Inhaled analgesia for pain management in labour (Review)

Klomp T, van Poppel M, Jones L, Lazet J, Di Nisio M, Lagro-Janssen ALM

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Inhaled analgesia for pain management in labour

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ABSTRACT

Background

Many women would like to have a choice in pain relief during labour and also would like to avoid invasive methods of pain management in labour. Inhaled analgesia during labour involves the self-administered inhalation of sub-anaesthetic concentrations of agents while the mother remains awake and her protective laryngeal reflexes remain intact. Most of the agents are easy to administer, can be started in less than a minute and become effective within a minute.

Objectives

To examine the effects of all modalities of inhaled analgesia on the mother and the newborn for mothers who planned to have a vaginal delivery.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2012), ClinicalTrials.gov, and Current Controlled Trials (2 June 2012), handsearched conference proceedings from the American Society of Clinical Anesthesia (from 1990 to 2011), contacted content experts and trialists and searched reference lists of retrieved studies.

Selection criteria

Randomised controlled trials comparing inhaled analgesia with other inhaled analgesia or placebo or no treatment or other methods of non-pharmacological pain management in labour.

Data collection and analysis

Review authors independently assessed trials for eligibility, methodological quality and extracted all data. Data were double checked for accuracy.

Main results

Twenty-six studies, randomising 2959 women, were included in this review.

Inhaled analgesia versus a different type of inhaled analgesia

Pain relief was measured using a Visual Analogue Scale (VAS) from 0 to 100 mm where 100 corresponds to the most relief. Pain intensity was measured using a VAS from 0 to 100 mm, where 0 corresponds to no pain at all and 100 corresponds to the worst pain. The highest score for pain relief is the most positive in contrast to 'pain intensity' in which the higher score is more negative.

Flurane derivatives were found to offer better pain relief than nitrous oxide in first stage of labour as measured by a lower pain intensity score (average mean difference (MD) 14.39, 95% confidence interval (CI) 4.41 to 24.37, three studies, 70 women), also a higher pain relief score for flurane derivatives compared with nitrous oxide (average MD -16.32, 95% CI -26.85 to -5.79, two studies, 70 women). Substantial heterogeneity was found in the analyses of pain intensity (P = 0.003) and in the analysis of pain relief (P = 0.002).These findings should be considered with caution because of the questionable design of the included cross-over trials. More nausea was found in the nitrous oxide group compared with the flurane derivatives group (risk ratio (RR) 6.60 95% CI 1.85 to 23.52, two studies, 98 women).

Inhaled analgesia versus placebo or no treatment

Placebo or no treatment was found to offer less pain relief compared to nitrous oxide (average RR 0.06, 95% CI 0.01 to 0.34, two studies, 310 women; MD -3.50, 95% CI -3.75 to -3.25, one study, 509 women). However, nitrous oxide resulted in more side effects for women such as nausea (RR 43.10, 95% CI 2.63 to 706.74, one study, 509 women), vomiting (RR 9.05, 95% CI 1.18 to 69.32, two studies, 619 women), dizziness (RR 113.98, 95% CI 7.09 to 1833.69, one study, 509 women) and drowsiness (RR 77.59, 95% CI 4.80 to 1254.96, one study, 509 women) when compared with placebo or no treatment.

There were no significant differences found for any of the outcomes in the studies comparing one strength versus a different strength of inhaled analgesia, in studies comparing different delivery systems or in the study comparing inhaled analgesia with TENS.

Due to lack of data, the following outcomes were not analysed within the review: sense of control; satisfaction with childbirth experience; effect on mother/baby interaction; breastfeeding; admission to special care baby unit; poor infant outcomes at long-term follow-up; or costs.

Authors' conclusions

Inhaled analgesia appears to be effective in reducing pain intensity and in giving pain relief in labour. However, substantial heterogeneity was detected for pain intensity. Furthermore, nitrous oxide appears to result in more side effects compared with flurane derivatives. Flurane derivatives result in more drowsiness when compared with nitrous oxide. When inhaled analgesia is compared with no treatment or placebo, nitrous oxide appears to result in even more side effects such as nausea, vomiting, dizziness and drowsiness. There is no evidence for differences for any of the outcomes comparing one strength verus a different strength of inhaled analgesia, comparing different delivery systems or comparing inhaled analgesia with TENS.

PLAIN LANGUAGE SUMMARY

Inhaled analgesia for relieving pain during labour

Labour pain and methods to relieve it are major concerns for pregnant women, healthcare workers and the general public. These concerns have implications for the course of labour, for the quality of maternal and infant outcomes as well as for the costs of obstetric health care.

Women in labour who need pain relief should not only have access to invasive methods such as an epidural, which may have considerable side effects, but other means of pain relief as well. Futhermore, even in hospitals with full-time obstetric anaesthesia coverage no one may be available to give an epidural, and in primary care, invasive methods for pain relief are not available at all.

All women in labour should have the opportunity to choose some non-invasive method of relatively effective and safe analgesia at short notice when they wish it during labour. Inhaled pain relief, such as nitrous oxide and some flurane derivatives, may be a very useful additional method for pain relief. It is relatively easy to administer, can be started in less than a minute, and become effective within a

minute. Nitrous oxide is more widely known and used as inhaled pain relief during labour compared to flurane derivatives, probably due to the availability of safe equipment, no pungent smell and the ease of administration.

In this review of 26 randomised controlled trials of 2959 women, the effectiveness and safety of inhaled analgesia as pain relief for women in labour were studied. It was found that inhaled analgesia may help relieve pain during labour but women have to be informed about the side effects, such as nausea, vomiting, dizziness and drowsiness.

Inhaled analgesia may help relieve labour pain without adversely increasing operative delivery rates (forceps or vacuum extraction, caesarian section), or affecting neonatal well being. Flurane derivatives were found to be slightly more effective than nitrous oxide for the reduction of pain and for pain relief although nitrous oxide also helped to relieve pain when compared with no treatment.

Women who used nitrous oxide were more likely to experience nausea compared with flurane derivatives. When nitrous oxide was compared with no treatment or placebo, nitrous oxide resulted in side effects such as nausea, vomiting, dizziness and drowsiness.

There was no information for satisfaction with childbirth experience or sense of control in labour in these studies and further research on these two important outcomes would be helpful.

BACKGROUND

Description of the condition

Labour pain and methods to relieve it are major concerns for women, healthcare workers and the general public (Caton 2002). These concerns have implications for the course of labour, for the quality of maternal and infant obstetric outcomes as well as for the costs of obstetric health care. In our modern society, pain has a negative connotation for the general public. Fear of labour pain is strongly associated with the fear of pain in general (Lowe 2002; Rosen 2002). Different views about the importance of pain during labour are reflected in great differences between countries worldwide with regard to the numbers of women who receive pain relief during labour, as well as the type of pharmacological analgesia that is used. Culture plays a significant role in attitudes towards childbirth pain, the definition of the meaning of childbirth pain, perceptions of pain and coping mechanisms used to manage pain in childbirth.

Description of the intervention

Inhaled analgesia during labour involves the inhalation of sub-anaesthetic concentrations of agents while the mother remains awake and her protective laryngeal reflexes remain intact. The use of inhaled analgesics for pain relief during labour dates back to 1847, when James Simpson used it for the first time for vaginal delivery (Rae 1997). Nitrous oxide was first used in 1881 by Stanislaw Klikovich, who studied the effects of pre-mixed nitrous oxide 80% in oxygen on women in labour (Richards 1976). In 1934, Minnitt introduced an apparatus for the self-administration of nitrous oxide (Minnitt 1934). Other possibilities for inhaled analgesia for pain relief in labour are isoflurane, sevoflurane, trichloroethylene in air, methoxyflurane and cyclopropane. Trichloroethylene cannot be administered through a CO_2 absorber and is flammable, while cyclopropane is explosive even in sub-anaesthetic concentrations. Both drugs are no longer used in the developed world and therefore must be seen as of historical interest only. Sevoflurane is not recommended as analgesia because it has no analgesic activity at sub-anaesthetic concentrations. Sub-anaesthetic concentrations of nitrous oxide, enflurane, isoflurane and methoxyflurane do not significantly decrease uterine contractions and are preferable for this reason. However, only the use of nitrous oxide is widespread in modern obstetric practice. The reason why is not clear but probably due to ease of administration, lack of flammability, lack of pungent odour, lack of effect on uterine contractions, lack of relation with pathologic temperature, minimal toxicity and minimal depression of the cardio-vascular system (KNOV 2009; Rosen 2002). The evidence on the use of nitrous oxide for relief of labour pain has been summarised in a systematic review (Rosen 2002). Nitrous oxide mixed with oxygen as labour pain management in labour is self-administered by labouring women by inhalation through a mouthpiece or facemask. Entonox is a trade marked name for a mix of 50% nitrous oxide and 50% oxygen in liquid state in a single pressured container. Alternatively, Entonox can be used by blending a fixed concentration of 50% nitrous oxide and 50% oxide by two separate cylinders or hospital pipeline supply; the distribution of Entonox is carried out through a small regulator apparatus (Nitronox™). The Midogas device is another way to inhale Entonox which allows adjustment of the nitrous oxide concentration within a narrow range. The cylinders are connected to a facemask or mouthpiece. The demand valve

opens only when the user applies a negative pressure by inspiring through the mouthpiece or well-sealed mask covering the parturient's mouth and nose. The demand valve eliminates flow when the parturient is not inhaling to minimise environmental contamination. Unlike the Entonox apparatus, the Nitronox apparatus allows exhaled gas to be scavenged. In countries such as Canada, Denmark, Finland, New Zealand, the United Kingdom and the United States of America, midwives are allowed to 1) set up the equipment for nitrous oxide, 2) instruct the woman how to use it and 3) monitor her use of it. The woman can self-administer it after initial supervision. Inhaled analgesia can be used by the woman either intermittently with discontinuation of use as the contraction pain eases or disappears, or continuously, by inhaling both during and between contractions. There is a rapid uptake/washout rate for most of the inhaled analgesia, which means a low blood/gas solubility ratio. The blood/gas solubility ratio for nitrous oxide is 0.47 at 37 degrees C; for Isoflurane: 1.4; for Sevoflurane: 0.69; for Enflurane: 1.64 and for Methoxuyflurane: 13. For Methoxyflurane, the onset of analgesia is relatively slow but in spite of the low solubility it is far more potent than any of these agents and is therefore still used for inhalational analgesia in some settings. Maximal effect for nitrous oxide is observed in 30 to 60 seconds and wash-out effect can be obtained in three or four exhalations (Talebi 2009).

However, there is controversy about the use of nitrous oxide because of concerns about the safety of nitrous oxide for the sub fecundability (reduction in the ability to conceive) of female maternity care professionals and an increased incidence of spontaneous abortions of the pregnant maternity care professionals (Ahlborg 1996; Axelsson 1996; Bodin 1999; Boivin 1997; Rooks 2011; Zielhuis 1999). The underlying cause is thought to be inactivation of methionine synthase by nitrous oxide (Sanders 2008). Cellular-level damage can begin during a maternity-care worker's shift in a poorly ventilated hospital where nitrous oxide is used without scavenging. The damage-producing process stops when the maternity-care worker leaves the hospital's contaminated environment. While she is away from the hospital, her body begins to repair any cellular-level damage. The healing of damage that has not caused actual pathology is referred to as *restitution.* If she returns to work in a nitrous oxide-polluted environment before restitution is complete, the damage-producing process resumes and restitution will be incomplete. Over time, the damage may accumulate enough to produce pathology (Rooks 2011).

Subfecundability in the form of maternal absorption of malformed conceptions has been found in animal studies of the reproductive effects of very prolonged exposures to very high doses of nitrous oxide (Sanders 2008). Nitrous oxide-induced fertility problems occur in rats at 1000 parts per million (ppm) but not at 500 ppm or lower. Rats are known to be particularly sensitive to damage from nitrous oxide.

More months on average to conceive was found in a study of dental assistants working in settings that did not use scavenging of exhaled nitrous oxide (Rowland 1992). It was estimated that the ambient air in which they worked was contaminated by greater than 1000 ppm of nitrous oxide.

Current standards in the Netherlands and United States call for limiting occupational exposure to nitrous oxide to not more than an eight-hour time-weighted average (TWA) concentration of 25 ppm (KNOV 2009). The UK, Finland, Germany and Sweden have set 100 ppm as their upper limits. The United States' 25 ppm standard was set arbitrarily during the 1970s without benefit of actual data. Nevertheless, the American Society of Anesthesiologists (ASA), the National Institute of Occupational Safety and Health (NIOSH) and the US Occupational Safety and Health Administration (OSHA) all believe that this standard has been effective in protecting American health workers. Concerns about reproductive toxicity from occupational exposure to nitrous oxide at levels below the 25-ppm standard are not supported by the available data, which, however, do not include findings from prospective studies.

The risk of reproductive failure related to occupational exposure to nitrous oxide is essentially eliminated when nitrous oxide labour analgesia is used in well-ventilated modern hospitals and 'scavenging' is used. The Boivin 1997 meta-analysis reached the same conclusion as the Rosen 2002 review: scavenging solves the problem. Epidemiological studies based on data obtained in the pre-scavenging era indicated an increased risk of spontaneous abortion.

Other side effects are maternal drowsiness, nausea and vomiting when inhaled analgesia is used too long or extensively, especially if the rule of self-administration is violated. Renal and hepatic toxicity and uterine relaxation are usually not of concern at analgesic levels of inhaled analgesia but we will include them if possible.

How the intervention might work

The precise mechanism of action of pain relief by inhaled analgesia remains uncertain. Maze and Fuginaga hypothesised that nitrous oxide induces the release of endogenous opioid peptides in the periaqueductual grey area of the midbrain (Maze 2000). The release of this substance in the midbrain could modulate pain stimuli through the descending spinal cord nerve pathways.

Why it is important to do this review

It is important to do this review because all women should have access to some form of relatively effective and safe analgesia during labour and to provide this analgesia when women need some form of pharmacological pain relief during labour (Rooks 2007). Even in hospitals with full-time obstetric anaesthesia coverage, no one may be available to place an epidural, provide another highly effective method of labour analgesia, or provide a labour-intensive non-pharmacological method to help the woman in pain.

More invasive options such as epidural analgesia are associated with significant side effects. Approximately 20% of women who had a vaginal delivery in the UK (DOH 2005; Khor 2000), 59% to 61% of women in the USA (Declercq 2007; Osterman 2011) and 10% of women in the Netherlands (PRN 2008) used an epidural injection as pain relief in labour. The use of an epidural injection in labour has steadily increased until the last decade in modern highly developed countries (Anim-Somuah 2005). In some countries these figures are expected to rise even more in the coming years, for example, in the Netherlands. The use of epidural analgesia, especially within primary obstetric care, determines a higher rate of deliveries in secondary or tertiary obstetric care hospitals, which increases medicalisation as well as healthcare costs. In conclusion, it is important to have other options for pain relief during labour in view of the side effects of the invasive options.

Inhaled pain relief during labour, especially by nitrous oxide, is relatively easy to administer, can be started in less than a minute and becomes effective within a minute. Since it does not affect the physiology of labour, it can be started whenever it is needed. However, the effectiveness and efficacy of nitrous oxide use for management of labour pain is hard to ascertain because of the few available data. The available data are out of date (Rosen 2002); thus a systematic assessment of the evidence regarding the safety and efficacy of inhaled analgesia for pain relief in labour is urgently needed as well as for anaesthesiologists, obstetricians, hospital administrators, midwives, nurses, women as for the general public.

