review selection criteria to pilot the form, to ensure that data obtained were adequate for the purposes of the review. We contacted study authors to obtain or to clarify missing or unclear data.

After extracting data, we performed double data entry and screened the database for inconsistencies as a quality assurance measure.

For dichotomous outcomes, we extracted the number with outcomes and the number of participants for the two groups. We found five studies that reported multiple comparison groups ([Dubois 1999](#); [Hsu 2000](#); [Martin-Larrauri 2004](#); [Mendonca 2001](#); [Yurino 1995](#)). We pooled appropriate groups by using the formula suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

For continuous outcomes, we extracted the mean and the standard deviation (SD) for each group. We found two studies that reported multiple comparison groups ([Hsu 2000](#); [Martin-Larrauri 2004](#)). To gain the means and standard deviations of our intervention and comparisons of interest, we estimated them by pooling the appropriate group using the formula suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Assessment of risk of bias in included studies

Two review authors (PB and SB) assessed the risk of bias of each trial according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Our assessment criteria were as follows.

1. Random sequence generation (selection bias): low, unclear, high risk.
2. Allocation concealment (selection bias): low, unclear, high risk.
3. Blinding (performance bias and detection bias): low, unclear, high risk. However, participant blinding during inhalation induction (performance bias) was inevitable.
4. Incomplete outcome data (attrition bias): low, unclear, high risk.
5. Use of intention-to-treat analysis: yes, no, no information.

We resolved conflicts during assessment through discussion and, if necessary, through evaluation by a third review author (PP).

Measures of treatment effect

We analysed continuous data (i.e. time to loss of eyelash reflex, time to drop a weighted object and time to successful insertion of a laryngeal mask airway) as mean differences (MDs) using the inverse variance method. We analysed continuous data that used different scales by using standardized mean differences, when appropriate. We used standard deviations to standardize mean differences to a single scale.

For proportions (dichotomous outcomes), namely, patient satisfaction, failed gas induction, cough, laryngospasm, breath holding, hypotension, salivation, epileptiform EEG and bradycardia, we used the Peto odds ratio (OR). Because apnoea and patient movement were reported at an incidence greater than 10%, we used the risk ratio (RR).

Unit of analysis issues

We expected no unit of analysis issues.

Dealing with missing data

We attempted to contact study authors to ask for missing data. If study authors did not respond, we extracted all available data from the publication. If data were missing because of participant dropout or losses to follow-up, we planned to conduct a primary analysis based on complete data and a sensitivity analysis with missing data imputed on the basis of worst-case and best-case scenarios.

Assessment of heterogeneity

We assessed heterogeneity by considering the Q test and the I^2 statistic (Higgins 2011). We considered heterogeneity to be high if I^2 was greater than 35% and the Q test returned a result with P value < 0.10.

As heterogeneity was high, we used a random-effects model in pooling results, when this was possible (Higgins 2011). If the I^2 statistic was greater than 75%, we did not pool the results because heterogeneity was high. We explored clinical heterogeneity and performed subgroup analyses when appropriate.

Assessment of reporting biases

If possible, we planned to assess reporting biases (such as publication bias) by using funnel plots. We planned to assess funnel plot asymmetry both visually by using formal tests.

We assessed selective outcome reporting bias as having low risk (all pre-specified, expected outcomes have been reported), high risk (not all pre-specified, expected outcomes have been reported) or unclear risk.

Data synthesis

We analysed data and displayed them by using the Review Manager (RevMan 5.3) software distributed by The Cochrane Collaboration.

The review differs from the protocol in several ways (Boonmak 2007); see [Differences between protocol and review](#). As a result of the small number of events, we used the Peto method for

dichotomous data. Therefore, we could not present the risk ratio (RR) as mentioned in the protocol (Boonmak 2007). Instead we used the odds ratio (OR) and its 95% confidence interval (CI). We combined data using the mean difference (MD) for continuous data and presented them together with 95% CIs. We agreed to add two continuous outcomes (time to endotracheal intubation and time to successful insertion of a laryngeal mask) to the analysis because both are clinically important outcomes. Only one study reported time to intubation (Dubois 1999). Two studies measured time to successful insertion of a laryngeal mask; this is reported below (Martin-Larrauri 2004; Singh 2014).

We were not able to examine publication bias by using a funnel plot because data were insufficient.

We presented key information for both primary and secondary outcomes in the 'Summary of findings' tables, which we created by using GRADEpro software (GRADEpro 2011). We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach to describe the overall quality of the outcome, rating quality as high, moderate, low or very low (Higgins 2011). We examined risk of bias, indirectness of evidence, inconsistency of results, imprecision of results and potential publication bias in making the assessment. We downgraded the quality of evidence from high if we found deficiencies in these domains. We included the following outcomes in the 'Summary of findings' table.

1. Time to loss of eyelash reflex.
2. Cough.
3. Laryngospasm.
4. Breath holding.
5. Apnoea.
6. Patient movement.
7. Bradycardia.

Subgroup analysis and investigation of heterogeneity

One primary outcome, time to loss of eyelash reflex (LOER), showed substantial heterogeneity between studies (poor overlapping of CIs, $I^2 = 91%$, P value < 0.0001). We performed subgroup analyses by age group (children vs adults), nitrous oxide supplement, opioid supplement, initial dose of sevoflurane and breathing technique, as stated in the protocol, and found substantial heterogeneity in all subgroups. We did not pool the results (Analysis 1.1).

Sensitivity analysis

We planned to perform sensitivity analyses based on risk of bias and allocation of missing data, as stated in the protocol (Boonmak 2007); see [Differences between protocol and review](#). However, we were not able to do this because of the small number of included studies for the primary outcome. We performed sensitivity analysis for the LOER outcome by removing one study, which seemed very different from all other studies (Hall 2000). A sensitivity analysis indicated no influence on effects.

RESULTS

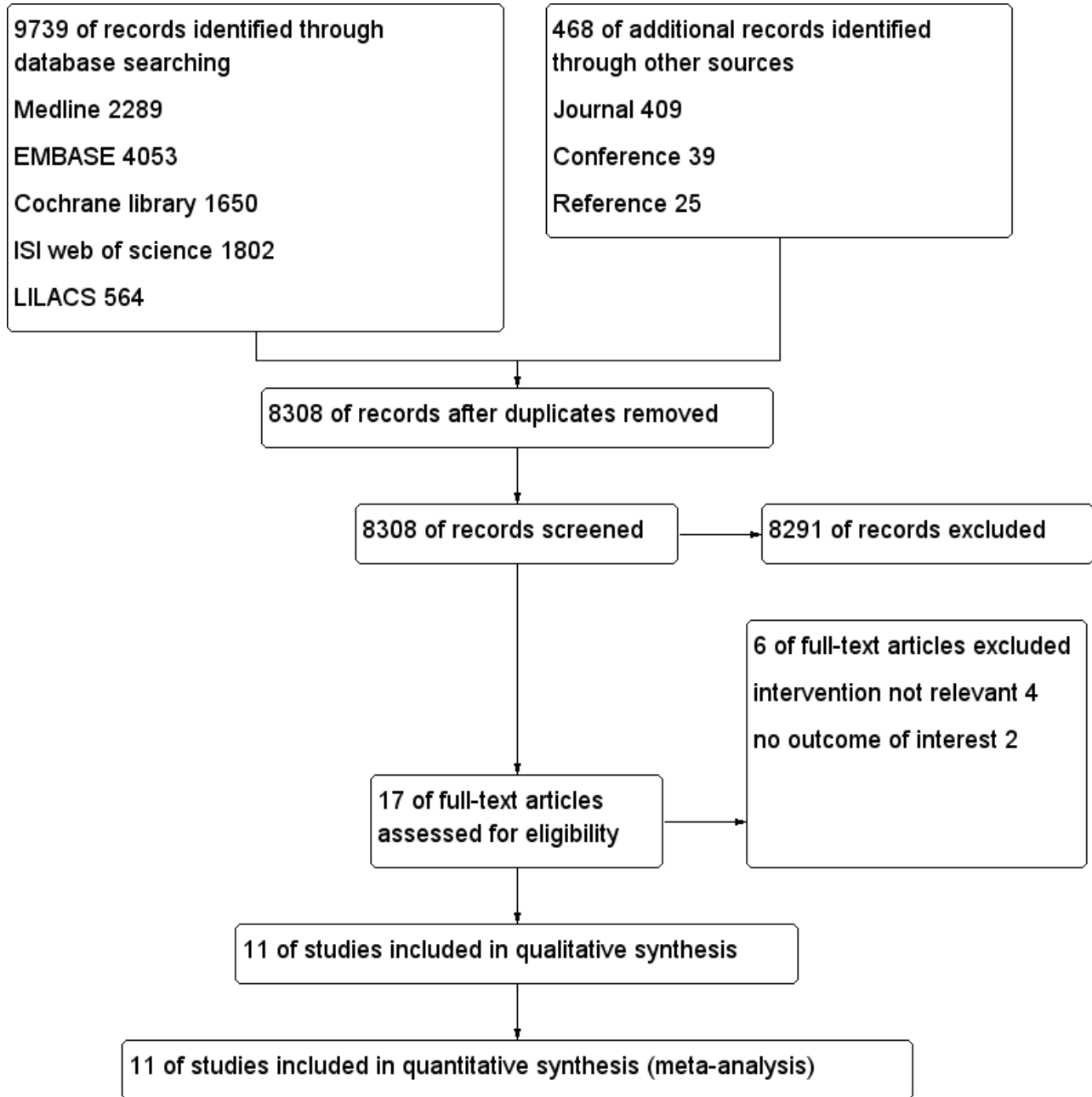
Description of studies

Results of the search

After we had removed duplicates, we identified 8308 citations from searches of databases, journals, and conference proceedings and

through citation review in this update (Figure 1). In the first version of our review, we assessed 13 full-text articles after screening by title and abstract; we included 10 of those 13 studies and excluded three studies (Boonmak 2012).