This review is one in a series of Cochrane reviews examining pain management in labour. These reviews contribute to an overview of systematic reviews of pain management for women in labour (Jones 2012), and share a generic protocol (Jones 2011).

OBJECTIVES

The main objective was to explore the efficacy and safety of inhaled analgesia as pain relief for women in labour planning a vaginal delivery. Although important to look at, the effects of occupational exposure and toxic effects on reproduction for maternity healthcare workers can only be found in large-scale epidemiological studies. Since we only included intervention studies (*see* Types of studies), we did not include these outcomes in this review.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and studies with a cross-over design were included. We did not include quasi-RCTs.

Types of participants

Women in labour including women in high-risk groups, e.g. preterm labour or following induction of labour.

Types of interventions

This review is one in a series of Cochrane reviews examining pain management in labour. These reviews contribute to an overview of systematic reviews of interventions for pain management in labour (Jones 2012), and share a generic protocol (Jones 2011). To avoid duplication, the different methods of pain management have been listed in a specific order, from one to 15. Individual reviews focusing on particular interventions include comparisons with only the interventions above it in the list. Methods of pain management identified in the future will be added to the end of the list. The current list is as follows.

1. Placebo/no treatment
2. Hypnosis (Madden 2011)
3. Biofeedback (Barragán 2011)
4. Intracutaneous or subcutaneous sterile water injection (Derry 2012)
5. Immersion in water (Cluett 2009)
6. Aromatherapy (Smith 2011a)
7. Relaxation techniques (yoga, music, audio)* (Smith 2011c)
8. Acupuncture or acupressure (Smith 2011b)
9. Manual healing methods including massage and reflexology* (Smith 2011d)
10. TENS (transcutaneous electrical nerve stimulation) (Dowswell 2009)
11. Inhaled analgesia (this review)
12. Opioids (Ullman 2010)
13. Non-opioid drugs (Othman 2011)
14. Local anaesthetic nerve blocks (Novikova 2011)
15. Epidural (including combined spinal epidural) (Anim-Somuah 2011; Simmons 2007)

Accordingly, this review only includes comparisons of inhaled analgesia with other inhaled analgesia or with: 1. placebo/no treatment; 2. hypnosis; 3. biofeedback; 4. sterile water injection; 5. immersion in water; 6. aromatherapy; 7. relaxation techniques (yoga, music, audio); 8. acupuncture or acupressure; 9. manual methods (massage, reflexology); or 10. TENS.

Interventions were any inhaled analgesia during labour such as isoflurane, enflurane methoxyflurane and nitrous oxide. We included any frequency or duration of administration, any dosage/intensity, any combinations of inhaled analgesia and any timing of labour (first, second or third stage).

Types of outcome measures

Primary outcomes

Effects of interventions

- Pain intensity (as defined by trialists) (Likert 1932)
- Satisfaction with pain relief (as defined by trialists) collected within 48 hours after birth
- Sense of control in labour (as defined by trialists)
- Satisfaction with childbirth experience (as defined by trialists)

Safety of interventions

- Effect on mother/baby interaction (skin-to-skin contact of mother and baby within the first hour of birth)
- Breastfeeding (at specified time points; within the first hour of birth, at discharge of the hospital)
- Assisted vaginal birth
- Caesarean section
- Side effects (nausea, vomiting, drowsiness, renal and hepatic toxicity, uterine relaxation)
- Admission to special care baby unit/neonatal intensive care unit (as defined by trialists)
- Apgar score less than seven at five minutes
- Need for rescue analgesia (mother or baby)
- Poor infant outcomes at long-term follow-up (as defined by trialists)

Other outcomes

- Cost (as defined by trialists)

Secondary outcomes

For the baby

- Differences in the one, two, five or 10 minute Apgar scores
- Neurological integrity scale of the newborn

For the professional

- Occupational exposure
- Toxic effects on reproduction

Search methods for identification of studies

Electronic searches

The Trials Search Co-ordinator was contacted to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2012).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched ClinicalTrials.gov, and Current Controlled Trials to identify ongoing trials (2 June 2012) using the search terms detailed in Appendix 1 and Appendix 2.

Searching other resources

We searched reference lists of identified studies and handsearched the conference proceedings from the *American Society of Clinical Anesthesia* (from 1990 to 2011). We also contacted content experts and trialists.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified through the search strategy. Any disagreement was resolved through discussion and, if there could not be achieved consensus, a third author was consulted.

Data extraction and management

A form was designed to extract data. For eligible studies, two review authors extracted the data using the agreed form. Discrepancies were resolved through discussion or, if required, by consulting a third author. Data were entered into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we contacted the authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor. To assess the risk of bias, the following items were evaluated:

(1) Random sequence generation (checking for possible selection bias)

The methods used to generate the allocation sequence were described for each included study in sufficient detail to allow an assessment of whether it should produce comparable groups.
The method were assessed as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

The methods used to conceal the allocation sequence were described for each included study and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
The methods were assessed as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding (checking for possible performance bias)

The methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received were described for each included study. Studies were considered at low risk of bias if they were blinded, or if was judged that the lack of blinding could not have affected the results. Blinding was assessed separately for different outcomes or classes of outcomes.
The methods were assessed as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

Partial blinding was used as an option because many of the administered inhaled analgesia cannot be completely blinded because of their odour. Partial blinding was also used for self-reported efficacy outcomes and when these outcomes are recorded by blinded personnel.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

The completeness of data including attrition and exclusions from the analysis were described for each included study and for each outcome or class of outcomes. Where attrition and exclusions were stated it was reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include the missing data in the analyses which we undertook. Methods were assessed as:

- low risk of bias (20% or less missing data);
- high risk of bias;
- unclear risk of bias.

(5) Selective reporting bias

How the possibility of selective outcome reporting bias was investigated and what was found was described for each included study (Sterne 2001).
The methods were assessed as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other sources of bias

Concurrent or prior use of analgesia was identified in the selected studies because the concurrent or prior use of analgesia can give some bias of the effects of the studied analgesia. Furthermore, any other important concerns about other possible sources of bias was described for each included study.
Each study was assessed whether the study was free of other problems that could put it at risk of bias:

- low risk of bias;
- high risk of bias;
- unclear risk of bias.

(7) Overall risk of bias

Explicit judgements were made about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). The likely magnitude and direction of the bias was assessed with reference to (1) to (6) above and whether it

was considered as likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

The following questions were considered for assessing risk of bias for cross-over trials.

- Was use of a cross-over design appropriate (Elbourne 2002)?
- Is it clear that the order of receiving treatments was randomised?
- Can it be assumed that the trial was not biased from carry-over effects? Inhaled analgesia has a relatively rapid uptake/washout effect. We take four exhalations as the safe cut-off point for no residual effect.
- Are unbiased data available (period effects)? Pain of uterine contractions are not consistent over time. The pain becomes more intense as the labour progresses until the start of delivery. Pain of the contractions change during the delivery of the baby. We looked for any control for labour progress at the start of the inhaled analgesia. If the start of the analgesia was not in the same stage of labour (in the active first stage after 3 cm dilatation) and second stage after 10 cm dilation until birth of the baby), we reported this risk of bias.

Measures of treatment effect

Dichotomous data

For dichotomous date, we presented results as summary risk ratio with 95% confidence intervals and, where relevant, as risk difference and number needed to treat either to benefit or to harm.

Ordinal data

Results of ordinal data were transformed to dichotomous data for analysis and described in the section on data analysis.

Continuous data

For continuous data, we used mean difference if outcomes were measured in the same way between trials. The standardised mean difference was used to combine trials that measured the same outcome, but used different methods. Where appropriate, we used standard inverse-variance random-effects meta-analysis to combine the trials (DerSimonian 2007). The method of Hozo 2005 was used to estimate the mean and variance from the median, range, and the size of the sample when the published reports of the included trials only reported the median, range and the size of trial.

Unit of analysis issues

Cross-over trials

Other unit of analysis issues

The appropriate analysis for continuous data from a two-period, two-intervention cross-over trial, a paired T-test was planned if neither carry-over, (a minimum of four exhalations with room air), nor period effects were thought to be a problem. This evaluates the value of 'measurement on experimental intervention (E)' minus 'measurement on control intervention (C)' separately for each participant. The mean and standard error of these different measures are the building blocks of an effect estimate and a statistical test. The effect estimate may be included in a meta-analysis using the generic inverse-variance method in RevMan 2011.

The simple formula of Hozo 2005 was used for small sample sizes below 25 participants to estimate the mean using the values of the median, low and high end of the range. The best estimator for sample sizes which exceeds 25 is the median itself. The known estimator Range/4 was used to estimate the standard variation for small sample sizes between 15 and 70 participants.

Dealing with missing data

Levels of attrition were noted for included studies. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

Analyses were carried out for all outcomes, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

Heterogeneity of treatment effects was measured between trials using the Chi^2 test and the I^2statistic (Deeks 2001; Higgins 2011), which describe the percentage of total variation across trials that is attributable to heterogeneity rather than to chance.

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If 10 or more studies had contributed data to meta-analysis for any particular outcome, we planned to investigate reporting biases (such as publication bias) using funnel plots. We would have assessed possible asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes, we would have used the test proposed by Egger 1997, and for dichotomous outcomes, we would have used the test proposed by Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

Statistical analysis were carried out using the Review Manager software (RevMan 2011). Fixed-effect meta-analysis was used for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, random-effects meta-analysis was used to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. Results were presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 where random-effects analysis was used.

Subgroup analysis and investigation of heterogeneity

If substantial heterogeneity was identified, for the primary outcomes, where data were available, we planned to carry out the following subgroup analyses.

1. Spontaneous labour versus induced labour.
2. Primiparous versus multiparous.
3. Term versus preterm birth.
4. Continuous support in labour versus no continuous support.
5. Mode of delivery: spontaneous vaginal, operative vaginal, mode of delivery mixed or unclear.
6. Different methods and doses of inhaled pain relief (inhalation agent regimen and doses).
7. Obese versus non obese women.

We also planned to look separately at results of studies in which a 50%/50% blend of N_2O and O_2 was self-administered by labouring women and distinguish the results of those studies from the results of studies in which:

a. the ratio of N_2O to O_2 was higher than 50%,
b. the ratio of N_2O to O_2 was lower than 50%,
c. the ratio of the gases could be changed by a professional,
d. the ratio could be changed by the labouring woman,
e. the ratio was 50%/50% but someone other than the woman who was inhaling it administered it to her.

We planned to assess differences between subgroups by interaction tests as described in the *Handbook* (Higgins 2011).

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, and for the cross-over trials as assessed by 'correct analyses for cross-over design used', with poor quality studies with high risk of bias being excluded from the analyses in order to assess whether this made any difference to the overall results. We planned to carry out sensitivity analyse for primary outcomes only.

RESULTS

Description of studies

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

Results of the search

A total of 54 reports of studies were identified from the search strategy. A total of 26 studies reporting data on 2959 women (31 reports) were included in this review (*see* Characteristics of included studies) and 21 studies (23 reports) were excluded (*see* Characteristics of excluded studies).

Included studies

Study design

Eighteen of the studies were parallel design (Abboud 1981; Abboud 1995; Arthurs 1979; Belfrage 1974; Cheng 2001; Einarsson 1996; Enrile 1973; Ji 2002; Jones 1969; Jones 1969a; MRC 1970; Rezaeipour 2008; Shao 2000; Stefani 1982; Swart 1991; Talebi 2009; Wang 1994; Zhang 2001) and eight cross-over design (Arora 1992; Bergsjo 1971; Carstoniu 1994; Chia 1990; McGuinness 1984; McLeod 1985; Wee 1993; Yeo 2007). One study had two parts (Chia 1990); the second part was a randomised cross-over study. For this study, we used only the data from the cross-over study (part II), and data were only available for the first period (before first cross-over). Two studies had three arms (Cheng 2001; Stefani 1982) and all the remaining studies had two comparison arms. We did not include the third arm of these two studies which were the control arms (no treatment). The main comparison groups included:

1. studies comparing one type of inhaled analgesia with another type of inhaled analgesia (Abboud 1981; Abboud 1995; Arora 1992; Belfrage 1974; Bergsjo 1971; Cheng 2001; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; Stefani 1982; Swart 1991; Wee 1993; Yeo 2007);

2. studies comparing the same types of inhaled analgesia of different strengths (Einarsson 1996; MRC 1970);

3. studies comparing the same types of inhaled analgesia using different delivery systems (Arthurs 1979; Enrile 1973);

4. studies comparing inhaled analgesia with placebo control/ no treatment (Carstoniu 1994; Cheng 2001; Ji 2002; Rezaeipour 2008; Shao 2000; Stefani 1982; Talebi 2009; Wang 1994; Zhang 2001);

5. and one study comparing inhaled analgesia with TENS (Chia 1990).

Sample sizes

Sample size in the included studies ranged from 18 (Wee 1993) to 509 patients (Talebi 2009).

Study location

The studies were conducted in the following locations: five studies were undertaken in the USA (Abboud 1981; Abboud 1995; Enrile 1973; Stefani 1982; Swart 1991); nine studies in the UK (Arora 1992; Arthurs 1979; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Wee 1993; Yeo 2007; two studies in Sweden (Belfrage 1974; Einarsson 1996); one study in Norway (Bergsjo 1971); one study in Canada (Carstoniu 1994); five studies in China (Cheng 2001; Ji 2002; Shao 2000; Wang 1994; Zhang 2001); one study in Singapore (Chia 1990); and two studies in Iran (Rezaeipour 2008; Talebi 2009).

Participants

One study recruited only women scheduled for induced labour (Talebi 2009) and one study only women in spontaneous labour (Arora 1992). Three studies recruited women in both spontaneous and induced labour (Chia 1990; Enrile 1973; Yeo 2007) and reporting on the onset of labour was unclear in the remaining studies. Fifteen studies recruited both primiparous and multiparous women (Abboud 1981; Abboud 1995; Arora 1992; Arthurs 1979; Belfrage 1974; Bergsjo 1971; Carstoniu 1994; Chia 1990; Einarsson 1996; Enrile 1973; Jones 1969; Jones 1969a; MRC 1970; Talebi 2009; Wee 1993); four studies recruited only primiparous women (Cheng 2001; Ji 2002; Rezaeipour 2008; Shao 2000); and in the remaining studies parity was not reported (McGuinness 1984; McLeod 1985; Stefani 1982; Swart 1991; Wang 1994; Yeo 2007; Zhang 2001). The interventions were administered at term in five studies (Cheng 2001; Ji 2002; Shao 2000; Talebi 2009; Yeo 2007) and term of birth was unclear in the remaining studies. The interventions were administered during the first stage of labour (until complete dilatation and before the urge of pushing started) for 16 studies (Arora 1992; Arthurs 1979; Bergsjo 1971; Carstoniu 1994; Cheng 2001; Chia 1990; Einarsson 1996; Ji 2002; McGuinness 1984; McLeod 1985; Rezaeipour 2008; Shao 2000; Talebi 2009; Wee 1993; Yeo 2007; Zhang 2001); in the second stage of labour (from the start of pushing until the baby is born) for six studies (Abboud 1981; Abboud 1995; Belfrage 1974; Enrile 1973; Stefani 1982; Swart 1991); in the first and second stages of labour in three studies (Jones 1969; Jones 1969a; MRC 1970); and stage of labour was unknown in one study (Wang 1994). Continuous support and obesity were not reported upon in any of the studies.