Figure 1. Study flow diagram.



For this update, we obtained four full papers that were potentially eligible for inclusion in the review. We included only one additional trial (Singh 2014) and excluded three of the four articles for reasons described under Characteristics of excluded studies. No trials are awaiting assessment.

Included studies

We included 11 trials (829 participants) in this update of the review (Baum 1997; Dubois 1999; Epstein 1998; Green 2000; Hall 2000; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Pancaro 2005; Singh 2014; Yurino 1995); see Characteristics of included studies.

Six studies compared high and low initial concentrations in participants with tidal volume breathing using nitrous oxide (N₂O) and oxygen (O₂) (Baum 1997; Dubois 1999; Epstein 1998; Green 2000; Hsu 2000; Singh 2014). Three studies compared high and low initial concentrations with vital capacity breathing with N₂O and O₂ in adult participants (Martin-Larrauri 2004; Mendonca 2001; Yurino 1995). Two studies compared high and low initial concentrations with tidal volume breathing with O₂ in adults (Hall 2000; Pancaro 2005).

Six studies reported LOER time (Dubois 1999; Epstein 1998; Hall 2000; Hsu 2000; Martin-Larrauri 2004; Singh 2014). Only one trial reported time to drop a weighted object (Mendonca 2001). Martin-Larrauri 2004 reported time to successful insertion of a laryngeal mask airway. Singh 2014 reported time from IV cannulation to laryngeal mask airway insertion but did not show time to laryngeal mask airway insertion. Dubois 1999 reported time to endotracheal intubation. Most studies reported complications such as cough, laryngospasm, breath holding, patient movement, bradycardia, apnoea, hypotension and salivation. However, no studies reported patient satisfaction or epileptiform EEG.

Excluded studies

We excluded six studies. Of those six studies, we excluded two because they did not report the outcome of interest (Munoz 1999; Nishiyama 1997) and four because they did not compare low and high initial concentrations (Julliac 2013; Kreuzer 2014; Lee 2013; Walpole 1999); see [Characteristics of excluded studies](#).

Studies awaiting classification

No studies are awaiting classification.

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

We assessed the risk of bias of included studies using the 'Risk of bias' tool developed by The Cochrane Collaboration (Higgins 2011). This risk of bias tool invites judgements on five items for each trial (selection bias, performance bias, detection bias, attrition bias, reporting bias). All review authors independently assessed risk of bias for each study and resolved disagreements by discussion. Please see [Figure 2](#) and [Characteristics of included studies](#) for our assessment of risk of bias in the included studies. Two studies were of high methodological quality (Green 2000; Pancaro 2005).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

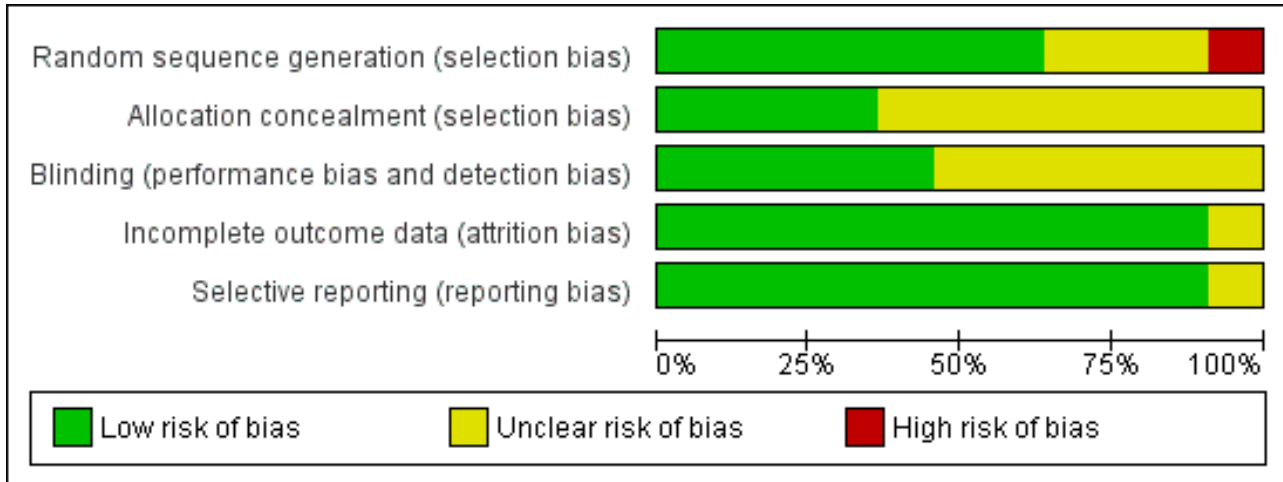
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Baum 1997	+	?	+	+	+
Dubois 1999	?	?	?	+	+
Epstein 1998	+	?	?	+	+
Green 2000	+	+	+	+	+
Hall 2000	?	?	+	+	+
Hsu 2000	?	?	?	+	+
Martin-Larrauri 2004	+	+	?	+	+
Mendonca 2001	+	+	?	+	+
Pancaro 2005	+	+	+	+	+
Singh 2014	+	?	?	?	?
Yurino 1995	-	?	+	+	+

Allocation

Four of the 11 included studies had adequate allocation concealment (Green 2000; Martin-Larrauri 2004; Mendonca 2001;

Pancaró 2005) (see Figure 3). Seven studies did not describe their allocation concealment (Baum 1997; Dubois 1999; Epstein 1998; Hall 2000; Hsu 2000; Singh 2014; Yurino 1995).

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Blinding

Five studies had adequate blinding (Baum 1997; Green 2000; Hall 2000; Pancaró 2005; Yurino 1995). The remaining six studies did not describe their blinding (Dubois 1999; Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Singh 2014).

Incomplete outcome data

None of the included studies reported any dropouts.

Selective reporting

We found that all planned outcomes were reported in 10 trials with no selective reporting of outcomes. However, one trial did not clearly describe adverse events (Singh 2014).

Other potential sources of bias

All 11 included studies reported between-group comparisons of baseline characteristics.

Effects of interventions

See: [Summary of findings for the main comparison High initial concentration versus low initial concentration for inhalational induction of anaesthesia](#)

See 'Summary of findings' for the main comparison.

Primary outcomes

Time to loss of eyelash reflex (LOER) (seconds)

See [Analysis 1.1](#).

Six studies reported LOER (Dubois 1999; Epstein 1998; Hall 2000; Hsu 2000; Martin-Larrauri 2004; Singh 2014). We noted considerable heterogeneity between the six studies ($I^2 = 91%$, P value < 0.0001). We explored the source of heterogeneity by performing the following subgroup analyses, as stated in the protocol (Boonmak

2007). We rated this outcome as having low-quality evidence because one study had high risk of selection bias (Yurino 1995), five studies had unclear risk of allocation concealment bias (Baum 1997; Dubois 1999; Epstein 1998; Hall 2000; Hsu 2000) and five studies had unclear risk of blinding bias (Dubois 1999; Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Singh 2014).

Subgroup analysis by age group of participants

We found considerable heterogeneity for both children ($I^2 = 94%$, P value < 0.00001) and adults ($I^2 = 84%$, P value = 0.01).

Subgroup analysis by supplement drugs

We noted substantial heterogeneity in four studies that used nitrous oxide as the supplement drug ($I^2 = 94%$, P value < 0.00001) (Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Singh 2014). One study did not apply nitrous oxide to participants (Hall 2000). Three included studies did not use opioid as a supplement drug and revealed considerable heterogeneity ($I^2 = 85%$, P value = 0.0002) (Epstein 1998; Hall 2000; Hsu 2000). One study used an opioid (Martin-Larrauri 2004).

Subgroup analysis by initial dose of sevoflurane

We observed considerable heterogeneity for both the 4% to 6% initial concentration group ($I^2 = 74%$, P value = 0.05) and the 6% to 8% initial concentration group ($I^2 = 93%$, P value < 0.00001).

Subgroup analysis by breathing techniques

We noted considerable heterogeneity for the tidal volume breathing technique ($I^2 = 93%$, P value < 0.00001). One study compared tidal volume and vital capacity breathing (Martin-Larrauri 2004).

We performed a sensitivity analysis by removing one study (Hall 2000) because of its differences from other studies. We found heterogeneity among the studies ($I^2 = 92%$, P value < 0.0001).

We found considerable heterogeneity across the included studies, which reflects the variety of initial sevoflurane concentrations, adjuvant drugs, characteristics of participants and clinical techniques used. Other possible reasons include variation in the magnitude of treatment effects in each study, differences in the number of participants between different treatment and control groups and small-study effects from one study (Hall 2000). Therefore, we could not combine the results statistically; instead we have reported the findings from individual studies (Analysis 1.1). Epstein 1998 had a shorter LOER in the high initial concentration group (MD 24.00 seconds, 95% CI 17.43 to 30.57 seconds, 40 participants, moderate-quality evidence). Hsu 2000 reported a shorter LOER in the high initial concentration group (MD 82.00 seconds, 95% CI 46.43 to 117.57 seconds, 13 participants, low-quality evidence). Hall 2000 had a shorter time to LOER in the high initial concentration group than in the low initial concentration group (MD 42.50 seconds, 95% CI 34.33 to 50.67 seconds, 99 participants, moderate-quality evidence). Dubois 1999 had a shorter time to LOER in the high initial concentration group (MD 30.98 seconds, 95% CI 23.25 to 38.71 seconds, 65 participants, low-quality evidence), and Martin-Larrauri 2004 had a shorter time to LOER in the high initial concentration group (MD 37.00 seconds, 95% CI 34.71 to 39.29 seconds, 126 participants, moderate-quality evidence). Singh 2014 had a shorter time to LOER in the high initial concentration group (MD 59.4 seconds, 95% CI 51.83 to 66.97 seconds, 100 participants, low-quality evidence).

Time to drop a weighted object (seconds)

Only one study reported time until the participant dropped a weighted object (Mendonca 2001) and found a statistically significant difference between low and high initial concentration groups (MD 33 seconds, 95% CI 19.67 to 46.33 seconds, 40 participants, moderate-quality evidence). We rated this as moderate-quality evidence because risk of blinding bias was unclear.

Time to successful insertion of laryngeal mask airway (seconds)

Only one study presented these data (Martin-Larrauri 2004). This study revealed a statistically significant shorter time to insert a laryngeal mask in the high initial concentration group compared with the low initial concentration group (MD 18 seconds, 95% CI 12 to 24 seconds, 126 participants, moderate-quality evidence). We rated this as moderate-quality evidence because risk of blinding bias was unclear.

Time to intubation (seconds)

Only one study presented time to intubation (Dubois 1999). This study revealed similar times with high initial concentrations and low initial concentrations (MD 30 seconds, 95% CI -1 to 61 seconds, 65 participants, low-quality evidence). We rated this as low-quality evidence because risk of selection bias, risk of allocation concealment bias and risk of blinding bias were unclear.

Secondary outcomes

Patient satisfaction

None of the 11 included studies looked at patient satisfaction.

Failed gas induction

Two studies aimed to assess this outcome (Hsu 2000; Mendonca 2001). However, Mendonca 2001 recorded no events. Hsu 2000

showed no significant differences in failed gas induction between high and low initial concentration groups (Peto OR 1.99, 95% CI 0.67 to 5.87, 180 participants, low-quality evidence). We rated this as low-quality evidence because risk of allocation concealment bias and blinding bias was unclear in one study.

Cough

See Analysis 1.2.

Eight studies showed no significant differences in the cough rate between high and low initial concentration groups (Peto OR 1.23, 95% CI 0.53 to 2.81, 589 participants, low-quality evidence) (Baum 1997; Dubois 1999; Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Pancaro 2005; Yurino 1995). We rated this outcome as providing low-quality evidence because risk of allocation concealment bias and blinding bias was unclear in one study.

Laryngospasm

See Analysis 1.3.

Seven studies aimed to report this outcome (Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Pancaro 2005; Singh 2014; Yurino 1995). However, investigators described only three incidences of laryngospasm - two in the high initial concentration group (Martin-Larrauri 2004; Singh 2014), and one in the low initial concentration group (Epstein 1998). These data provided no evidence of a significant difference in laryngospasm between high and low initial concentration groups (Peto OR 1.59, 95% CI 0.16 to 15.92, 588 participants, low-quality evidence). We rated this outcome as providing low-quality evidence because one study had high risk of selection bias, five studies had unclear risk of allocation concealment bias and five studies had unclear risk of blinding bias.

Breath holding

See Analysis 1.4.

Five studies showed no significant differences in breath holding between high and low initial concentration groups (Peto OR 1.16, 95% CI 0.47 to 2.83, 389 participants, low-quality evidence) (Baum 1997; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Yurino 1995). We rated this outcome as providing low-quality evidence because one study had high risk of selection bias, three studies had unclear risk of allocation concealment bias and two studies had unclear risk of blinding bias.

Apnoea

See Analysis 1.5.

Two studies suggested a significant difference in apnoea between high and low initial concentration groups (RR 3.14, 95% CI 1.72 to 5.70, 160 participants, low-quality evidence) (Dubois 1999; Pancaro 2005). We rated this outcome as providing low-quality evidence because one study had unclear risk of allocation concealment bias and blinding bias.

Patient movement

See Analysis 1.6.

Five studies showed no significant differences in patient movement between high and low initial concentration groups (RR 1.14, 95% CI

0.69 to 1.89, 445 participants, low-quality evidence) (Dubois 1999; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Pancaro 2005). We rated this as low-quality evidence because two studies had unclear risk of allocation concealment bias, and four studies had unclear risk of blinding bias.

Hypotension

The two studies that assessed this outcome reported no hypotension in high or low initial concentration groups (139 participants) (Epstein 1998; Hsu 2000). We rated this outcome as providing low-quality evidence because one study had unclear risk of selection bias, and two studies had unclear risk of allocation concealment bias and blinding bias.

Salivation

See [Analysis 1.7](#).

Six studies did not show evidence of a significant difference in salivation between high and low initial concentration groups (Peto OR 1.23, 95% CI 0.36 to 4.21, 487 participants, low-quality evidence) (Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Pancaro 2005; Yurino 1995). We rated this as moderate-quality evidence because two studies had unclear risk of allocation concealment bias, and four studies had unclear risk of blinding bias.

Epileptiform EEG

None of the 11 included studies looked at this outcome.

Bradycardia

See [Analysis 1.8](#).

Three studies found no evidence of differences in bradycardia between high and low initial concentration groups (Peto OR 0.80, 95% CI 0.22 to 2.88, 119 participants, low-quality evidence) (Epstein 1998; Green 2000; Hsu 2000). We rated this as low-quality evidence because two studies had unclear risk of allocation concealment bias.

We have presented some of the secondary outcomes in [Summary of findings for the main comparison](#).

DISCUSSION

Summary of main results

Review authors found that included studies were conducted so differently, especially with regard to the number of subgroups, with varying concentrations of sevoflurane, addition of nitrous oxide and opioids and different patient groups (adults vs children) that it is impossible to offer reliable conclusions. Evidence from six studies of 443 participants contributing data to the primary outcome of this review showed that the high initial concentration technique reduced time to loss of eyelash reflex (LOER). Combining the studies was not possible, but analysis of individual studies revealed that LOER appears to be quicker, typically by 24 to 82 seconds (six studies, 443 participants, low-quality evidence). We found low-quality evidence of increased apnoea (two studies, 160 participants) associated with the high initial concentration technique. However, the incidence of other complications was similar in each group and was generally low. Data were comparable in the incidence of cough (eight studies, 589 participants, low-quality evidence), laryngospasm (seven

studies, 588 participants, low-quality evidence), breath holding (five studies, 389 participants, low-quality evidence), bradycardia (three studies, 199 participants, low-quality evidence) and patient movement (five studies, 445 participants, low-quality evidence).

Overall completeness and applicability of evidence

The short duration of the included trials meant that no study reported incomplete data. All studies reported outcomes needed to evaluate the sevoflurane induction technique. All trials took place in recent years and used drug and anaesthetic techniques in current practice. However, the main limitations of these findings were the quality of the evidence and the small numbers of participants for many outcomes, so it is difficult for review authors to draw firm conclusions regarding many of our outcome measures. We included only 11 studies in the review (829 participants), and the number of participants for individual outcomes varied between 139 and 589 participants. Some included studies reported unclear blinding because participant blinding was inevitable. Other included studies had inadequate allocation concealment. Overall applicability of the results of this review is limited because of the great variety of techniques and participants included, although the techniques remain current.