Types of intervention

Thirteen studies compared nitrous oxide 30% to 60% with a different form of inhaled analgesia (flurane derivatives): enflurane 0.25% to 1.25% (Abboud 1981; McGuinness 1984; Stefani 1982); desflurane 1.4% to 5% (Abboud 1995; Swart 1991); methoxyflurane 0.3% to 0.8% (Bergsjo 1971; Belfrage 1974; Jones 1969; Jones 1969a); sevoflurane 0.7% (Yeo 2007); isoflurane 0.2% to 0.75% (McLeod 1985; Cheng 2001); isoflurane 0.2% to 0.25% and nitrous oxide 50% (Arora 1992; Wee 1993). One study Belfrage 1974, studied nitrous oxide 70% with methoxyflurane 0.3% to 0.8%. Of these studies, in five the interventions were administered on a continuous basis (Abboud 1981; Abboud 1995; Jones 1969; Stefani 1982; Yeo 2007) and in seven on an intermittent basis (Arora 1992; Bergsjo 1971; Cheng 2001; Jones 1969a; McGuinness 1984; McLeod 1985; Wee 1993). In one study the method of administration was not reported (Swart 1991) and in one study it reported that the drugs were self-administered (Belfrage 1974).

In two studies nitrous oxide 50% was compared with nitrous oxide 70% ((Einarsson 1996; MRC 1970). In one of these studies the intervention was administered on a intermittent basis (Einarsson 1996) and in one study the administration was not reported (MRC 1970). In one study intermittent nitrous oxide 50% alone was compared with intermittent nitrous oxide 50% plus continuous nasal supplementation of nitrous oxide 50% (Arthurs 1979). In one study nitrous oxide 50% delivered via a Penthrane® Analgizer was compared with nitrous oxide 50% delivered via a Cyprane® inhaler (Enrile 1973).

Nine studies compared inhaled analgesia with placebo control/ no treatment (Carstoniu 1994; Cheng 2001; Ji 2002; Rezaeipour 2008; Shao 2000; Stefani 1982; Talebi 2009; Wang 1994; Zhang 2001). In five studies nitrous oxide 30% to 50% was compared with oxygen or compressed air (Carstoniu 1994; Cheng 2001; Rezaeipour 2008; Talebi 2009; Zhang 2001) and in four studies nitrous oxide 30% to 50% was compared with no treatment (Ji 2002; Shao 2000; Stefani 1982; Wang 1994).

One study compared nitrous oxide 50% with TENS (Chia 1990). *See* Characteristics of included studies.

Outcome measures

The following primary outcomes on effects of interventions were reported upon in the studies: pain intensity (linear analogue pain score - mean standard deviation (SD), LAS mean SD, mean pain intensity, visual analogue scale (VAS), WHO pain scale, Mulleetr's pain in labour scale) (Arora 1992; Arthurs 1979; Carstoniu 1994; Cheng 2001; Chia 1990; Ji 2002; McGuinness 1984; McLeod 1985; MRC 1970; Rezaeipour 2008; Shao 2000; Talebi 2009; Wang 1994; Wee 1993; Yeo 2007; Zhang 2001); satisfaction with pain relief (within 48 hours birth, after delivery) (Abboud 1981; Abboud 1995; Arthurs 1979; Belfrage 1974; Bergsjo 1971; Chia 1990; Jones 1969; Jones 1969a; MRC 1970; Rezaeipour 2008; Stefani 1982; Swart 1991). No study reported upon satisfaction with childbirth experience and no study reported upon sense of control in labour.

The following primary outcomes on safety of interventions were reported upon in the studies: assisted vaginal birth (Abboud 1995; Arora 1992; Belfrage 1974; Bergsjo 1971; Ji 2002; Jones 1969; McGuinness 1984; MRC 1970; Rezaeipour 2008; Stefani 1982; Yeo 2007); caesarean section (Arora 1992; Belfrage 1974; Bergsjo 1971; Enrile 1973; Ji 2002; McGuinness 1984; MRC 1970; Rezaeipour 2008; Yeo 2007; Zhang 2001); side effects (vomiting, amnesia, dizziness, nausea, hypoxaemia, post-partum haemorrhage, anoxia newborn, neonatal asphyxia) (Abboud 1981; Abboud 1995; Arora 1992; Arthurs 1979; Bergsjo 1971; Einarsson 1996; Enrile 1973; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Shao 2000; Swart 1991; Talebi 2009; Wang 1994; Wee 1993; Yeo 2007; Zhang 2001); admission to special care baby unit/neonatal intensive care (Chia 1990); Apgar score (Abboud 1981; Arthurs 1979; Belfrage 1974; Cheng 2001; Chia 1990; Enrile 1973; Jones 1969; Rezaeipour 2008; Stefani 1982; Talebi 2009; Wang 1994; Wee 1993; Ji 2002). No studies reported upon the need of rescue analgesia or upon effect on mother/baby interaction, breastfeeding or poor infant outcomes at long-term follow-up.

The only secondary outcome reported upon in the studies was neurological integrity scale of the newborn (Abboud 1995; Cheng 2001; Stefani 1982; Swart 1991). No study reported upon outcomes of the professionals attending the birth.

Excluded studies

We excluded 21 studies: *see* Characteristics of excluded studies. Six studies were not randomised controlled trials (Arozenius 1980; Chessor 2005; Cosmi 1969; Davies 1975; McAneny 1963; Roberts 1957) and five studies used quasi methods of randomisation (Arthurs 1981; Davies 1974; Major 1967; Rosen 1969; Rosen 1972). In two studies the studies were investigating the effect of general anaesthesia in women undergoing caesarean section and not during childbirth (Crawford 1975; Krantz 1974) and in three studies the comparison interventions are no longer used in practice (trichloroethylene; cyclopropane) (Major 1966; Phillips 1971; Shnider 1963). In five studies the comparison interventions were opioids, epidural or other multidrug interventions and therefore did not meet the inclusion criteria of this review according to the pain management hierarchy (Clark 1979; Creasser 1974; Howell 2001; Robinson 1980; Volmanen 2005).

Risk of bias in included studies

See Figure 1; Figure 2, for further details regarding 'Risk of bias' assessment.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

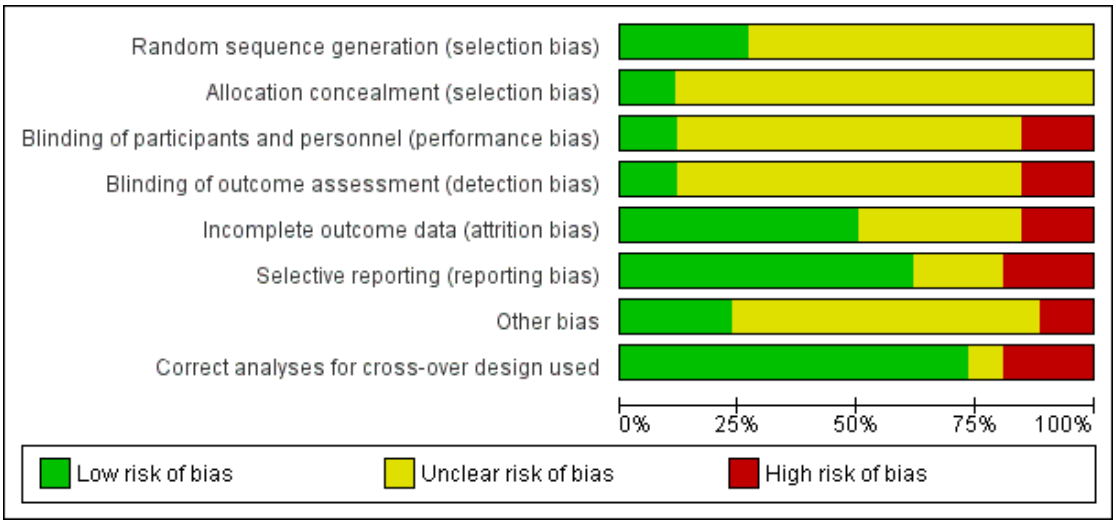
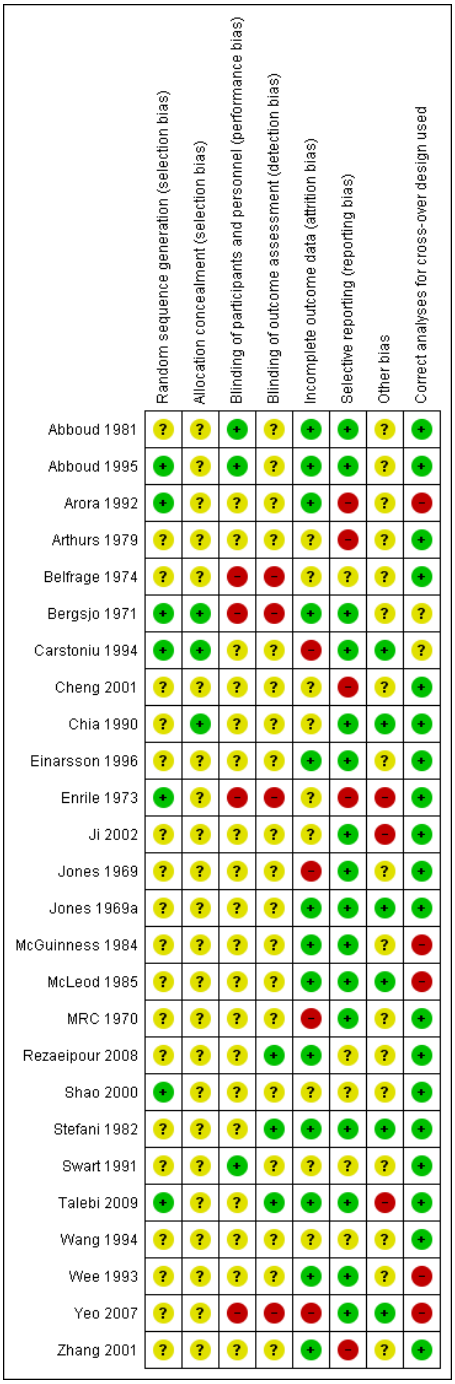


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Random sequence generation

Seven of the trials (27%) were rated as low risk of bias for sequence generation (Abboud 1995; Arora 1992; Bergsjo 1971; Carstoniu 1994; Enrile 1973; Shao 2000; Talebi 2009) and in the remaining trials the method of sequence generation was unclear (Abboud 1981; Arthurs 1979; Belfrage 1974; Cheng 2001; Chia 1990; Einarsson 1996; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Rezaeipour 2008; Stefani 1982; Swart 1991; Wang 1994; Wee 1993; Yeo 2007; Zhang 2001).

Allocation concealment

In only three studies (11%) was allocation concealment rated as low risk of bias (Bergsjo 1971; Carstoniu 1994; Chia 1990) and unclear in the remaining trials (Abboud 1981; Abboud 1995; Arora 1992; Arthurs 1979; Belfrage 1974; Cheng 2001; Einarsson 1996; Enrile 1973; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Rezaeipour 2008; Shao 2000; Stefani 1982; Swart 1991; Talebi 2009; Wang 1994; Wee 1993; Yeo 2007; Zhang 2001).

Blinding

Blinding of participants and personnel was at low risk of bias three studies (11%) (Abboud 1981; Abboud 1995; Swart 1991), high risk in four studies (Belfrage 1974; Bergsjo 1971; Enrile 1973; Yeo 2007) and unclear in the remaining studies (Arora 1992; Arthurs 1979; Carstoniu 1994; Cheng 2001; Chia 1990; Einarsson 1996; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Rezaeipour 2008; Shao 2000; Stefani 1982; Swart 1991; Talebi 2009; Wang 1994; Wee 1993; Zhang 2001).
Blinding of outcome assessment was at low risk of bias in three studies (Stefani 1982; Rezaeipour 2008; Talebi 2009) (9%), high risk in four studies (Belfrage 1974; Bergsjo 1971; Enrile 1973; Yeo 2007) and unclear in the remaining studies (Abboud 1981; Abboud 1995; Arora 1992; Arthurs 1979; Carstoniu 1994; Cheng 2001; Chia 1990; Einarsson 1996; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Shao 2000; Swart 1991; Wang 1994; Wee 1993; Zhang 2001).

Incomplete outcome data

Thirteen (50%) of the trials were rated as low risk of bias for incomplete outcome data (Abboud 1981; Abboud 1995; Arora 1992; Bergsjo 1971; Einarsson 1996; Jones 1969a; McLeod 1985 McGuinness 1984; Rezaeipour 2008; Stefani 1982; Talebi 2009; Wee 1993; Zhang 2001) and at high risk of bias in four (Carstoniu 1994; Jones 1969; MRC 1970; Yeo 2007). In the remaining studies risk of bias for incomplete outcome data was unclear (Arthurs 1979; Belfrage 1974; Cheng 2001; Chia 1990; Enrile 1973; Ji 2002; Shao 2000; Swart 1991; Wang 1994).

Selective outcome reporting

Sixteen (62%) of the trials were rated as low risk of bias for selective outcome reporting (Abboud 1981; Abboud 1995; Bergsjo 1971; Carstoniu 1994; Chia 1990; Einarsson 1996; Ji 2002; Jones 1969; Jones 1969a; McGuinness 1984; McLeod 1985; MRC 1970; Stefani 1982; Talebi 2009; Wee 1993; Yeo 2007) and at high risk of bias in five (Arora 1992; Arthurs 1979; Cheng 2001; Enrile 1973; Zhang 2001). In the remaining studies risk of bias for was unclear (Belfrage 1974; Rezaeipour 2008; Shao 2000; Swart 1991; Wang 1994).

Other bias

Six (23%) of the trials were rated as being at low risk of bias for 'other bias' (Carstoniu 1994; Chia 1990; Jones 1969a; McLeod 1985; Stefani 1982; Yeo 2007) and at high risk of bias in three studies (baseline imbalance including no information of prior or concurrent use of other analgesia; delivery systems for interventions not comparable) (Enrile 1973; Ji 2002; Talebi 2009). In the remaining 17 studies (65%), risk of bias for was unclear (Abboud 1981; Abboud 1995; Arora 1992; Arthurs 1979; Belfrage 1974; Bergsjo 1971; Cheng 2001; Einarsson 1996; Jones 1969; McGuinness 1984; MRC 1970; Rezaeipour 2008; Shao 2000; Swart 1991; Wang 1994; Wee 1993; Zhang 2001).

Cross-over trials

All eight cross-over trials randomised the order of interventions. Three studies (Arora 1992; Bergsjo 1971; Carstoniu 1994) were at low risk of bias for method of randomisation due to well described randomisation and five studies (Chia 1990; McGuinness 1984; McLeod 1985; Wee 1993; Yeo 2007) are with unclear risk of bias due to unclear description of randomisation.
In one study (Chia 1990), the study was divided into two parts: the first part was not randomised and the second part was a randomised cross-over trial. The data from the first period of the cross-over trial were used and analysed as a parallel trial. One study (McLeod 1985) had an adequate wash-out period of two contractions. Two studies (Arora 1992; Bergsjo 1971) used one contraction with air breathing between the two different agents, long enough to ensure an adequate four wash-out exhalation period. Three cross-over trials (Carstoniu 1994; McGuinness 1984; Wee 1993) reported no information on a wash-out period, but the inhaled analgesia were self-administered during contractions. This means that an adequate wash-out period of a minimum of four exhalations was met in the pause between two contractions. In the study by Yeo 2007, the wash-out period is unclear, due to

the fact that participants were given the option, if they wished, to omit the wash-out period of breathing room air over one contraction between the different agents. No information was given on how many participants took this option. However, the minimum wash-out period of four exhalations was probably met, due to the method of self-administering the inhaled analgesia in this study. It is very likely that the women will have rested for a moment between the contractions, probably without inhaling the agent.

The double cross-over design of Yeo 2007 and Wee 1993 included compensation for the progressive nature of labour and therefore are evaluated as a good and appropriate design. The five cross-over studies of Arora 1992; Bergsjo 1971; Carstoniu 1994; McGuinness 1984 and McLeod 1985 were all single cross-over studies but are believed to have an appropriate design due to the short duration of the intervention and comparison period (from three to five contractions in active part of labour). In these single cross-over studies progression of labour is not thought to be of influence.

All the eight cross-over studies (Arora 1992; Bergsjo 1971; Carstoniu 1994; Chia 1990; McGuinness 1984; McLeod 1985; Wee 1993; Yeo 2007) were carried out during the first stage in active (established) labour until 10 cm dilation or when women felt the urge to push (end of the first stage and start second stage). We were only able to obtain individual patient data from one study (Wee 1993) which appeared to be incomplete. We decided to use only the data of the first part of this study as a parallel group trial. The appropriate data necessary to include from a paired analysis were only available for the incidence of side effects from one study (Yeo 2007). However, because of concern over carry-over effects, outcome data for side effects for cross-over studies were not included in any analyses.

In two studies (McGuinness 1984; McLeod 1985), the Wilcoxon paired T-sample test was performed for the effect estimate of pain relief and pain intensity. No data were available on individual patients for the meta-analysis. It was not possible to extract the paired data from these two studies (McGuinness 1984; McLeod 1985). In five cross-over studies, continuous data on pain intensity or pain relief were reported (Arora 1992; McGuinness 1984; McLeod 1985; Wee 1993; Yeo 2007), and data were represented as mean/SD (Arora 1992) or median/range (McGuinness 1984, Yeo 2007) or mean/range (McLeod 1985) or individual VAS after one hour (Wee 1993) before the first cross-over. These data were available only for the whole experimental and comparison group periods separately and analysed as if the trials were a parallel group trial of experimental verus comparison. This statistical method is of high risk due to the conservative way that studies are under weighted, rather than over weighted (Elbourne 2002).

Correct analysis for cross-over design used

Five of the cross-over studies (63%) were rated as high risk of bias for 'correct analysis for cross-over design used' (Arora 1992; McGuinness 1984; McLeod 1985; Wee 1993; Yeo 2007).

Effects of interventions

We included data from 23 trials (2599 women) using different modalities of inhaled analgesia for pain management in labour for our meta-analyses. In three studies (Carstoniu 1994; Shao 2000; Wang 1994), data could not be included in the meta-analyses. In the Carstoniu 1994 study, data were not reported in a form that could be included in the meta-analyses (only in figures). In Shao 2000 and Wang 1994, the data are limited in the translation of the papers, which were not published in English. We included only the data of the first period before the first cross over for the Wee 1993 cross-over trial, because the data from the second and third periods were incomplete. Wee 1993 was analysed as if the trial was a parallel group study design. We used the data from the whole of each intervention period for the following four cross-over studies Arora 1992, McGuinness 1984, McLeod 1985 and Yeo 2007 and analysed the data as if it were from a parallel study. We did not combine results from parallel and cross-over studies in the analyses, but analysed these separately.

1) Inhaled analgesia nitrous oxide versus a different type of inhaled analgesia (flurane derivatives)

Primary outcomes

Effects of interventions

1.1) Pain intensity

Pain intensity was measured using a VAS from 0 to 100 mm, where 0 corresponds to no pain at all and 100 corresponds to the worst pain. Measurements were taken during the first stage of labour (until pushing occurred) and the data were reported as continuous data. Three studies with 123 measurements of 70 women (Analysis 1.1) reported on this outcome. The three studies were all cross-over trials with an adequate wash-out period of minimum of four exhalations. No period effect was present, because the trials started in active labour with regular contractions to 4 cm dilatation, during a period of three to five consecutive contractions (McGuinness 1984; McLeod 1985) to one hour (Wee 1993). We could not analyse the outcomes for the first period, before the first cross-over took place, because only the Wee 1993 study gave the individual patient data after correspondence with the trialist. The other two studies (McGuinness 1984; McLeod 1985) did not report on this first period and we did not succeed in contacting the trialist for the original data. The data for a paired analysis were not available. We decided to analyse the studies conservatively, as if the trials had a parallel group design, thereby under-estimating rather than over-estimating any differences between interventions.

There was substantial heterogeneity indicated by the I^2 statistics ($Tau^2 = 32.85$, $I^2 = 42\%$) and therefore we applied a random-effects model. The flurane derivatives group reported a lower intensity of pain compared with the nitrous oxide group (average mean difference (MD) 14.39, 95% confidence interval (CI) 4.41 to 24.37), Analysis 1.1.

1.2) Pain relief

Pain relief was measured using a VAS from 0 to 100 mm in the first stage of labour where 100 means the most relief. The highest score is the most positive contrary to 'pain intensity' in which the higher scores is more negative. Continuous data on pain relief of women in the first stage of labour were reported from two cross-over trials with 158 measurements of 70 women (Analysis 1.2). The two studies were both cross-over trials with no data available to use for paired analysis. We also decided to analyse these studies in the conservative way. There was substantial heterogeneity indicated by the I^2 statistics ($Tau^2 = 24.42$, $I^2 = 40\%$) and therefore, we applied a random-effects model. The Flurane derivatives group reported better pain relief compared with the nitrous oxide group (average MD -16.32, 95% CI -26.85 to -5.79).

1.3) Satisfaction with pain relief

Satisfaction with pain relief scores assesses to what extent women are satisfied with the form of pain relief, rather than scoring the extent of pain itself. Satisfaction of pain relief was measured during the first and second stages of labour as considerable to complete and reported as dichotomous data. A considerable to complete score means the women were satisfied with the amount of pain relief. It was reported in two studies with 98 women (Analysis 1.3). There was no difference in satisfaction with pain relief for women receiving methoxyflurane (continuous (mean 0.22%) or intermittent (0.35%)) compared with women receiving nitrous oxide (continuous (41.2%) or intermittent (50%)) (risk ratio (RR) 0.97, 95% CI 0.80 to 1.18).

1.4) Satisfaction with pain relief

This was measured during the second stage of labour as good to excellent and was reported in four studies with 323 women (Analysis 1.4). A good to excellent score means the women were satisfied with the amount of pain relief.There was no difference in satisfaction with pain relief for women receiving nitrous oxide (self-administered, intermittent or continuous) compared with women receiving an agent from the flurane derivatives group (self-administered or continuous) (RR 0.89, 95% CI 0.78 to 1.01).

No trials reported on the following outcomes: sense of control in labour and satisfaction with childbirth experience.

Safety of interventions

1.5) Assisted vaginal birth (vacuum extraction or forceps)

Numbers of assisted vaginal births are given in five studies (Abboud 1981; Abboud 1995; Belfrage 1974; Jones 1969; Stefani 1982) with 371 women (Analysis 1.5). There was substantial heterogeneity indicated by the I^2 statistics ($I^2 = 34\%$, $Tau^2 = 0.10$) and therefore, we applied a random-effects model. There were no differences in assisted vaginal births between women receiving nitrous oxide and those receiving a flurane derivative (average RR 0.71, 95% CI 0.44 to 1.15). All the trials were conducted in the second stage of labour.

1.6) Caesarean section

Caesarean section was reported in one trial (Belfrage 1974) with 98 women (Analysis 1.6). There were no caesarean sections in either group.

1.7) Amnesia

Amnesia in women, which was scored as a dichotomous outcome, was reported in three studies with 245 women (Analysis 1.7). There was significant heterogeneity indicated by the I^2 statistics ($I^2 = 74\%$, $Tau^2 = 2.76$) and therefore we applied a random-effects model. There was no difference in amnesia between groups with these three trials (average RR 0.26, 95% CI 0.03 to 2.38). We repeated the analysis excluding Abboud 1981 due to using a different flurane derivative, (enflurane instead of desflurane). In the remaining studies of Abboud 1995; Swart 1991, both using desflurane 0.1 to 4.5%, $I^2 = 0\%$, we applied a fixed-effects model. There was less amnesia in nitrous oxide group compared to desflurane group (RR 0.09, 95% CI 0.02 to 0.48).

1.8) Drowsiness

Drowsiness in women, which was scored with VAS, 0 to 100 mm, was reported in one study with 18 women (Analysis 1.8). There was no difference in drowsiness between the nitrous oxide group and the Isoflurane group (MD -11.64, 95% CI -16.04 to 39.32).

1.9) Nausea

Nausea in women, which was scored as a dichotomous outcome, was reported in two trials with 98 women (Analysis 1.9). The nitrous oxide group reported more nausea compared with the flurane derivatives group (RR 6.60, 95% CI 1.85 to 23.52).

1.10) Vomiting

Vomiting in women, which was scored as a dichotomous outcome, was reported in three trials with 203 women (Analysis 1.10). There was no difference in vomiting between nitrous oxide group compared with the flurane derivatives group (RR 2.02, 95% CI 0.75 to 5.46).

1.11) Blood loss

Blood loss in the third stage of labour, which was scored as a continuous outcome in ml, was reported in two studies with 185 women (Analysis 1.11). Data from Abboud 1995 were not reported in a form that could be included in the meta-analysis (mean without standard error). There was no difference in blood loss between groups (MD 6.0 ml, 95% CI -32.91 to 44.91, one trial, 105 women).

1.12) Apgar score less than seven at five minutes

Apgar scores of less than or equal to seven or less than seven at five minutes were reported in five trials with 373 women with single births (Analysis 1.12). There were no differences between groups, although each study used slightly different parameters. Abboud 1981; Belfrage 1974; Cheng 2001 and Stefani 1982 reported the percentages of babies in each group with Apgar scores less than eight at five minutes and Abboud 1995 reported the percentage of babies with Apgar scores less than seven at five minutes. Two babies were reported with an Apgar score of less than eight at five minutes postpartum in the Flurane derivatives group in one study (RR 0.22, 95% CI 0.01 to 4.47) and none in the nitrous oxide group. There were no low Apgar scores in the other five trials.

No trials reported on effect on mother/baby interaction or skin to skin contact of mother and baby within the first hour of birth; breastfeeding at specified time points, i.e. within the first hour of birth and at discharge of the hospital; admission to special care baby unit or neonatal intensive care unit; need for rescue analgesia for mother or baby; poor infant outcomes at long-term follow-up.

Other outcomes

No trials reported on any cost outcome.

Secondary outcomes

For the infant

1.13) Neurologic Adaptive Capacity Scores (NACS) lower than 35 at two hours after delivery

NACS were reported in three studies with 170 babies (Analysis 1.13). There were no differences in NACS between groups (RR 1.45, 95% CI 0.91 to 2.33).

No trials reported on differences in the one, two, five or 10 minute Apgar scores of the baby.

For the professional

No trials reported on differences in occupational exposure and toxic effects on reproduction for the professional.

2) Inhaled analgesia (same type) of one strength versus a different strength

Primary outcomes

Effects of interventions

2.1) Satisfaction with pain relief

Satisfaction with pain relief during the first stage of labour was scored on an ordinal scale as good to complete and reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.1). There was no difference in satisfaction with pain relief as good to complete between groups (RR 1.05, 95% CI 0.94 to 1.17).

2.2) Satisfaction with pain relief

Satisfaction with pain relief in the second stage of labour was scored on an ordinal scale as good to complete in one study with 501 women (Analysis 2.2). This study compared nitrous oxide 50% with nitrous oxide 70%. There was no difference in satisfaction with pain relief as good to complete between groups (RR 0.97, 95% CI 0.87 to 1.08).

No trials reported on effect on mother/baby interaction or skin-to-skin contact of mother and baby within the first hour of birth; breastfeeding at specified time points, i.e. within the first hour of birth and at discharge of the hospital; admission to special care baby unit or neonatal intensive care unit; need for rescue analgesia for mother or baby; poor infant outcomes at long-term follow-up; sense of control in labour; satisfaction with childbirth experience.

Other outcomes

No trials reported on any cost outcome.

Safety of interventions

2.3) Caesarean section

Caesarean section was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.3). There was no difference in caesarean section rate between groups (RR 0.31, 95% CI 0.06 to 1.53).

2.4) Assisted vaginal birth

Assisted vaginal birth was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.4). There was no difference in assisted vaginal birth rate between groups (RR 0.83, 95% CI 0.61 to 1.14).

2.5) Vomiting

Vomiting, scored as a dichotomous outcome, was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.5). There was no difference in vomiting between groups (RR 1.29, 95% CI 0.86 to 1.94).

2.6) Postpartum haemorrhage

Postpartum haemorrhage, which was scored as a dichotomous outcome and not defined (probably more than 500 mL blood loss due to being an English report and international standards), was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.6). There was no difference in postpartum haemorrhage between groups (RR 0.80, 95% CI 0.38 to 1.70).

2.7) Hypoxaemia in mother

Hypoxia of the mother, which was scored as a dichotomous outcome, was reported in one study of 24 women comparing nitrous oxide 50% with nitrous oxide 70% (Analysis 2.7). There was no difference in hypoxia of the mother between groups (RR 1.00, 95% CI 0.07 to 14.21).

Secondary outcomes

No trials reported on the following outcomes: differences in the one, two, five or 10 minute Apgar scores, neurological integrity scale of the newborn, occupational exposure and toxic effects on reproduction for the professional.

3) Inhaled analgesia using one type of delivery system versus a different system

Primary outcomes

Effects of interventions

3.1) Satisfaction with pain relief

Satisfaction with pain relief during the first stage of labour was scored on an ordinal scale as considerable to complete in one study with 42 women. The study compared nitrous oxide 50% with nasal supplement of nitrous oxide 50% versus nitrous oxide 50% and no supplement (Analysis 3.1). There was no difference in satisfaction with the pain relief between groups (RR 1.18, 95% CI 0.94 to 1.48).

Other outcomes

No trials reported on any cost outcome.

Safety of interventions

3.2) Caesarean section

Caesarean section was reported in one study with 26 women (Analysis 3.2). The study compared methoxyflurane delivered from a Penthrane® analgizer versus methoxyflurane delivered from a Cyprane® inhaler.There was no difference in caesarean section rate between groups (RR 2.60, 95% CI 0.12 to 58.48).

3.3) Vomiting (N2O/N2O with nasal supplement)

Vomiting, which was scored as a dichotomous outcome, was reported in one study with 49 woman (Analysis 3.3). The study compared nitrous oxide 50% with continuous nasal supplementation of nitrous oxide 50% versus nitrous oxide 50% with no inhalation. There was no difference in vomiting between groups (RR 1.76, 95% CI 0.77 to 4.00).