Quality of the evidence

We included in this review 10 studies with 829 participants. Two studies (Green 2000; Pancaro 2005) had low risk of bias. Six studies (Dubois 1999; Epstein 1998; Hsu 2000; Martin-Larrauri 2004; Mendonca 2001; Singh 2014) were unclear with regard to blinding technique. Seven studies (Baum 1997; Dubois 1999; Epstein 1998; Hall 2000; Hsu 2000; Singh 2014; Yurino 1995) did not state whether allocation was concealed. Only one study (Yurino 1995) had high risk of bias associated with the sampling technique. We have presented details in the risk of bias tables and in [Figure 2](#). We found that overall the quality of the evidence for most outcomes was low or moderate as the result of performance bias and selection bias. However, performance bias (sevoflurane concentration blinding) had no effect on LOER nor on other adverse events.

Sufficient studies measured time to LOER that we could perform subgroup analysis according to age group, supplemental drug (nitrous oxide and opioid), initial dose of sevoflurane and technique of administration. The high initial concentration sevoflurane technique showed a consistently shorter time to LOER than was seen with the low initial concentration sevoflurane technique.

Possible effects of study design on our findings include considerable clinical variation in techniques used; different studies applied different initial sevoflurane concentrations, breathing techniques, priming techniques, drug supplementation and anaesthetic circuits.

Initial concentrations in the low initial inhalational induction groups described varied from 2% to less than 4% before sevoflurane was increased, but in the high initial concentration groups we noted initial concentrations ranging from 4% to 8%. Differences between groups in a particular study would be more likely if the difference between starting concentrations was large. However, after subgroup analysis, we determined time to LOER differences in both groups. The initial concentration in the high concentration group might be only one cause of the difference. Other than initial concentration, breathing techniques

varied from single to multiple vital capacity breathing and tidal volume breathing in both groups. The effect of different breathing techniques on LOER is unpredictable, although vital capacity breathing seemed to have shorter time to LOER than tidal volume breathing (Baker 1999; Lejus 2006; Liu 2010). Opioid, a sedative drug, and nitrous oxide supplementation varied in dose and time of administration. These adjuncts will influence time to LOER and rate of complications, but again not in a predictable way. In other studies, nitrous oxide supplementation had variable effects on time to LOER and complications (Bordes 2006; Fassoulaki 2015; Fernandez-Alcantud 2008; Goldman 2003; Kihara 2003; O'Shea 2001; Siau 2002).

Furthermore, measurements of induction time may be inaccurate among included studies. Investigators used two different measures - time to LOER and time to drop a weighted object. Time to LOER was defined as time from the start of induction until the patient lost his or her eyelash reflex, whilst time to drop a weighted object was defined as time from the start of induction until the patient dropped a 20 mL syringe full of water from between his or her thumb and index finger. We could not pool these induction outcomes. The frequency at which the eyelash reflex was tested varied from every two seconds to every 10 seconds across studies, which might have led to inaccuracies in measurement.

The complications that we aimed to study were also variously defined, with many study authors using their own particular definitions and reporting only adverse events of interest to them. Overall incidence might be greater than in the studies. We found no trials comparing high and low initial concentrations that reported patient satisfaction, nor any that aimed to monitor the EEG for epileptiform activity.

Potential biases in the review process

We followed standard approaches of the Cochrane review process and believe that no specific biases apply to this review. However, differences between protocol and review might cause bias. We considered that evidence for significant heterogeneity was present when $I^2 > 35\%$ instead of $I^2 > 50\%$, as mentioned in the protocol. We used the Peto odds ratio for rare events (incidence $< 10\%$ in the low initial concentration group) but used the risk ratio for apnoea and patient movement (incidence $> 10\%$).

Agreements and disagreements with other studies or reviews

Our review suggests that the high initial concentration sevoflurane technique seems to offer a shorter induction time than is seen with a low initial concentration. This result was also reported in other reviews (Bordes 2006; Ghatge 2003; Lerman 2009) and was consistent across all age groups, with or without nitrous oxide supplementation.

Complications in the high and low initial concentration induction groups were comparable except for apnoea, which appeared more common in the high initial concentration group. Previous studies have reported comparable complications during inhalational induction (Bordes 2006; Ghatge 2003; Lerman 2009; Nathan 2004) but have presented no clear conclusions about the effects of differential concentrations of sevoflurane on bradycardia, the epileptiform EEG and apnoea.

Bradycardia (three studies; 199 participants) was comparable between the groups in our review (66 per 1000). Narrative reviews have provided no firm conclusions about bradycardia with high concentrations in healthy adults and children (Bordes 2006; Nathan 2004). Retrospective studies (Bai 2010; Kraemer 2010) and a review article (Walia 2016) showed higher prevalence of bradycardia associated with higher sevoflurane concentrations and Down syndrome.

Apnoea (two studies; 160 participants) was more common in high than in low initial concentration groups (141:1000). A previous narrative review suggested increased apnoea in children receiving a high concentration with midazolam (Lerman 2009).

Cough (38:1000 in the low concentration group), laryngospasm (6:1000 in the low concentration group), breath holding (56:1000 in the low concentration group), patient movement (145:1000 in the low concentration group) and salivation (21:1000 in the low concentration group) were comparable between groups in our review. Other studies reported that a high initial concentration sevoflurane technique is not associated with these clinical side effects (Bordes 2006; Ghatge 2003; Lerman 2009; Nathan 2004).

No study reported epileptiform EEG. However, Merquiol 2006 found that high initial (6%) sevoflurane induction had more epileptiform EEG than incremental sevoflurane induction in children (abstract only). Gibert 2012 and Schultz 2012 found that end-tidal sevoflurane concentrations 4% or greater can cause epileptiform EEG in children. Kreuzer 2014 reported that 8% sevoflurane induction showed higher epileptiform EEG than 6% sevoflurane induction in children. In adults, Smith 2016 reported epileptiform EEG during 8% sevoflurane induction before elective carotid endarterectomy.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests that the high initial concentration sevoflurane technique probably results in shorter time to induction of anaesthesia than is seen with the low initial concentration sevoflurane technique (difference of 24 to 82 seconds). Likewise, the difference in complication rates is unlikely to be great. We do not have sufficient evidence to determine effects of the high initial concentration sevoflurane technique on complication rates, although apnoea was more common with the high initial concentration. No trial reported patient satisfaction and epileptiform EEG with these techniques.

Implications for research

We required high-quality evidence to examine the effects of high initial concentration induction on adverse events, especially on epileptiform EEG. Larger studies with allocation concealment and blinding are needed for a firm conclusion. We also required standardized definitions of adverse events for comparison between groups. Variation in induction techniques (breathing techniques, priming techniques, anaesthetic circuits, supplement drug) prevented comparison between groups that would lead to meaningful conclusions. We recommend that future trials must focus on each induction technique along with patient satisfaction with each technique.

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mask induction of anaesthesia with brief administration of 8% sevoflurane. *PLoS One* 2012;**7**(7):e40903. [PUBMED: 22829896]

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Boonmak 2012

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Baum 1997

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of participants: no Study period: not stated
Participants	Number: 46 enrolled Inclusion criteria: un-pre-medicated paediatric patients (6 months to 8 years) scheduled for elective ambulatory surgery under general anaesthesia who had ASA physical status I to II, no known reactive airway, no history of malignant hyperthermia Exclusion criteria: not stated
Interventions	All groups received 70% N ₂ O with total flow 6 LPM, tidal volume breathing technique and paediatric circle circuit Group 1: 8% sevoflurane with priming technique Group 2: incremental sevoflurane Group 3: incremental halothane
Outcomes	Time to complete calmness Time to eye closure Child's distress (modified Observation Scale of Behavioral Distress) Complication
Notes	Location: USA Setting: operating room Source of funding: Abbott Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients had anaesthesia induced by one of three methods, as assigned by means of a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Video recordings were analysed off-line by a different paediatric anaesthesiologist"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Baum 1997 (Continued)

Selective reporting (re-reporting bias)	Low risk	Study authors reported all planned outcomes
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Dubois 1999

Methods	Randomization and treatment allocation method: not stated
	Blinding of outcome assessment: no
	Blinding of participants: no
	Study period: not stated

Participants	Number: 65 enrolled
	Inclusion criteria: children 2 to 10 years of age, ASA physical status I to II, scheduled for tonsillectomy, entered the study
	Exclusion criteria: not stated

Interventions	All groups received 0.3 mg/kg midazolam rectally
	Anaesthesia was induced by face mask and open circuit without carbon dioxide absorber according to
	Group 1: 2%, 4%, 6%, 7% sevoflurane in 100% O ₂
	Group 2: 7% sevoflurane in 100% O ₂
	Group 3: 7% sevoflurane in 50% N ₂ O and 50% O ₂

Outcomes	Quality of mask acceptance
	Degree of airway obstruction during induction
	Quality of tracheal intubation
	Time to loss of eyelash reflex
	Time to obtain central pupils
	Time to intubation
	Adverse events (coughing, apnoea, laryngospasm, bronchospasm, secretions, vomiting, dysrhythmia, agitation and oxygen desaturation < 95%)
	End-tidal gas concentration
	Systolic and diastolic arterial pressure, heart rate, oxygen saturation

Notes	Location: France
	Setting: operating room
	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
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Dubois 1999 (Continued)

Random sequence generation (selection bias)	Unclear risk	Information insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "trainee was in charge of recording induction events and monitoring parameters"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Epstein 1998

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: unclear Blinding of participants: no Study period: not stated
Participants	Number: 40 enrolled Inclusion criteria: 4 months to 15 years of age, ASA physical status I to II, undergoing elective surgical procedures for which mask induction of general anaesthesia was planned Exclusion criteria: not stated
Interventions	No pre-medication Group 1: 8% sevoflurane in 66% N ₂ O tidal volume breathing technique Group 2: incremental sevoflurane in 66% N ₂ O tidal volume breathing technique
Outcomes	Induction time (loss of the eyelash reflex) Induction co-operation Complication
Notes	Location: USA Setting: operating room Source of funding: Abbott Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were assigned to one of two induction groups according to a table of random numbers"

Epstein 1998 (Continued)

Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Green 2000

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: yes Blinding of participants: no Study period: not stated
Participants	Number: 60 enrolled Inclusion criteria: healthy infants (6 weeks to 20 months), elective surgery Exclusion criteria: cardiac and respiratory disease
Interventions	No pre-medication. Tidal volume breathing technique, Ayre's T-piece Group 1: 2% sevoflurane in 67% N ₂ O Group 2: 8% sevoflurane in 67% N ₂ O
Outcomes	Bradycardia Nodal rhythm Airway complication Hypoxia
Notes	Location: UK Setting: operating room Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated randomly to receive interventions using a computer-generated random number allocation and close envelope technique"

Green 2000 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Patients were allocated randomly to receive interventions using a computer-generated random number allocation and close envelope technique"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "...by an observer blinded to method of induction"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Hall 2000

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: unclear Blinding of participants: no Study period: not stated
Participants	Number: 14 enrolled. Inclusion criteria: healthy volunteers, between 20 and 30 years of age Exclusion criteria: not stated
Interventions	No pre-medication. Circle system was primed Group 1: 3% tidal volume sevoflurane in O ₂ Group 2: 8% tidal volume sevoflurane in O ₂
Outcomes	Time to loss of eyelash reflex Vital signs (blood pressure, heart rate, ECG)
Notes	Location: UK Setting: operating room Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement

Hall 2000 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "..assessed by a blinded investigator"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Hsu 2000

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: unclear Blinding of participants: no Study period: not stated
Participants	Number: 120 enrolled Inclusion criteria: children 3 to 10 years old, ASA physical status I, undergoing ambulatory surgery Exclusion criteria: uncommunicative, unco-operative in using face mask
Interventions	Unprimed paediatric circle circuit with tidal volume breathing technique Group 1: 2% sevoflurane in 50% N ₂ O Group 2: 4% sevoflurane in 50% N ₂ O Group 3: 6% sevoflurane in 50% N ₂ O Group 4: 8% sevoflurane in 50% N ₂ O
Outcomes	Time to loss of eyelash reflex Responses of airway reflex Involuntary movement Blood pressure, heart rate and oxygen saturation Untoward events (cough, laryngospasm, secretions, breath holding, vomiting and bronchospasm)
Notes	Location: Taiwan Setting: operating room Source of funding: Abbott Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
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Hsu 2000 (Continued)

Random sequence generation (selection bias)	Unclear risk	Information insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Martin-Larrauri 2004

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: unclear Blinding of participants: no Study period: not stated
Participants	Number: 125 enrolled Inclusion criteria: adult patients of ASA physical status I to II 19 to 65 years old undergoing short surgical procedures under general anaesthesia with spontaneous ventilation via LMA Exclusion criteria: allergy or sensitivity to volatile anaesthetics, suspected malignant hyperthermia, abnormal hepatic or renal function test, pregnant female, any condition that may increase risk
Interventions	Fentanyl (1 mcg/kg) before receiving study anaesthetics Group 1: incremental sevoflurane Group 2: 4.5% sevoflurane Group 3: 8% vital capacity inhalation rapid inhalation induction technique and primed Bain circuit
Outcomes	Time to loss of eyelash reflex Time to cessation of finger tapping on the trolley Time to end of laryngeal mask insertion Time to spontaneous breathing after mask insertion Time from mask insertion to spontaneous breathing Time from loss of eyelash reflex to mask insertion Ease of laryngeal mask placement Any side effects occurring during the induction process Severe postoperative nausea and vomiting

Martin-Larrauri 2004 (Continued)

Notes

Location: Spain

Setting: operating room

Source of funding: Abbott Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This was a randomized, open label, multicentre study with three groups in parallel"
Allocation concealment (selection bias)	Low risk	Quote: "The treatment assignment for each patient number was contained in sequentially ordered individually sealed envelopes that were opened on the day of the scheduled surgery; afterwards the study design was open"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Mendonca 2001

Methods	<p>Randomization and treatment allocation method: yes</p> <p>Blinding of outcome assessment: unclear</p> <p>Blinding of participants: no</p> <p>Study period: not stated</p>
Participants	<p>Number: 60 enrolled</p> <p>Inclusion criteria: ASA physical status II to III patients scheduled to undergo general anaesthesia, 50 years of age and older with a history of smoking 10 cigarettes a day for 20 years</p> <p>Exclusion criteria: severe cardiovascular disease, morbid obesity, allergy to inhalational anaesthetics, requiring rapid sequence induction</p>
Interventions	<p>No pre-medication and a Mapleson D breathing system</p> <p>Group 1: 8% vital capacity breathing in 66% N₂O</p> <p>Group 2: 8% tidal breathing in 66% N₂O</p> <p>Group 3: incremental tidal breathing sevoflurane in 66% N₂O</p>
Outcomes	<p>Time to dropping the weighted syringe</p> <p>Induction event (single cough, laryngospasm, breath holding, movement of a limb, excessive salivation, hypotension and hypoxia were recorded)</p>

Mendonca 2001 (Continued)

Smell of the anaesthetic

Notes

Location: UK

Setting: operating room

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients were randomly allocated using sealed envelopes to one of the three breathing techniques"
Allocation concealment (selection bias)	Low risk	Quote: "...patients were randomly allocated using sealed envelopes to one of the three breathing techniques"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Pancaro 2005

Methods

Randomization and treatment allocation method: yes

Blinding of outcome assessment: yes

Blinding of participants: no

Study period: not stated

Participants

Number: 131 enrolled

Inclusion criteria: healthy females, ASA physical status I, undergoing gynaecological procedures under general anaesthesia as day patients

Exclusion criteria: not stated

Interventions

 Group 1: incremental in O₂ with unprimed circuit

 Group 2: decremental-incremental concentrations (8% to 4%, then 8% vs 8% concentration in O₂ with unprimed circuit)

Outcomes

Time to loss of consciousness

Apnoea incidence and duration

Notes

Location: Italy

Setting: operating room

Pancaro 2005 (Continued)

Source of funding: University of Perugia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "day patients were randomly allocated to three groups with carefully prepared opaque sealed envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "day patients were randomly allocated to three groups with carefully prepared opaque sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "An intern blinded to the anaesthetic technique observed whether and for how long the patients stopped breathing; in addition, any adverse events during induction of anaesthesia were recorded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

Singh 2014

Methods	Randomization and treatment allocation method: yes Blinding of outcome assessment: no Blinding of participants: no Study period: not stated
Participants	Number: 100 enrolled Inclusion criteria: 1- to 8-year-old patients undergoing ophthalmological examination under anaesthesia Exclusion criteria: seizure disorder, craniofacial abnormalities/difficult airway, cardiopulmonary or neuromuscular defects, hepatic or renal insufficiency, expected difficult intravenous cannulation
Interventions	Midazolam 0.5 mg/kg orally about 30 minutes before induction of anaesthesia Group 1: incremental sevoflurane (increased by 1% every 3 breaths) in 50% N ₂ O with fresh gas flow of 6 LPM Group 2: 8% sevoflurane with priming circuit in 50% N ₂ O with 6 LPM
Outcomes	Time to loss of consciousness (loss of eyelash reflex and jaw relaxation) Time to intravenous cannulation and LMA insertion Liquid sevoflurane consumed during induction and LMA insertion Adverse events
Notes	Location: not stated Setting: operating room

Singh 2014 (Continued)

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were divided into 2 groups of 50 each using a computer-generated table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Selective reporting (reporting bias)	Unclear risk	Quote: "The number of adverse events was also similar. The most common problem noted was temporary breath holding in both groups, which resolved spontaneously. One patient in the high-concentration group experienced laryngospasm and was excluded from analysis because of change in the management plan"