3.4) Vomiting (Penthrane® versus Cyprane®)

Vomiting, which was scored as a dichotomous outcome, was reported in one study with 26 women (Analysis 3.4). The study compared methoxyflurane delivered from a Penthrane® analgizer versus methoxyflurane delivered from a Cyprane® inhaler. There

was no difference in vomiting between groups (RR not estimable). There was no vomiting in either group.

3.5) Postpartum haemorrhage

Postpartum haemorrhage, which was scored as a dichotomous outcome probably scored above 500 mL blood loss due to the United States report and international standards, was reported in one study with 26 women (Analysis 3.5). The study compared methoxyflurane delivered from a Penthrane® analgizer versus methoxyflurane delivered from a Cyprane® inhaler. There was no difference in postpartum haemorrhage between groups (RR 0.29, 95% CI 0.01 to 6.50).

3.6) Mild pre-eclampsia

Mild pre-eclampsia was reported in one study with 26 women (Analysis 3.6). The study compared methoxyflurane delivered from a Penthrane® analgizer versus methoxyflurane delivered from a Cyprane® inhaler. There was no difference in mild pre-eclampsia between groups (RR 0.86, 95% CI 0.06 to 12.28).

3.7) Apgar score less than seven at five minutes (continuous data)

Apgar score at five minutes was reported in one study with 26 women with 14 observations in Analgizer group and 10 observations in Cyprane group. There were two missing observations in this Cyprane group (Analysis 3.7).The missing data could not be obtained from the original investigators.The study compared methoxyflurane delivered from a Penthrane® analgizer versus methoxyflurane delivered from a Cyprane® inhaler. There was no difference in Apgar scores between groups (MD 0.00, 95% CI -0.37 to 0.37). The two missing data of AS are assumed to be 'not missing at random'. At first we imputed these two missing data and assumed them to be poor outcomes with Apgars scores of six at five minutes. There was still no difference apparent (MD 0.50, 95% CI -0.30 to 1.30). Secondly we imputed these data as means of both nine for the missing data in the Cyprane group (MD 0.00 95% CI -0.35 to 0.35), and still no difference in Apgar Scores was found between groups.

3.8) Apgar score less than seven at five minutes (continuous data) N2O/N2O with nasal supplementation

Apgar score at five minutes was reported in one study with 49 women (Analysis 3.8). The study compared nitrous oxide 50% versus nitrous oxide 50% with nasal supplementation of nitrous oxide 50%. There was no difference of Apgar score between groups (MD -0.30, 95% CI -0.81 to 0.21).

Secondary outcomes

No trials reported on the following outcomes: differences in the one, two, five or 10 minute Apgar scores, neurological integrity scale of the newborn, occupational exposure and toxic effects on reproduction for the professional.

4) Inhaled analgesia versus placebo control/no treatment

Primary outcomes

Effects of interventions

4.1) Pain intensity (dichotomous)

Pain intensity during the first stage of labour reported as clear or severe to intense or extreme was reported in two studies with 310 women (Analysis 4.1). There was substantial heterogeneity indicated by the I^2 statistics (I^2 = 51%, Tau^2 = 1.08) and therefore we applied a random-effects model. The inhaled analgesia group of nitrous oxide 30% to 50% reported less pain compared with the control (O2 100%) or no treatment group (average RR 0.06, 95% CI 0.01 to 0.34).

4.2) Pain intensity (continuous)

Pain intensity in the first stage of labour reported with the VAS (VAS, 0-10) after one hour was reported in one study with 509 women (Analysis 4.2). The study compared nitrous oxide 50% versus oxide 50%. The nitrous oxide group reported less pain compared with the oxide group (MD -3.50, 95% CI -3.75 to -3.25).

Other outcomes

No trial reported on cost outcomes.

Safety of interventions

4.3) Assisted vaginal birth

Assisted vaginal birth was reported in one study with 200 women (Analysis 4.3). The study compared nitrous oxide 50% versus

no analgesic. There was no difference in assisted vaginal births between groups (RR 1.50, 95% CI 0.44 to 5.15).

4.4) Caesarean section

Caesarean section was reported in three studies with 465 women (Analysis 4.4). The studies compared nitrous oxide 30% to 50% versus no analgesia or oxygen 100%. There was no difference in caesarean section rate between groups (RR 1.20, 95% CI 0.75 to 1.91).

4.5) Vomiting

Vomiting, which was scored as a dichotomous outcome, was reported in two studies with 619 women (Analysis 4.5). The studies compared nitrous oxide 30% to 50% versus oxide 50% to 100%. The nitrous oxide group reported more vomiting compared with the oxide group (RR 9.05, 95% CI 1.18 to 69.32).

4.6 - 4.7 - 4.8) Nausea, dizziness and drowsiness

Dichotomous data on nausea, dizziness and drowsiness were reported in one study with 509 women (Analysis 4.6, Analysis 4.7, Analysis 4.8).The study compared nitrous oxide 50% versus oxygen 50%. The nitrous oxide group reported significantly more nausea (RR 43.10, 95% CI 2.63 to 706.74), dizziness (RR 113.98, 95% CI 7.09 to 1833.69) and drowsiness (RR 77.59, 95% CI 4.80 to 1254.96) compared with the oxygen group.

4.9) Neonatal asphyxia

Neonatal asphyxia, which was scored as a dichotomous outcome without definition, was reported in one study with 110 women (Analysis 4.9). The study compared nitrous oxide 30% to 50% versus oxygen 100%. There was no difference between groups (RR 1.11, 95% CI 0.26 to 4.73).

4.10) Apgar score the same or less than seven at five minutes

Apgar scores lower than eight at five minutes postpartum were reported in one study with 200 women (Analysis 4.10). The study compared nitrous oxide 50% versus no analgesic use. There were 4/100 low Apgar scores in the nitrous oxide group and none in the control group, with no difference between groups (RR 9.00, 95% CI 0.49 to 165.00).

4.11) Apgar score (continuous data at five minutes)

Apgar scores (continuous data) were reported in one study with 509 women (Analysis 4.11). The study compared nitrous oxide 50% versus oxygen 50%. There was no difference between groups (MD 0.00, 95% CI -0.13 to 0.13).

Secondary outcomes

No trials reported on the following outcomes: differences in the one, two, five or 10 minute Apgar scores, neurological integrity scale of the newborn, occupational exposure and toxic effects on reproduction for the professional.

5) Inhaled analgesia versus TENS

Primary outcomes

Effects of interventions

5.1) Satisfaction with pain relief

Satisfaction with pain relief in the first stage of labour was scored on an ordinal scale as partial to complete and was reported in one study with 20 women (Analysis 5.1). The study compared nitrous oxide 50% versus TENS. There was no difference between groups (RR 0.56, 95% CI 0.29 to 1.07).

5.2) Pain intensity first stage of labour, ordinal moderate to severe

Pain intensity in the first stage of labour was scored on an ordinal scale as moderate to severe was reported in one study with 19 women (Analysis 5.2). The study compared nitrous oxide 50% versus TENS. There was no difference between groups (RR 1.10, 95% CI 0.84 to 1.45).

Other outcomes

No trial reported on cost outcomes.

Secondary outcomes

No trials reported on the following outcomes: differences in the one, two, five or 10 minute Apgar scores, neurological integrity scale of the newborn, occupational exposure and toxic effects on reproduction for the professional.

Assessment of reporting biases

Due to the fact that there were not 10 or more studies (as we described in our protocol) in any meta-analysis, assessment of reporting biases (such as publication bias) was not appropriate.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were not carried out because a complete breakdown of the separate subgroup categories was not provided in the published articles.

Sensitivity analysis

Planned sensitivity analysis for studies of poor quality, as assessed by 'high risk of concealment of allocation' were not conducted because all studies were assessed as either low or unclear risk of bias for this item.

We could not conduct planned sensitivity analysis for the cross-over trials of poor quality, as assessed by high risk of bias of 'correct analysis for cross-over design used' because all studies were assessed as high risk of bias for this item.

DISCUSSION

Summary of main results

This review demonstrated that women in labour using flurane derivatives as inhaled analgesia during the first stage of labour reported better pain relief and less intense pain than nitrous oxide, and reported less nausea. However, these findings should be considered with caution because of the way we analysed the data from the cross-over studies. The cross-over studies did not provide data in the form of a correct paired analysis. We were therefore only able to include data in meta-analyses from the whole of each intervention period for four of the studies (Arora 1992; McGuinness 1984; McLeod 1985; Yeo 2007) and from the first period before cross-over for one study (Wee 1993). We therefore analysed the data from the cross-over studies as if they were parallel group trials. The results for flurane derivatives are based on data from 13 studies. However, there was a high level of heterogeneity for the analyses of pain relief and for intensity of pain, and so these results should also be examined with caution. Although we reported on drowsiness with regards to safety of the intervention, we also know that drowsiness is often seen as a beneficial side effect.

This review also demonstrated that women reported less pain intensity for intermittent (self-administered) nitrous oxide 50% when compared to no analgesia, during the first stage of labour and less intense pain intensity for intermittent (self-administered) nitrous oxide 50% when compared to oxygen 50% in the first stage of labour. More vomiting was observed with intermittent (self-administered) nitrous oxide 30% to 50% when compared to oxygen 50% to 100%, and more nausea, dizziness and drowsiness was observed with intermittent (self-administered) nitrous oxide 50% when compared to oxygen 50%. These results are based on data from three studies. There was a high level of heterogeneity for the analysis of pain intensity for nitrous oxide 50% versus no analgesia. Therefore, this result should also be examined with caution.

There were no significant differences found for any of the outcomes in the studies comparing one strength versus a different strength of inhaled analgesia, in studies comparing different delivery systems or in the study comparing inhaled analgesia with TENS.

All these conclusions need to be considered in the context of small sample sizes (range 27 to 320); only three trials achieved a sample size of more than 200; blinding to the intervention was hardly possible in many studies, due to the smell of the agent; and many outcomes were only considered in one or two trials in specific groups of comparison. These factors limit the interpretation of the results.

A sensitivity analysis was planned in order to explore the impact of excluding the cross-over trials, assessed as being at a high risk of bias for the item 'correct analysis for cross-over design used', to see if this would make a difference to the overall results. We could not perform this analysis for 'pain intensity' or 'pain relief' because these analyses only included cross-over trials and all of these were at high risk of bias for 'correct analysis for cross-over design used.' The majority of cross-over trials were analysed as if they were parallel group trials, using the data from the overall outcome of the intervention versus the overall outcome of the comparison agent. This statistical method is at high risk of bias due to the conservative way, that studies are under weighted rather than over weighted (Elbourne 2002).

Overall completeness and applicability of evidence

The completeness and applicability of the evidence is limited from the 26 included trials, with no trial at a low risk of bias on all domains. A weakness of a number of the trials is the inclusion of relatively few outcomes and for all trials omission of clinical safety outcomes for the professional. Although almost all participants across the included trials were considered at low risk of complications because of the following exclusion criteria within the individual trials: major uterine abnormalities, multiple gestation, cardiovascular or respiratory instability and acute or chronic obstetric pathologies such as pre-eclampsia and mostly participants in spontaneous labour, one trial (Chia 1990) explicitly included nulliparous with induced labour in the second part of the study, which was randomised. This trial (Chia 1990) is the only trial in the comparison group 'Inhaled analgesia versus TENS' and therefore,

it was not possible to assess for subgroup differences. There were also no significant differences found between inhaled analgesia of nitrous oxide 50% and TENS for the two outcomes analysed. In 19% of the trials prior or additional use of other analgesia was an exclusion criteria (Carstoniu 1994; Chia 1990; McLeod 1985; Rezaeipour 2008; Talebi 2009). In 50% of the trials additional or prior use of other analgesia was unclear (Abboud 1981; Abboud 1995; Arora 1992; Cheng 2001; Einarsson 1996; Ji 2002; MRC 1970; Shao 2000; Swart 1991; Wang 1994; Wee 1993; Yeo 2007; Zhang 2001). In 31% of the trials prior or additional use of other analgesia was available and used by the participants but not controlled for in the analysis of the effect estimate. Due to the fact that use of other analgesia can influence women's perception of the use of inhaled analgesia, results must be taken with caution.

The findings of this review may not be applicable to current practice due to the differences in obstetric care in different countries worldwide, especially for low-risk women. Nitrous oxide is relatively inexpensive, has no pungent smell and is easy to administer by the women themselves with the right equipment and circumstances. It can also be used in primary care which means labouring women under supervision of primary care midwives or general practitioners. These births can take place either in a hospital, in a birthing centre or at home.

Inhaled analgesia from the flurane derivatives are also relatively inexpensive depending on which agent is used. They may be more expensive if the agent still has a patent. However, administration of these agents needs to be controlled by a well trained anaesthesia professional in order to ensure the right concentration of the agent and thus prevent unconsciousness or other administration problems. This is probably the main reason why use of flurane derivatives is not widespread and also why little research is done on this form of inhaled analgesia for the management of labour pain.

Quality of the evidence

The 'Risk of bias' tables (Figure 1; Figure 2) demonstrate that inhaled analgesia has not been consistently subjected to consistent rigorous study. The quality of reporting was poor in over 50% of trials. The risk of bias was low in respect of randomisation (27% and 11%). In all the other trials randomisation was unclear. Not one trial was rated at a low risk of bias on all domains. For many studies, blinding of participants and personnel was not possible because of the different smells of different agents and the use of different apparatus. In many studies there was no information on blinding, and reporting indicated that the influence on the outcomes was unclear, with only 11% of the trials being at low risk of this bias. In 50% of the trials, the rates of follow-up were high, with only a small number of trials reporting a relatively substantial loss of participants. The small numbers of trials within comparisons and lack of high-quality trials suggests there remains insufficient evidence of a consistent treatment effect from inhaled analgesia. We contacted some authors of trials in order to request additional methodological and statistical information. However, only one author responded (Wee 1993).

The quality of evidence was affected by unexplained heterogeneity in some comparisons arising from both the heterogeneity of the clinical interventions, outcome assessments, and study designs. The small numbers of trials within comparisons, and lack of high-quality trials prevented further exploration of heterogeneity to assess its impact on treatment effects.

It is questionable whether the findings of the old study of Enrile 1973 can still be generalised to the current situation. Any paper from 1973 that looks at caesarean section rate and postpartum haemorrhage from a generation ago has to now be interpreted in the context of a period when the caesarean section rate was less than 10%, as well as many other changes to clinical practice.

Potential biases in the review process

We attempted to minimise publication bias. The search was comprehensive and there were no language restrictions. However, some of the articles were in Chinese and Iranian, and although these were translated, it is not possible to rule out the possibility of missed data. The variation in the duration, concentration, administration and concurrent or prior use of other analgesia suggest that inhaled analgesia may not have been therapeutically effective and in some cases may not represent best clinical practice.