Yurino 1995

Methods	<p>Randomization and treatment allocation method: no</p> <p>Blinding of outcome assessment: yes</p> <p>Blinding of participants: yes</p> <p>Study period: not stated</p>
Participants	<p>Number: 68 enrolled.</p> <p>Inclusion criteria: non-pre-medicated healthy adult volunteers with ASA physical status I to II</p> <p>Exclusion criteria: not stated</p>
Interventions	<p>No pre-medication. Unprimed circle circuit</p> <p>Group 1: 3% sevoflurane in O₂</p> <p>Group 2: 4.5% sevoflurane in O₂</p> <p>Group 3: 6% sevoflurane in O₂</p> <p>Group 4: 7.5% vital capacity rapid inhalation induction in O₂</p>
Outcomes	<p>Induction time</p> <p>Time to absence of response to the verbal command</p> <p>Excitatory phenomena (cough, laryngospasm, limb movements, breath holding, secretions)</p>

Yurino 1995 (Continued)

Notes

Location: Japan

Setting: operating room

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "assigned to one of four groups of 17 subjects in sequential order of entry"
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Subjects were blinded to the inhalation anaesthetic used, as well as its concentration of anaesthetic vapour" and "an independent observer, who was blinded to the concentration used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study authors reported all planned outcomes

ASA: American Society of Anesthesiologists physical status classification; ECG: electrocardiography; kg: kilogram; L: litre; LMA: laryngeal mask airway; LPM: litre per minute; mg: milligram; min: minute; Mo: morphine; N₂O: nitrous oxide; O₂: oxygen; yr: year

Characteristics of excluded studies [ordered by year of study]

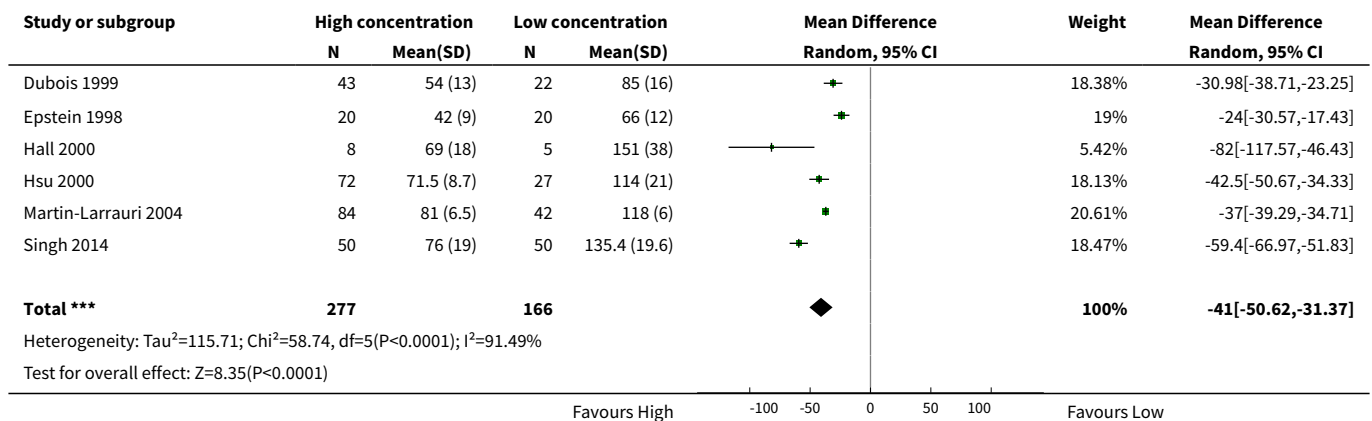
Study	Reason for exclusion
Nishiyama 1997	Study did not report outcome of interest
Munoz 1999	Study did not report outcome of interest
Walpole 1999	Comparison between 4% and 8% sevoflurane induction was included in high concentration groups
Lee 2013	Comparison between 8% sevoflurane with and without nitrous oxide
Julliac 2013	Target-controlled induction at 2.5% and 8% sevoflurane induction was included in high concentration groups
Kreuzer 2014	Comparison between 6% and 8% sevoflurane induction was included in high concentration groups

DATA AND ANALYSES

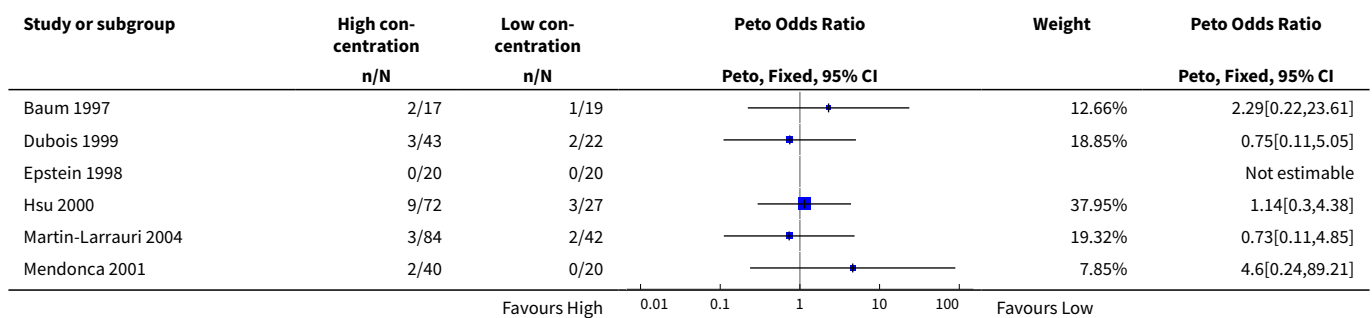
Comparison 1. High initial concentration versus low initial concentration

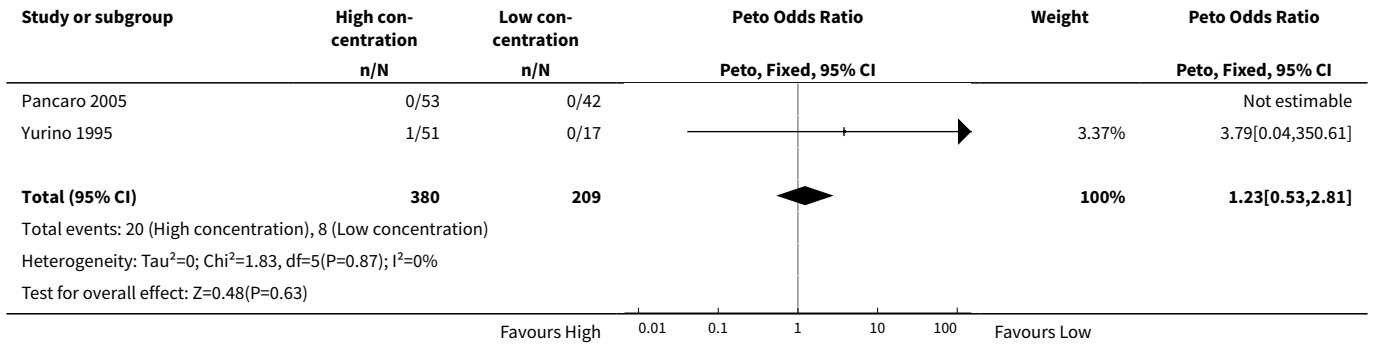
Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to loss of eyelash reflex (seconds)	6	443	Mean Difference (IV, Random, 95% CI)	-39.00 [-50.62, -31.37]
2 Cough	8	589	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.53, 2.81]
3 Laryngospasm	7	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.16, 15.92]
4 Breath holding	5	389	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.47, 2.83]
5 Apnoea	2	160	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [1.72, 5.70]
6 Patient movement	5	445	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.69, 1.89]
7 Salivation	6	487	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.36, 4.21]
8 Bradycardia	3	199	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.22, 2.88]

Analysis 1.1. Comparison 1 High initial concentration versus low initial concentration, Outcome 1 Time to loss of eyelash reflex (seconds).