Agreements and disagreements with other studies or reviews

There is no other systematic review with meta-analysis of inhaled analgesia. Nevertheless, there is one other systematic review without meta-analysis of nitrous oxide as inhaled analgesia for relief of labour pain (Rosen 2002). Rosen 2002 included studies that were excluded from this review because we were unable to ascertain the randomisation details or because the trial did not meet our eligibility criteria. Nevertheless, our findings and conclusions concerning the role of inhaled analgesia for the comparisons of nitrous oxide for pain relief in labour are similar (Rosen 2002). Rosen 2002 suggests that inhaled analgesia offers safe, reasonably effective pain relief for many women. However, our review also highlights some of the adverse effects (such as nausea and drowsiness) associated with some types of inhaled analgesia such as nitrous oxide with our meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Despite limitations in the 'Risk of bias' assessment of the randomised clinical trials with regards to trial design and representation of the results in the papers, the statistically significant results for reduction in pain intensity and increase in pain relief indicates that inhaled analgesia may be a useful form of pain management for some women in labour. Inhaled analgesia may be beneficial for those women in labour who want to have some form of pharmacological pain relief, without invasive methods. It was not possible to draw any conclusions in relation to poorer outcomes for the newborns or the mothers due to a paucity of evidence.

Implications for research

Further randomised controlled trials should be adequately powered and include relevant clinical outcomes as described in this review especially for three primary outcomes: 1) sense of control in labour and 2) satisfaction with childbirth and 3) breastfeeding experience of women. Particularly studies without the confounding factor of co-administration of other analgesia, would be very helpful. Moreover, there is a need for improving the quality and relevant, uniform reporting of future cross-over trials to make these trials useful to incorporate in a systematic review. It is highly desirable that authors report the results from each treatment in each period separately (Elbourne 2002). Cost-benefit analysis should be incorporated, whenever possible, into the design of future studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abboud 1981

Methods	Randomised control trial conducted in Department of Obstetrical Anesthesia, University of Southern California, Los Angeles, California, USA
Participants	105 participants, 50 in the experimental group and 55 in the controls Inclusion criteria: healthy parturients undergoing normal delivery
Interventions	Experimental group received continuous 30% to 60% N2O titrated by an anaesthesiologist, while control group received continuous Enflurane 0.25% to 1.25% based on anaesthesiologist titration, mean 0.5%, both during second stage of labour
Outcomes	Satisfactory pain relief and use again for future delivery, Total blood loss, fluoride levels serum and urine, Apgar score, cord blood gases, values for biochemical findings in maternal blood and urine and in neonatal urine
Notes	Not controlled for concurrent or prior use other analgesia.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant and clinician are both unaware of which drug is administered
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Both groups comparable but not controlled for prior or concurrent use of other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over design.

Abboud 1995

Methods	Randomised control trial conducted in Department of Anesthesiology, Los Angeles County and University of Southern California Medical Center, Los Angeles, California, USA
Participants	80 participants, 40 in each group. Inclusion criteria: healthy parturients undergoing normal vaginal delivery Exclusion criteria: any clinical significant history of gastrointestinal hepatic, renal, endocrine or respiratory disease, convulsive or neurological disorder, fetal distress, any history of chronic alcohol or drug use
Interventions	Experimental group received Desflurane 1% to 4.5% and oxygen during second stage of labour, while control group received nitrous oxide, 30% to 60% oxygen during second stage of labour
Outcomes	Patient, anaesthesiologist and obstetrician assessment of quality of pain relief. Patient willingness to receive again the same agent. Blood loss estimated the obstetrician, Apgar score at 1 and 5 minutes, cord acid base status and NASC at 2 and 24 hours of age of the baby, Hb, Ht, before use of analgesia and after 12 and 24 hours postpartum, osmolality and sodium ion concentrations of urine of the mother at the same time postpartum
Notes	No information regarding concurrent or prior use of analgesia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using computer generated randomisation table
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patient, obstetrician and paediatrician unaware of drug.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Both groups comparable but not controlled for prior or concurrent use of other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over design.

Arora 1992

Methods	Single cross-over study conducted in Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK
Participants	39 participants, 20 in the experiment group and 19 in the controls Inclusion criteria: patients in normal labour with regular painful uterine contractions who required inhalation analgesia.
Interventions	Experimental group received Entonox-isoflurane 0.25%, while control group received Entonox (50% nitrous oxide premixed in oxygen) in first stage of labour during 5 consecutive contractions
Outcomes	Pain relief, patient's responsiveness, patient's cooperation, reaction to odour and any adverse effects
Notes	6^{th} contraction wash-out period with room air (supposed to be minimal 4 exhalation) Afterwards trial there was use of other anaesthetics during labour No information regarding concurrent or prior use of analgesia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number sequence.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The Oxford Miniature Vaporizer (OMV) was concealed in a box from the view of both investigator and mother but 1 agent has a particular smell (blinding not possible), unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women, unable to come to any decision on a linear analogue scale scores for pain relief
Selective reporting (reporting bias)	High risk	Baby outcomes not clear.
Other bias	Unclear risk	None apparent but not controlled for prior or concurrent use of other analgesia
Correct analyses for cross-over design used	High risk	Paired samples using Wilcoxon Rank Sum Test but mean/SD for experimental intervention alone and control (intervention)

		alone, not possible to extract paired data

Arthurs 1979

Methods	This trial was conducted in Maelor General Hospital, Wrexham, UK. 3 studies were conducted in this trial: Kinetic studies: observational study, the expired concentration of nitrous oxide was measured and recorded continuously with a mass spectrometer to measure the maximum concentrations and the end-tidal nitrous oxide concentration and its effects on mothers and babies Within patient studies: observational study to measure patient preference. Between patient studies: randomised trial, comparing self-administration of Entonox with a nasal supplement of Entonox with self-administration of Entonox with no nasal supplement for the evaluation of pain, mothers opinion, midwives opinion, acceptability of nasal catheter and maximum tolerable flow
Participants	49 participants 24 in the study group and 25 in the control group
Interventions	Experiment group received self-administered Entonox and continuous nasal supplement of Entonox and controls received self-administered Entonox and no continuous nasal inhalation, probably during first and second stage of labour ("recording until delivery")
Outcomes	Pain on linear analogue after 2, 4, 6 contractions, pain rated immediately after delivery and between 24 and 48 hours later, how much inhalation helped, satisfaction with pain relief (memory of pain in labour), nausea and vomiting, caesarean section, Apgar score - mean at 1 and 5 minutes, pain relief as assessed by midwives
Notes	Only data from between patient studies used in this review. Opiods also available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Arthurs 1979 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	High risk	Pain data after 6 contractions and immediately after delivery not reported
Other bias	Unclear risk	Baseline characteristics seems comparable but other opioids also available and no information of the use of these other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over design.

Belfrage 1974

Methods	Randomised trial conducted in Karolinska Sjukhuset Hospital, Stockholm, Sweden
Participants	98 participants, 47 in the experiment group and 51 in the control group
Interventions	Experiment group received 0.3% to 0.8% of Methoxyflurane and controls received nitrous oxide 70% with 30% oxygen in second stage of labour
Outcomes	Pain scores, assisted vaginal birth, caesarean section.
Notes	Concurrent or prior use of pethidine.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Women were randomly divided into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Women were randomly divided into 2 groups.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear from translation.

Belfrage 1974 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unclear from translation.
Other bias	Unclear risk	No baseline characteristics and concurrent use of pethidine in both groups
Correct analyses for cross-over design used	Low risk	Not cross-over design.

Bergsjo 1971

Methods	Randomised single cross-over trial conducted in Aker Hospital Oslo, Norway
Participants	63 participants, 26 in the experiment group and 37 in the control group Inclusion criteria: women in established labour with obvious pain and expected labour to be normal Exclusion criteria: history of liver and kidney disease.
Interventions	Experimental group received Nitrous oxide mixed with oxygen in 50% concentration inhaled intermittent, followed by methoxyflurane, while control group received first 0. 5% to 0.8% methoxyflurane, inhaled intermittent, followed by nitrous oxide/oxygen 50% in first stage of labour during 3 consecutive contractions
Outcomes	Drug of preference, degree of analgesic effect, unpleasant subjective side effects, other side effects scored by observer, Apgar scores, total labour time and additional drugs needed after the trial stopped
Notes	A wash-out period of 1 contraction with air breathing. Concurrent or prior use of opioids or diazepam.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A list of random numbers.
Allocation concealment (selection bias)	Low risk	List of random numbers to decide in which order the drugs are given owned by office personnel, not seen by the doctors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Entonox is inhaled through anaesthetic face masks working by inhaled flow, and methoxyflurane is inhaled by a specially made Analgizer which is a cylindrical tube with a mouthpiece

Bergsjo 1971 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Entonox is inhaled through anaesthetic face masks working by inhaled flow, and methoxyflurane is inhaled by a specially made Analgizer which is a cylindrical tube with a mouthpiece
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants did not scored their preference.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	1 group older, but should have no impact on results, prior or concurrent use of opioids or diazepam
Correct analyses for cross-over design used	Unclear risk	Single cross-over design.

Carstoniu 1994

Methods	Single cross-over randomised trial conducted in Toronto Hospital, Toronto, Ontario, Canada
Participants	26 participants, 14 in the experimental group and 12 controls Exclusion criteria: age < 18 years, maternal cardiorespiratory disease, fetal distress, any condition affecting the accuracy of pulse oximetry or the use of opioids or regional anaesthesia
Interventions	Experimental group received self-administered 50% nitrous oxide and oxygen for 5 consecutive contractions. For the next 5 contractions compressed air was self-administered. Control group received same gases in reverse order. Used in first stage of labour
Outcomes	VAS pain scores, the lowest Spo2 (maternal haemoglobin oxygen saturation) observed after a contraction, ability correctly to identify the order of the gases in the 2 groups, only reported in figures
Notes	No wash-out period (comparison with compressed air). No concurrent or prior use of other analgesia.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes.

Carstoniu 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Valves hidden from participants but nurses are the ones hiding it and who open randomisation envelope
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded for not completing the trial.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Both groups comparable.
Correct analyses for cross-over design used	Unclear risk	Data for paired groups only in figures, not possible to extract paired data

Cheng 2001

Methods	Randomised controlled trial conducted in Third Affiliated Hospital, Henan Medical University, Zhengzhou, China
Participants	75 participants, 25 in each group. Inclusion criteria: healthy full term 22-30 years old singleton vertex presentation primipara
Interventions	Group 1 received isoflurane 0.2% to 0.75% and oxygen. Group 2 received nitrous oxide 30% to 50% and oxygen. Group 3 - controls - received air.
Outcomes	Pain intensity - effectiveness of inhalation analgesia, duration of each stage of labour, mode of delivery, postpartum haemorrhage, gas analysis of neonatal umbilical artery and vein, Apgar score and NACS
Notes	Concurrent or prior use of other analgesia not known.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Cheng 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Semi-closed anaesthetic method.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Semi-closed anaesthetic method.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	High risk	Data on pain intensity and mode of delivery reported upon in another article which was not referenced
Other bias	Unclear risk	No baseline characteristics and prior or concurrent use of other analgesia unknown
Correct analyses for cross-over design used	Low risk	Not cross-over design.

Chia 1990

Methods	This study was conducted in National University Hospital, Singapore in 2 parts. Part I is a quasi-randomised trial and part II is a cross-over trial, first period data available
Participants	20 participants, 10 in each group. Inclusion criteria were nulliparous who were to have surgical induction of labour and exclusion criteria included desire for epidural analgesia, in advanced labour or given any other form of analgesia
Interventions	Group C received TENS and group D received Entonox (a switch over of the modes of pain relief was made when labour pain was no longer tolerable; patient using TENS was commenced on Entonox and vice versa). Any use of wash-out time or time indication of switch-over period not reported
Outcomes	Pain intensity, satisfaction with pain relief (nil, partial, complete), birthweight admission to NICU and Apgar score
Notes	Only data from part II trial used in this review. Any information of wash-out period is not reported No prior or concurrent use of other analgesia (excluded).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised.

Chia 1990 (*Continued*)

Allocation concealment (selection bias)	Low risk	"randomly allocated by use of sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Both groups are comparable, no use of other analgesia.
Correct analyses for cross-over design used	Low risk	Only use of part II, this part is a randomised controlled trial (parallel groups)

Einarsson 1996

Methods	Randomised controlled trial conducted in Dept Obstetrics and Gynaecology, Sahlgrenska University Hospital, Sweden
Participants	24 participants, 12 in each group. Inclusion criteria: women undergoing vaginal delivery. Exclusion criteria: maternal cardiorespiratory disease, pre-eclampsia, any evidence of fetal distress or used opioid or regional analgesia
Interventions	Experimental group received 50% nitrous oxide and control group received 70% nitrous oxide
Outcomes	Inspiratory and end-tidal (E') concentrations of carbon dioxide (CO_2), oxygen and nitrous oxide, pulse oximetry (Spo_2) respiratory rate, tidal volume and expiratory minute ventilation volume (V_E).
Notes	No information regarding use of prior or concurrent other analgesia, but presumably not because intervention started when women first requested analgesia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Allocated randomly.

Einarsson 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Both groups comparable but no information of use of other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Enrile 1973

Methods	Randomised controlled trial conducted in Cleveland Metropolitan General Hospital, Cleveland, Ohio, USA
Participants	26 participants, 14 in the experiment group and 12 in the controls Inclusion criteria: American Society of Anaesthesiologists classification of physical status (ASA) Class 1 or 2
Interventions	Both groups received Methoxyflurane but the experiment group used Analgizer while controls used Cyprane Inhaler
Outcomes	Cord blood PH, Methoxyflurane concentration in maternal blood, Apgar score (2 missing in Cyprane group), orientation, motor co-ordination, level of analgesia, level of amnesia, caesarean section, satisfaction with analgesia, nausea and vomiting
Notes	Inhaler and pudendal block possible (7p in Cyprane, 7p in Penthrane), and spinal (3p in Cyprane, 5p in Penthrane)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Enrile 1973 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported but both delivery systems completely different from each other
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported but both delivery systems completely different from each other
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported. 2 missing in Cyprane group for Apgar score is less than 20% (low risk of bias)
Selective reporting (reporting bias)	High risk	Some of outcomes incompletely reported upon -results reported for only 1 of the groups, e.g. evaluation of pain, satisfaction pain relief, nausea and vomiting
Other bias	High risk	The patients utilising a mask attached to the analgizer obtained better pain relief than those using the analgizer without a mask because the diluter hole in the analgizer was left open during administration resulting in a lower concentration of Methoxyflurane available for inhalation
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Ji 2002

Methods	Randomised controlled trial conducted in Qingdao Municipal Hospital, Qingdao, China. From January 2001 to November 2001
Participants	300 participants, 100 in each arm. Inclusion criteria: primiparous with single fetus, no significant cephalopelvic disproportion, with no contraindications to anaesthesia
Interventions	Group 1 received combined spinal epidural analgesia. Group 2 received 50% nitrous oxide and 50% oxygen, at a rate of 0-15 L every minute Controls received no treatment.
Outcomes	Analgesic effect, duration of labour, method of delivery, postpartum bleeding, rate of newborn anoxia, maternal radial artery blood for blood gas analysis and fetal umbilical blood for blood gas analysis
Notes	Only data from group 2 (nitrous oxide) versus control included in this review Control group did not receive any analgesia, no information regarding prior or concurrent use of other analgesia in nitrous oxide group

Ji 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated as per translation.
Allocation concealment (selection bias)	Unclear risk	Not stated as per translation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated as per translation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated as per translation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated as per translation.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	High risk	No baseline characteristics, no information of use of other analgesia in nitrous oxide group
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Jones 1969

Methods	Randomised control trial conducted in Department of Anaesthetics, Royal Infirmary, Cardiff, UK
Participants	48 participants, 24 in each group. Inclusion criteria: normal labour. Exclusion criteria: received instruction in psychoprophylaxis or hypnosis
Interventions	Experimental group received methoxyflurane continuous, while control group received nitrous oxide continuous
Outcomes	Efficacy assessment by 4-point scale just after delivery, nausea during labour (intrapartum or first 24 hours), vomiting, dreams and Apgar score 1 minute
Notes	Prior use of pethidine in the 4 hours preceding the beginning of inhalation (11p N2O-group, 14p meth.-group),
Risk of bias	

Jones 1969 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random basis.
Allocation concealment (selection bias)	Unclear risk	Random basis.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 mothers not questioned after birth because of stress (abnormal child and severe nausea and vomiting).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Both groups comparable but use of pethidine as analgesia prior
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Jones 1969a

Methods	Randomised control trial conducted in Department of Anaesthetics, Royal Infirmary, Cardiff, UK
Participants	50 participants, 25 in each group. Inclusion criteria: normal labour. Exclusion criteria: received instruction in psychoprophylaxis or hypnosis
Interventions	Experimental group received self-administered intermittent N2O 50%, while control group received self-administered intermittent methoxyflurane 0.35%
Outcomes	Assessment of efficacy by 4-point scale just after delivery, nausea, vomiting, hazy memory, noted the smell of the gas, dreams, numbness or buzzing in the ears or 'pins and needles', Apgar score 1, 2, 5 and 10 minutes
Notes	Concurrent or prior use of pethidine (64% meth. group, 68% N2O group)

Risk of bias

Bias	Authors' judgement	Support for judgement

Jones 1969a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Random basis.
Allocation concealment (selection bias)	Unclear risk	Random basis.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Low risk	Both groups comparable (also comparable in prior use of pethidine)
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

McGuinness 1984

Methods	Randomised cross-over trial conducted in Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff, UK
Participants	20 participants, 20 measurements for each intervention, total 40 measurements Inclusion criteria: fit women who were in early normal labour
Interventions	Experimental group received enflurane during 3 consecutive contractions (no wash-out time used), while control group received Entonox (50% N2O and 50% O2) during 3 consecutive contractions
Outcomes	Pain assessment with linear analogue scale, drowsiness and nausea by linear analogue scale
Notes	No wash-out time between agents. Concurrent or prior use of opioids before or during use of N2O

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.

McGuinness 1984 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Randomly given 1 of the analgesic agents. Not described how.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The orientation of the tap (agents delivered via the same tubing and mouthpiece) was concealed from the operator Different odour of agents, not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Both groups comparable, prior or concurrent use of pethidine in 1 group
Correct analyses for cross-over design used	High risk	Linear analogues scales were compared with the Wilcoxon matched-pairs signed-rank test, but no data of individual patients. Overall median/range of experimental group and comparison group separately, not possible to extract paired data

McLeod 1985

Methods	Randomised cross-over trial conducted in Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK
Participants	32 participants with 31 measurements of entonox and 31 measurements of isoflurane Inclusion criteria: in ASA 1 group (completely healthy patient), in normal established labour, requiring analgesia Exclusion criteria: receiving any other analgesic or sedative agent during labour
Interventions	Experimental group received Isoflurane 0.75% during 5 consecutive contractions in first stage of labour (with a break of 2 contractions to allow of elimination of the first agent) , while control group received nitrous oxide during 5 consecutive contractions in first stage of labour
Outcomes	Linear analogue scores for pain measured before starting the trial (0 point) and after each contraction, drowsiness measured after the 5 contractions of each agent, comment of both analgesics and patients preference after delivery

McLeod 1985 (*Continued*)

Notes	Wash-out period of 2 contractions. No concurrent or prior use of opioids (were excluded). Total 31 measurements of Entonox and total 31 measurements of Isoflurane, in total 62 measurements, unknown why not 64 measurements, probably one women did not completed the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomized', not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 because of smell of isoflurane.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Low risk	Both groups comparable.
Correct analyses for cross-over design used	High risk	Pain scores were compared using the Wilcoxon rank sum test for paired samples but no data of individual patients. Overall mean/range of experimental and comparison group separately, not possible to extract paired data

MRC 1970

Methods	Randomised trial conducted in 7 hospitals: Aberdeen Maternity Hospital, Cardiff Royal Infirmary and Maternity Hospital, Simpson Memorial Maternity Pavilion (Edinburgh) , Hammersmith Hospital, Kingsbury Maternity Hospital, Kingston Hospital and Westminster Hospital
Participants	601 participants, 259 in the experiment group and 242 in the control group Exclusion criteria: multiple birth expected or if special delivery procedures were likely to be needed

MRC 1970 (*Continued*)

Interventions	Experimental group received intermittent 50% nitrous oxide, while control group received intermittent 70 % nitrous oxide
Outcomes	Pain assessment , drowsiness and nausea, dreams, side effects
Notes	No information regarding concurrent or prior use of other analgesia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	21 were excluded from the initial analysis, 12 because they had given birth to twins and 9 because the information on the forms was incomplete. Also 277 cases were excluded from the main analysis, some being rejected for more than 1 reason
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Both groups comparable but no information of prior or concurrent use of other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Rezaeipour 2008

Methods	Randomised controlled trial conducted in Orumieh Hospital, Tehran, Iran
Participants	155 participants, 78 in the experiment group and 77 in the control group Inclusion criteria: primipara, 18-35 years of age, not have used any anaesthesia, not for inducing labour. With no restrictions in using Entonox (due to respiratory problems, pneumothorax, and trauma to the head in the past) and have dilated 4 cm

Rezaeipour 2008 (*Continued*)

	Exclusion criteria: any complications during labour and delivery and the need to induce labour
Interventions	Experiment group received Entonox while control group inhaled oxygen
Outcomes	Pain as measured by VAS, mothers vital signs, fetal heart rate, Apgar score at 1 and 5 minutes, postpartum haemorrhage, mode of delivery, side effects for mother (drowsiness and mouth stiffness) and satisfaction with delivery
Notes	No use of prior or concurrent other analgesia.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Single blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 women from the intervention (Entonox) group and 3 from the control group had to be excluded from the study due to the need for emergency caesarean sections
Selective reporting (reporting bias)	Unclear risk	Not clear from translation.
Other bias	Unclear risk	No baseline characteristics.
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Shao 2000

Methods	Randomised parallel study conducted from 20th May to 9th December 1998 in Zhejiang Yuyao People's Hospital, Yuyao, China.
Participants	250 participants, 125 in each group.
Interventions	Experiment group inhaled the laughing gas and control group no treatment

Shao 2000 (*Continued*)

Outcomes	Pain intensity (degree of labour pains), method of delivery, Apgar scores, intrapartum haemorrhage, postpartum haemorrhage, other side effects (mild dizziness, fatigue and sleepiness)
Notes	No information regarding other used analgesia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Unclear risk	No information as per translation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information as per translation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information as per translation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information as per translation.
Selective reporting (reporting bias)	Unclear risk	Can not tell completely from the translation.
Other bias	Unclear risk	No information as per translation, no information of use of other analgesia
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Stefani 1982

Methods	Randomised control trial conducted in University Hospital Southern California, USA
Participants	61 participants, 22 in the experiment group1, 18 in the experiment group 2 and 21 in the controls Inclusion criteria: healthy full-term parturients.
Interventions	Experimental group 1 received enflurane 0.3% to 0.8%, experimental group 2 received nitrous oxide (30% to 50%), while control group received no treatment
Outcomes	NACS using the Early Neurobehavioral Scale, satisfactory pain relief

Stefani 1982 (*Continued*)

Notes	Concurrent or prior use of other analgesia: 50% to 41% received no narcotics, the other group received small doses of opioids, 66% pudendal block

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned randomly.
Allocation concealment (selection bias)	Unclear risk	Assigned randomly.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Two examiners, blind to both the nature and duration of analgesia simultaneously evaluated and scored the neuro behavioural status of infants."
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Low risk	Both groups comparable and use of other analgesia in both groups seems similar
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Swart 1991

Methods	Randomised trial conducted in Department of Anesthesiology, Los Angeles County - University of southern California Medical Centre, Los Angeles, California, USA
Participants	60 participants, 30 in each group.
Interventions	Experimental group received desflurane 1% to 4.5% and oxygen while control group received nitrous oxide 30% to 60% and oxygen
Outcomes	Analgesia assessment, blood loss, Apgar score, blood acidity and NACS
Notes	Abstract (poster session) only - data limited. No information regarding concurrent or prior use of other analgesia

Risk of bias

Swart 1991 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both patient and obstetrician did not know the gas.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information about the numerical results in the abstract
Other bias	Unclear risk	Groups characteristics not reported in the abstract.
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Talebi 2009

Methods	Randomised control trial conducted from September 2004 to 2006 in Department of Anaesthesiology, Arak University Hospital, Arak, Iran
Participants	534 ASA I and II parturients, 260 in experimental group and 249 in control group Inclusion criteria: scheduled for elective labour, term (38-42 weeks) in active stage of labour (dilation more then 4 cm). Exclusion criteria: any evidence of fetal distress, or abnormal fetal heart pattern, maternal cardiorespiratory disease or any condition effecting the accuracy of pulse oximetry, history of taking opioids, administrations of sedation or regional analgesia (pudendal block, local infiltration), intolerance of Entonox, during trial when birth ended in caesarean section or forceps
Interventions	Experimental group received self-administration of pre-prepared mixture of 50% nitrous oxide and oxygen started as early as the onset of pain with each contraction (when patient first requested analgesia), while control group received self-administration of 50% oxygen as early as the onset of pain with each contraction
Outcomes	Pain scores of contractions by VAS (time at the start of inhaled analgesia and every hour from time 1 to 5), the lowest spO2 (by pulse oxymeter) and mean arterial blood pressure of the mother, Apgar scores of 1 and 5 minutes postpartum. Side effect as nausea,

Talebi 2009 (*Continued*)

	vomiting dizziness, dry mouth from gas, pins and needles or numbness and drowsiness measured at the end of the study
Notes	No concurrent or prior use of other analgesia (excluded).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation with a coin.
Allocation concealment (selection bias)	Unclear risk	Randomisation with a coin.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants rating of pain was recorded by someone blind to allocation, plus arterial pressure and Apgar score
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 523 loss to follow-up. No patient excluded after randomisation. Intention to treat not known
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	High risk	More primipara in nitrous oxide group. This would be in favour of control group regarding pain.
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Wang 1994

Methods	Randomised study conducted in The Third Affiliated Hospital of Henan Medical School, China
Participants	84 participants, 34 in the experiment group and 50 controls.
Interventions	Experiment group received nitrous oxide and control group received no treatment
Outcomes	Analgesic effects, respiratory and circulatory functions, uterine contractions, progress of labour, Apgar score and postpartum bleeding
Notes	No information of prior or concurrent use of other analgesia

Wang 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Only the abstract translated.
Other bias	Unclear risk	Only the abstract translated.
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

Wee 1993

Methods	Randomised cross-over trial conducted in St Michael's Hospital, Bristol, UK
Participants	18 participants with 17 measurements of drowsiness and 18 measurements of pain intensity after 1 hour in first period before the first cross-over ended Inclusion criteria: between 16 and 38 years old, in ASA grade 1, in normal labour and requesting inhalation analgesia (mothers were allowed to opt out if inhalational analgesia subsequently proved to be unsatisfactory)
Interventions	Experimental group received E-I-E sequence, mothers inhaled Entonox alone at the first hour, Entonox and 0.2% Isoflurane for the second and Entonox alone for the third hour, while control group received I-E-I sequence, mother inhaled Entonox and 0.2% isoflurane at the first hour, Entonox alone for the second and Entonox and 0.2% isoflurane for the third hour
Outcomes	Pain and drowsiness assessment measured with VAS, baseline score before any inhalation, subsequently scores recorded at 20 minutes intervals, obtained as soon as possible after each contraction during the hour of 1 agent (intervention and comparison group), baby Apgar score 1 and 5 minutes. The differences in median scores in both groups between baseline and the first hour, the first and the second hour, the second and the third hour were calculated

Wee 1993 (*Continued*)

Notes	No information on wash-out period between agents but inhalation agent was used for 1 complete hour and efficacy was scored after 20 minutes. Moreover the inhalation gases were self-administered during contractions. This means that the minimal wash-out period of 4 exhalations must have passed during the pauses between contractions Probably no prior or concurrent use of other analgesia because women were allowed to drop out if analgesia was not satisfactory. We used only data of the first period (measurements after 1 hour) with 18 participants and 11 measurements of Entonox use and 8 measurements of Isoflurane/Entonox use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman did not complete the study.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported upon.
Other bias	Unclear risk	Baseline not reported for the 2 groups, no information about other additional drugs
Correct analyses for cross-over design used	High risk	Probably paired t-test in this trial (no information). Overall mean/SD for experimental and comparison groups separately calculated by individual data for first period after one hour, analysed as parallel group data

Yeo 2007

Methods	Randomised, open label, double cross-over trial conducted in Anaesthetic Department, The County Hospital, Union Walk, Hereford, UK

Participants	31 participants, 15 in the experiment group and 16 in the controls with 37 measurements of Entonox and 43 measurements of enflurane Inclusion criteria: active labour (≥ 3 cm cervical dilatation) with contractions occurring at least 1 every 3 minutes, spontaneous or induced, ≥ 37 weeks' gestation with prior consent Exclusion criteria: women who had no knowledge of the study before, major uterine abnormalities, multiple gestation, cardiovascular or respiratory instability, acute or chronic obstetric pathology and women who received any analgesia before recruited
Interventions	Experimental group received Entonox/Sevoflurane 0.7%/Entonox (ESE), each agent during 10 contractions, while control group received Sevoflurane 0.7%/Entonox/Sevoflurane 0.7% (SES), each agent during 10 contractions. Between each agent a wash-over period of breathing room air during 1 contraction, participant could omit this wash-over period if they wished
Outcomes	VAS of overall pain relief with each contraction, pain intensity, sedation, mood and coping before and after each of 10 contractions with a specific agent, inspired and expired gas concentration, maternal ventilator frequency, intermittent non invasive arterial pressure, heart rate and maternal arterial oxygen saturation, fetal heart rate and maternal contractions on cardiotocograph, type of analgesia used after trial, mode of delivery, and preferred agent scored within 48hours after delivery
Notes	Between agent a wash-out period during 1 contraction, participant could omit this wash-over period if they wished (no information on numbers) but the agents were self-administered so probably there was a minimum of 4 exhalations between the 2 agents No prior use of other analgesia before treatment (excluded), no information on concurrent use. We extracted 43 measurements with Enflurane and 37 measurements with Entonox

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'randomised.'
Allocation concealment (selection bias)	Unclear risk	'randomised.'
Blinding of participants and personnel (performance bias) All outcomes	High risk	'open label.'
Blinding of outcome assessment (detection bias) All outcomes	High risk	'open label.'
Incomplete outcome data (attrition bias) All outcomes	High risk	2 women withdrew after the first contraction because of unpleasant odour of sevoflurane (preferred Entonox), 1 woman

		withdrew before inhalation of any administration (requested an epidural), these 3 women were not followed up because of the early withdrawal (before first cross-over) 5 withdrew because of requested epidural analgesia whilst in the Entonox phase of the study, 4 in the ESE group in the last phase using Entonox and 1 in the SES group, 2 withdrawals because of starting the second stage of labour before ending the trial
Selective reporting (reporting bias)	Low risk	Aall prespecified outcomes reported upon.
Other bias	Low risk	Both groups comparable and no use of other analgesia.
Correct analyses for cross-over design used	High risk	Overall pain relief scores of experimental and comparison groups separately

Zhang 2001

Methods	Randomised study conducted in The Third Affiliated Hospital of Henan Medical School, China
Participants	110 participants, 60 in the experimental group and 50 in the control group
Interventions	Experiment group received 30% to 50% nitrous oxide and oxygen 5L/min while controls received only oxygen 5L/min
Outcomes	Labour pain, mode of delivery, Apgar score, postpartum haemorrhage, vomiting and neonatal asphyxia
Notes	Concurrent or prior use of other analgesia not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly chosen.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.