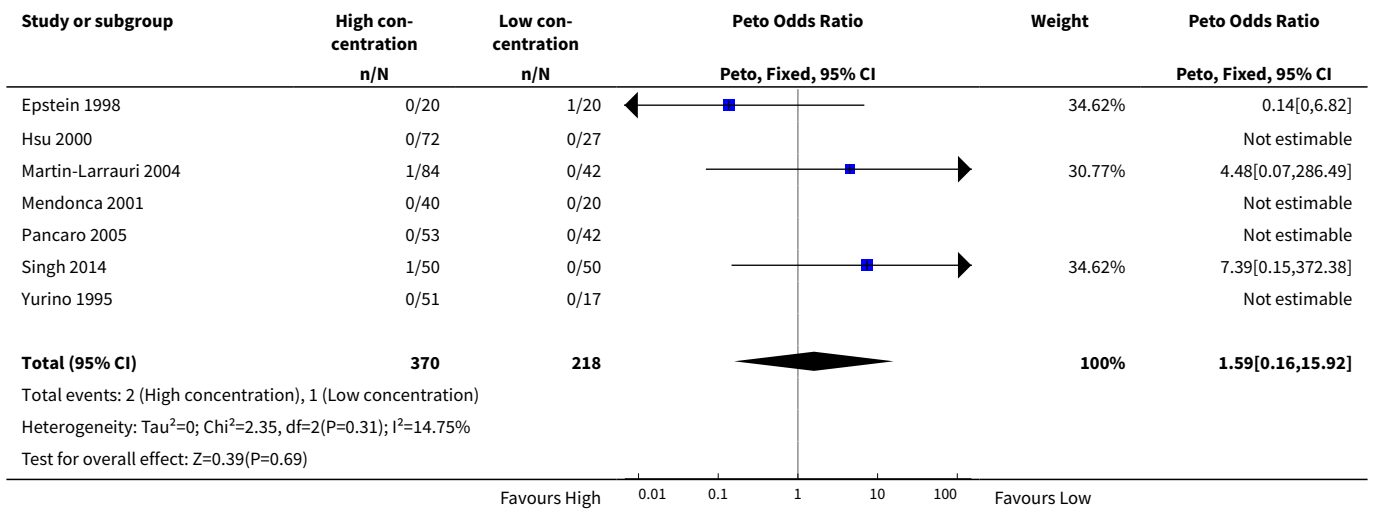


Analysis 1.2. Comparison 1 High initial concentration versus low initial concentration, Outcome 2 Cough.

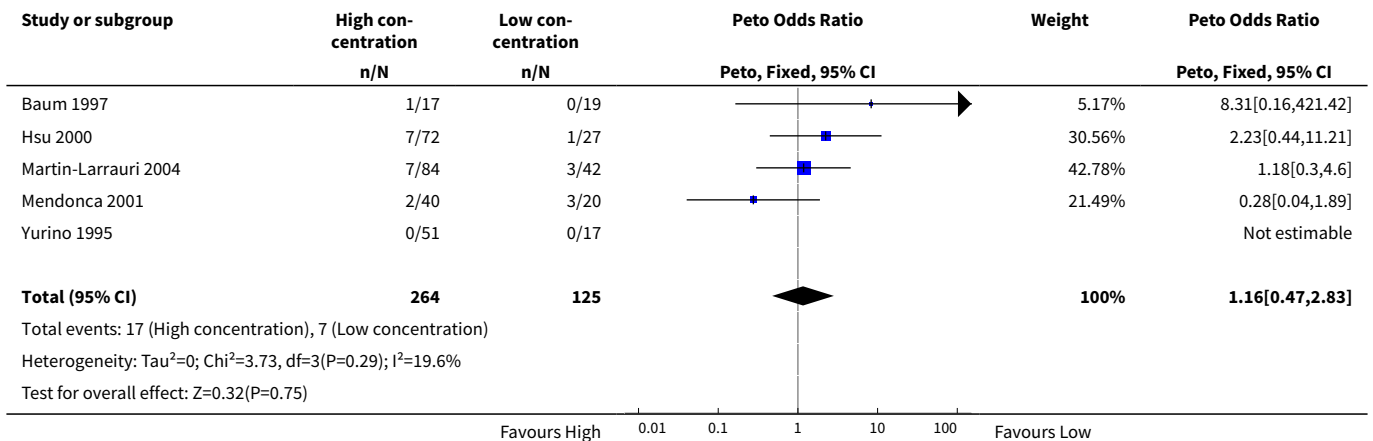




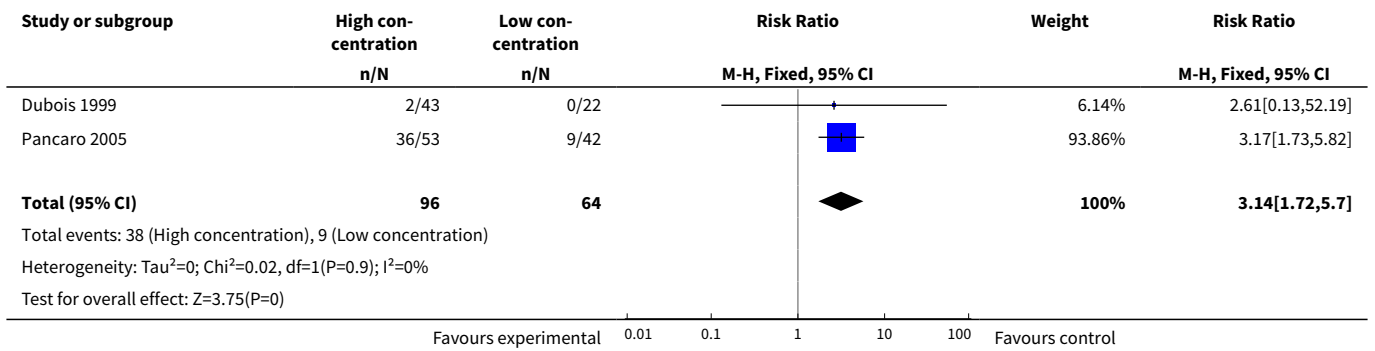
Analysis 1.3. Comparison 1 High initial concentration versus low initial concentration, Outcome 3 Laryngospasm.



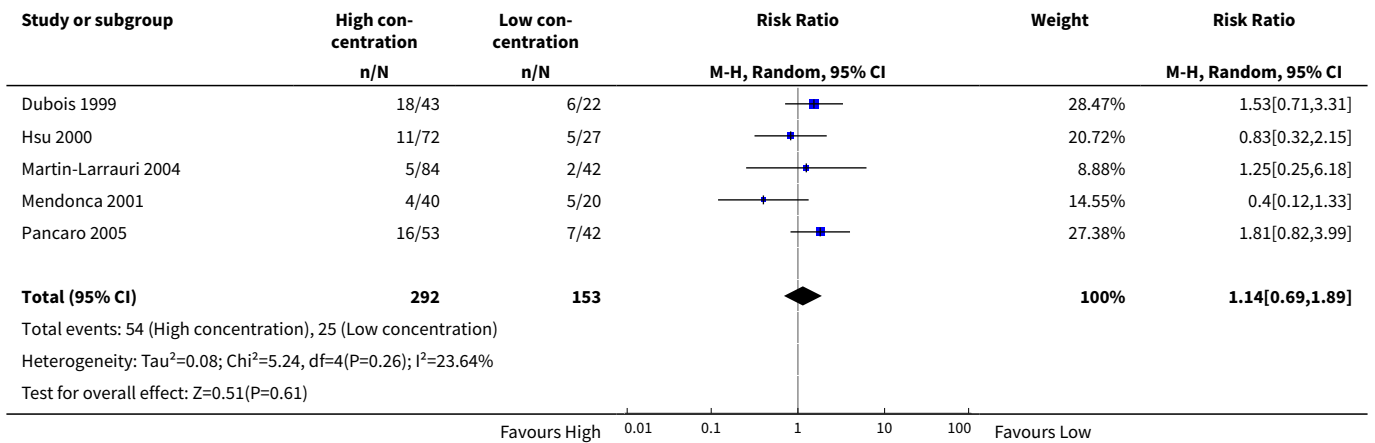
Analysis 1.4. Comparison 1 High initial concentration versus low initial concentration, Outcome 4 Breath holding.



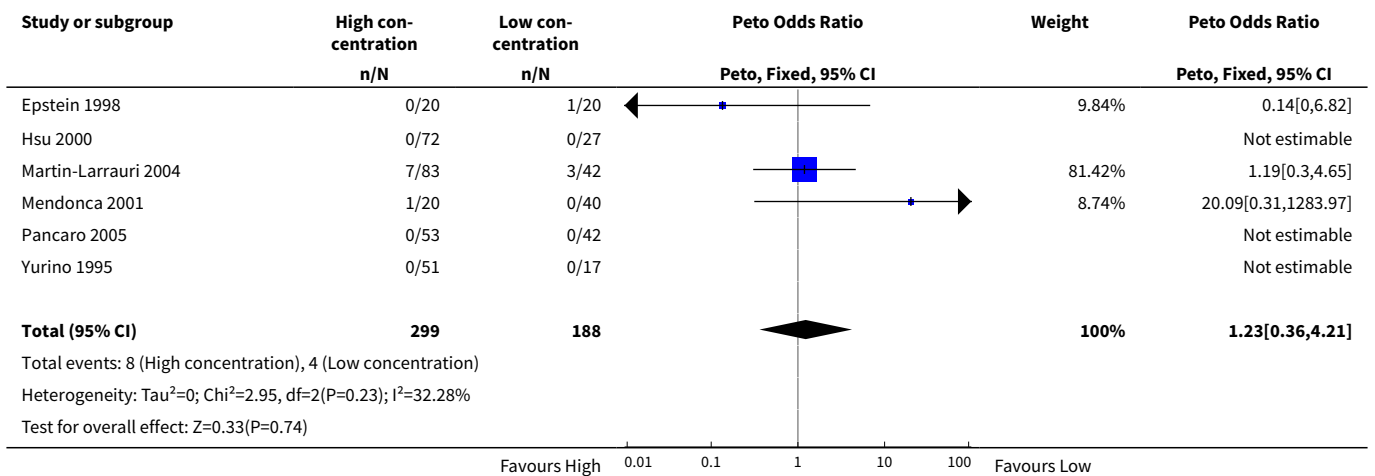
Analysis 1.5. Comparison 1 High initial concentration versus low initial concentration, Outcome 5 Apnoea.



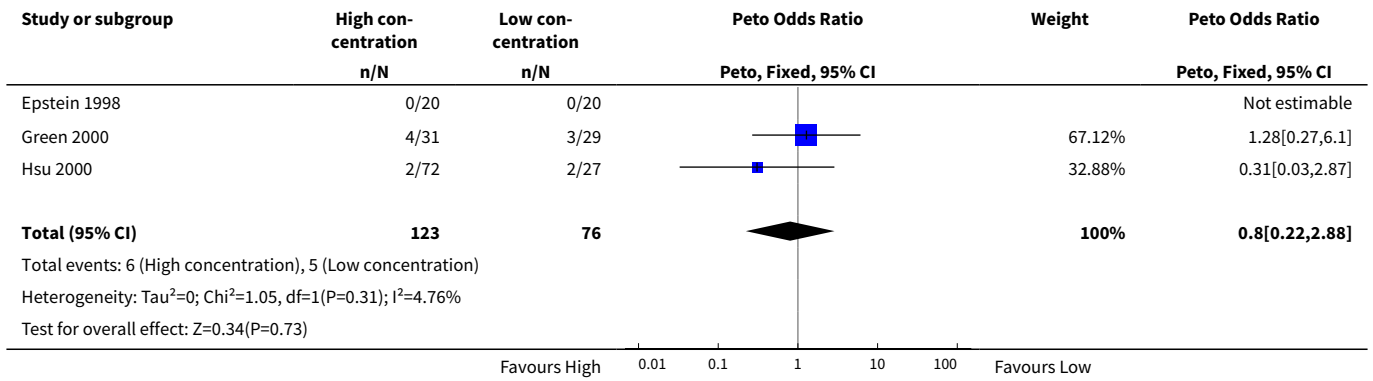
Analysis 1.6. Comparison 1 High initial concentration versus low initial concentration, Outcome 6 Patient movement.



Analysis 1.7. Comparison 1 High initial concentration versus low initial concentration, Outcome 7 Salivation.



Analysis 1.8. Comparison 1 High initial concentration versus low initial concentration, Outcome 8 Bradycardia.



APPENDICES

Appendix 1. Search strategy for MEDLINE (Ovid SP)

#1 (Sevofluran* or Sevorane or Ultane).ti,ab.
#2 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh.
#3 #1 and #2

Appendix 2. Search strategy for CENTRAL

#1 sevofluran* or sevorane or ultane
#2 MeSH descriptor Anesthesia explode all trees
#3 MeSH descriptor Laryngeal Masks explode all trees
#4 MeSH descriptor Intubation, Intratracheal, this term only
#5 intubat* or LMA endotracheal
#6 laryngeal near mask*
#7 an?esthesia near general
#8 (#2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 (#1 AND #8)

Appendix 3. Search strategy for EMBASE (Ovid SP)

#1 exp sevoflurane/
#2 (sevofluran* or sevorane or ultane).ti,ab.
#3 #1 or #2
#4 exp general-anesthesia/ or exp laryngeal-mask/ or exp endotracheal-intubation/
#5 (an?esthesia adj3 general).ti,ab. or (laryngeal adj3 mask*).mp. or (intubat* or LMA or endotracheal).mp.
#6 #4 or #5
#7 #6 and #3
#8 (RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/ or (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab.) and human*.ec,hw,fs.
#9 #8 and #7

Appendix 4. Search strategy for LILACS (BIREME)

"sevofluran\$" or "ultane" or "SEVOFLURANE" or "SEVOFLURANO" or "SEVOFLURANO" or "SEVORANE" or "SEVORANO"

Appendix 5. Search strategy for ISI Web of Science

#1 TS=(Sevofluran* or Sevorane or Ultane)
#2 TS=(clinical trial*)
#3 TS=random*

#4 TS=placebo*
#5 #4 OR #3 OR #2
#6 TS=animal*
#7 TS=human*
#8 #6 NOT (#6 AND #7)
#9 #5 NOT #8
#10 #9 AND #1

Appendix 6. Data extraction form

Data extraction form		Review
Study ID:	Medline journal ID:	Language:
Authors:		
Year of publication:	Country:	Type of study:
Comment on study design		
Randomizations and allocation concealment	Adequate: e.g. numbered, sealed opaque envelopes	
	Unclear	
	Inadequate	
	Not used	
Blinding of treatment	Adequate (participant, physician, assessor)	
	Unclear	
	Inadequate (participant, physician, assessor)	
Blinded outcome assessment	Adequate	
	Unclear	
	Inadequate	
Use of intention-to-treat analysis	Yes	
	No	
	No information	
PARTICIPANTS:		
Number of eligible participants		Number of males

(Continued)

Number enrolled in study	Number of females		
Age, years	< 15		> 60
Intervention:			
High concentration			
Low concentration			
COMMENT ON TREATMENT:			
Withdrawals	yes	no	unclear
Outcome	High concentration		Low concentration
Time to LOER (seconds)			
Time to drop a weighted object (seconds)			
Patient satisfaction (NRS)			
Failed inhalational induction			
Cough			
Laryngospasm			
Breath holding			
Apnoea			
Patient movement			
Hypotension			
Bradycardia			
Epileptiform EEG			
Other complications			

(Continued)

Changes in protocol:

Contact with study authors:

Comment on this study:

WHAT'S NEW

Date	Event	Description
2 February 2016	New search has been performed	We reran our searches in February 2016. We found one new included study and three excluded studies.
2 February 2016	New citation required but conclusions have not changed	The conclusions of the review did not change

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 9, 2012

Date	Event	Description
2 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Polpun Boonmak (PB), Suhattaya Boonmak (SB), Porjai Pattanittum (PP).

Conceiving of the review: PB.

Co-ordinating the review: SB.

Undertaking manual searches: PB, SB.

Screening search results: PB, SB.

Organizing retrieval of papers: PB.

Screening retrieved papers against inclusion criteria: PB, SB.

Appraising the quality of papers: PB, SB.

Abstracting data from papers: PB, SB.

Writing to authors of papers to ask for additional information: PB.

Providing additional data related to papers: PB.

Obtaining and screening data on unpublished studies: PB.

Managing data for the review: PB, PP.

Entering data into Review Manager ([RevMan 5.3](#)): PB, SB.

Analysing RevMan statistical data: PB, PP.

Performing double entry of data: data entered by person one PB, data entered by person two SB.

Interpreting data: PB, PP.

Performing statistical analysis: PP.

Writing the review: PB, SB.

Writing the effects of interventions part: PP.

Creating 'Summary of findings' tables: PP, PB.

Commenting on the 'Summary of findings' tables: PB, SB.

Securing funding for the review: PB.

Performing previous work that was the foundation of the present study: PB.

Serving as guarantor for the review (one review author): PB.

Taking responsibility for reading and checking the review before submission: PB, SB, PP.

DECLARATIONS OF INTEREST

Polpun Boonmak: none known.

Suhattaya Boonmak: none known.

Porjai Pattanittum: none known.

SOURCES OF SUPPORT

Internal sources

- Systematic review grant, Faculty of Medicine, Khon Kaen University, Thailand.
- Thai Cochrane Network, Thailand.

External sources

- The Thailand Research Fund, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title to "High initial concentration versus low initial concentration sevoflurane for inhalational induction of anaesthesia".

We added two outcomes that we did not plan in the protocol ([Boonmak 2007](#)) - time to endotracheal intubation and time to successful insertion of a laryngeal mask airway.

We did not use the risk ratio for dichotomous data, but we used the Peto odds ratio because events were rare.

We considered $I^2 > 35\%$ as a sign of heterogeneity instead of $I^2 > 50\%$, as mentioned in the protocol.

If I^2 was greater than 75%, we did not attempt to pool the results.

We conducted all analyses while using RevMan software version 5.3.5, not version 4.2.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Inhalation [adverse effects] [*methods]; Anesthetics, Inhalation [*administration & dosage] [adverse effects]; Methyl Ethers [*administration & dosage] [adverse effects]; Sevoflurane; Time Factors

MeSH check words

Humans