Zhang 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss.
Selective reporting (reporting bias)	High risk	Apgar score mentioned in abstract of study, but no results were reported within the results section of the paper
Other bias	Unclear risk	Not clear.
Correct analyses for cross-over design used	Low risk	Not cross-over trial.

ASA: American Society of Anaesthesiologists
NACS: neurologic and adaptive capacity score
NICU: neonatal intensive care unit
OMV: Oxford Miniature. Vaporizer
SD: standard deviation
VAS: visual analogue scale

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

Study	Reason for exclusion
Arozenius 1980	Not randomised.
Arthurs 1981	Quasi-randomised trial.
Chessor 2005	Not randomised.
Clark 1979	Comparison with opioids which are higher than inhalation in the pain management hierarchy
Cosmi 1969	Spinal block compared to general anaesthesia study. Not randomised
Crawford 1975	Participants not women in labour. Study on general anaesthesia and it's side effects in caesarean section
Creasser 1974	Complex intervention -all women had a pudendal block. 1 group received methoxyflurane and the other group received intramuscular analgesia + nitrous oxide. Does not fit in with our hierarchy
Davies 1974	Quasi-randomised trial. Study mainly concerned with resistance of the delivery system
Davies 1975	Not randomised.

(*Continued*)

Howell 2001	Intervention investigated was epidural and both groups received Entonox. Fits in with epidural review according to pain management hierarchy
Krantz 1974	General anaesthesia trial and participants were not women in labour
Major 1966	Controls treatment (Trichloroethylene) not used any more since 1975. Quasi-randomised trial
Major 1967	Quasi-randomised trial.
McAneny 1963	Participants were distributed between groups and not randomised
Phillips 1971	Controls treatment (Trichloroethylene) not used any more since 1975 and all groups got pethidine
Roberts 1957	Not randomised. Comparison of nitrous oxide to opioids which are higher in the pain management hierarchy
Robinson 1980	Epidural is higher than inhalation in the pain management hierarchy The main comparison is between opioids and inhaled analgesic versus epidural analgesia
Rosen 1969	Quasi-randomised trial.
Rosen 1972	Quasi-randomised trial. Controls were not pregnant.
Shnider 1963	Cyclopropane no longer used in practice. Study conducted during episiotomy repair after delivery
Volmanen 2005	Comparison of nitrous oxide to opioids which are higher in the pain management hierarchy

Characteristics of studies awaiting assessment *[ordered by study ID]*

Su 2002

Methods	Unclear - article in Chinese, awaiting translation. In English abstract just states "women in labour were divided into two groups"
Participants	1300 cases of term primiparous women in labour.
Interventions	Study group (n = 658) 50% nitrous oxide in oxygen. Control group (n = 642) intermittent inhalation of 50% oxygen
Outcomes	Duration of labour; delivery mode; meconium-stained amniotic fluid; postpartum bleeding volume; neonatal Apgar score; blood gas analysis
Notes	Awaiting translation June 2012.

DATA AND ANALYSES

Comparison 1. Nitrous oxide versus flurane derivatives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity (VAS 0-100 first stage)	3	70	Mean Difference (IV, Random, 95% CI)	14.39 [4.41, 24.37]
2 Pain relief (VAS 0-100 as 100 is the most pain relief, first stage)	2	70	Mean Difference (IV, Random, 95% CI)	-16.32 [-26.85, -5.79]
3 Satisfaction with pain relief (first and second stage, considerable to complete)	2	98	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.18]
4 Satisfaction with pain relief (second stage, good to excellent)	4	323	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.01]
5 Assisted vaginal birth	5	371	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.15]
6 Caesarean section	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Amnesia	3	245	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.38]
8 Drowsiness (VAS 0-100 mm)	1	18	Mean Difference (IV, Fixed, 95% CI)	11.64 [-16.04, 39.32]
9 Nausea	2	98	Risk Ratio (M-H, Fixed, 95% CI)	6.6 [1.85, 23.52]
10 Vomiting	3	203	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.75, 5.46]
11 Blood loss in mL	2	185	Mean Difference (IV, Fixed, 95% CI)	6.0 [-32.91, 44.91]
12 Apgar score less than seven at five minutes	5	373	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.47]
13 NACS < 35 at 2 hours after delivery	3	170	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.91, 2.33]

Comparison 2. Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Satisfaction with pain relief (first stage, good to complete)	1	501	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.17]
2 Satisfaction with pain relief (second stage, good to complete)	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
3 Caesarean section	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.06, 1.53]
4 Assisted vaginal birth	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.14]
5 Vomiting	1	501	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.86, 1.94]
6 Postpartum haemorrhage	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.70]
7 Hypoxaemia mother	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.21]

Comparison 3. Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Satisfaction with pain relief (first stage, considerable to complete)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]
2 Caesarean section	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.6 [0.12, 58.48]
3 Vomiting (N2O + nasal)	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.77, 4.00]
4 Vomiting dichotomous Penthr./Cypr.	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Postpartum haemorrhage	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.50]
6 Mild pre-eclampsia	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.06, 12.28]
7 Apgar score (continuous, at 5 min.Penthr/Cypr)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.37, 0.37]
8 Apgar score (continuous N2O/N2O with nasal suppl.)	1	49	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.81, 0.21]

Comparison 4. Inhaled analgesia versus placebo control/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity (first stage, clear/severe to intense/extreme)	2	310	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.34]
2 Pain intensity (first stage, VAS 0-10 after 1 hour)	1	509	Mean Difference (IV, Fixed, 95% CI)	-3.50 [-3.75, -3.25]
3 Assisted vaginal birth	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.44, 5.15]
4 Caesarean section	3	465	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.75, 1.91]
5 Vomiting	2	619	Risk Ratio (M-H, Fixed, 95% CI)	9.05 [1.18, 69.32]
6 Nausea	1	509	Risk Ratio (M-H, Fixed, 95% CI)	43.10 [2.63, 706.74]
7 Dizziness	1	509	Risk Ratio (M-H, Fixed, 95% CI)	113.98 [7.09, 1833.69]
8 Drowsiness	1	509	Risk Ratio (M-H, Fixed, 95% CI)	77.59 [4.80, 1254.96]
9 Neonatal asphyxia	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.26, 4.73]
10 Apgar score 5 min. < 7 dich.	1	200	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.49, 165.00]
11 Apgar score 5 min.cont.	1	509	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.13, 0.13]

Comparison 5. Inhaled analgesia versus TENS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Satisfaction pain relief first period ordinal partial to complete	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.07]
2 Pain intensity first period ordinal moderate to severe	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.84, 1.45]

Analysis 1.1. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 1 Pain intensity (VAS 0-100 first stage).

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 1 Pain intensity (VAS 0-100 first stage)

Study or subgroup	Nitrous oxide N	Mean(SD)	-Fluranegroup N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
McGuinness 1984	10	53 (12.5)	10	48 (16.5)		34.2 %	5.00 [-7.83, 17.83]
McLeod 1985	16	63 (17)	16	46.6 (16.75)		37.9 %	16.40 [4.71, 28.09]
Wee 1993	11	74.6 (17.8)	7	51.4 (14.8)		27.9 %	23.20 [8.01, 38.39]
Total (95% CI)	**37**		**33**			**100.0 %**	**14.39 [4.41, 24.37]**

Heterogeneity: $Tau^2 = 32.85$; $Chi^2 = 3.46$, df = 2 (P = 0.18); $I^2 = 42\%$

Test for overall effect: Z = 2.83 (P = 0.0047)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 2 Pain relief (VAS 0-100 as 100 is the most pain relief, first stage).

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 2 Pain relief (VAS 0-100 as 100 is the most pain relief, first stage)

Study or subgroup	Nitrous oxide N	Mean(SD)	-Fluranegroup N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Arora 1992	19	58 (15)	20	70 (15)		60.7 %	-12.00 [-21.42, -2.58]
Yeo 2007	15	51 (21.75)	16	74 (16.75)		39.3 %	-23.00 [-36.73, -9.27]
Total (95% CI)	**34**		**36**			**100.0 %**	**-16.32 [-26.85, -5.79]**

Heterogeneity: $Tau^2 = 24.42$; $Chi^2 = 1.68$, df = 1 (P = 0.20); $I^2 = 40\%$

Test for overall effect: Z = 3.04 (P = 0.0024)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 3 Satisfaction with pain relief (first and second stage, considerable to complete).

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 3 Satisfaction with pain relief (first and second stage, considerable to complete)

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jones 1969	19/24	19/24		47.5 %	1.00 [0.75, 1.34]
Jones 1969a	20/25	21/25		52.5 %	0.95 [0.73, 1.24]
Total (95% CI)	**49**	**49**		**100.0 %**	**0.98 [0.80, 1.18]**

Total events: 39 (Nitrous oxide), 40 (-Fluranegroup)

Heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.26 (P = 0.80)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 4 Satisfaction with pain relief (second stage, good to excellent).

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 4 Satisfaction with pain relief (second stage, good to excellent)

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abboud 1981	38/50	49/55		37.3 %	0.85 [0.71, 1.02]
Abboud 1995	25/40	25/40		20.0 %	1.00 [0.71, 1.40]
Belfrage 1974	33/51	34/47		28.3 %	0.89 [0.68, 1.17]
Stefani 1982	13/18	20/22		14.4 %	0.79 [0.58, 1.09]
Total (95% CI)	**159**	**164**		**100.0 %**	**0.89 [0.78, 1.01]**

Total events: 109 (Nitrous oxide), 128 (-Fluranegroup)

Heterogeneity: Chi^2 = 1.12, df = 3 (P = 0.77); I^2 =0.0%

Test for overall effect: Z = 1.81 (P = 0.071)

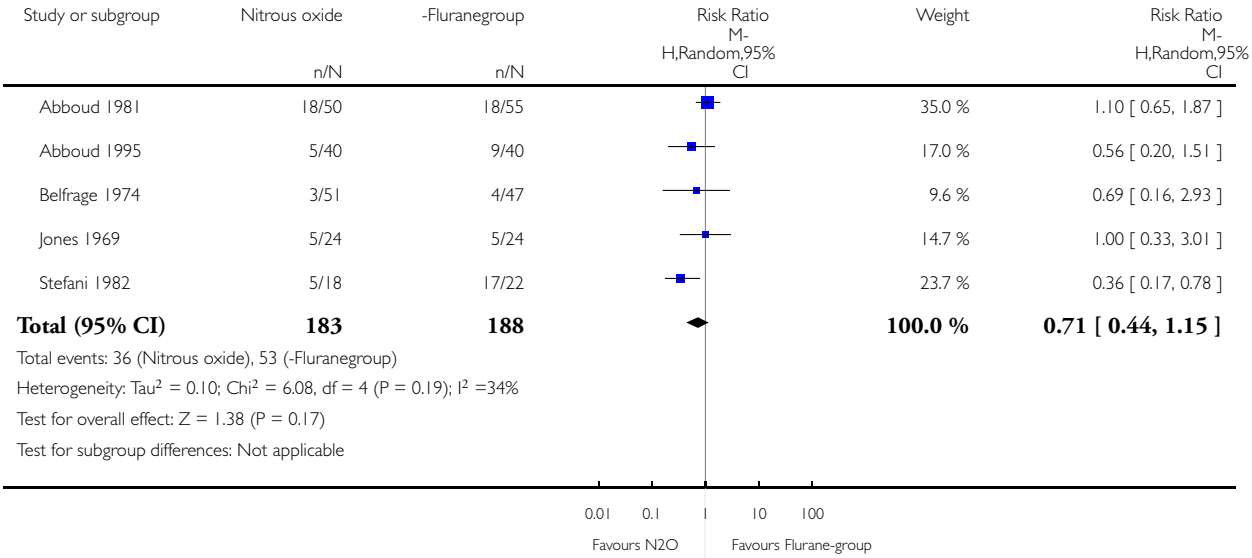
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 5 Assisted vaginal birth.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 5 Assisted vaginal birth



Analysis 1.6. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 6 Caesarean section.

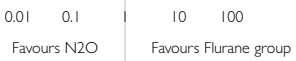
Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 6 Caesarean section

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Belfrage 1974	0/51	0/47		0.0 [0.0, 0.0]
Total (95% CI)	**51**	**47**		**0.0 [0.0, 0.0]**

Total events: 0 (Nitrous oxide), 0 (-Fluranegroup)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 7 Amnesia.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 7 Amnesia

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abboud 1981	5/50	4/55		40.2 %	1.38 [0.39, 4.84]
Abboud 1995	0/40	9/40		26.5 %	0.05 [0.00, 0.87]
Swart 1991	1/30	8/30		33.4 %	0.13 [0.02, 0.94]
Total (95% CI)	**120**	**125**		**100.0 %**	**0.26 [0.03, 2.38]**

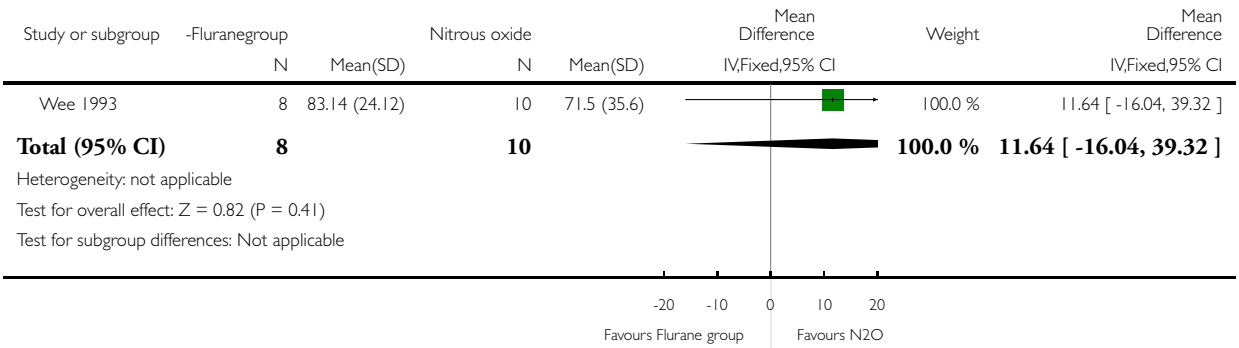
Total events: 6 (Nitrous oxide), 21 (-Fluranegroup)
Heterogeneity: $Tau^2 = 2.76$; $Chi^2 = 7.62$, df = 2 (P = 0.02); $I^2 = 74\%$
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 8 Drowsiness (VAS 0-100 mm).

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 8 Drowsiness (VAS 0-100 mm)

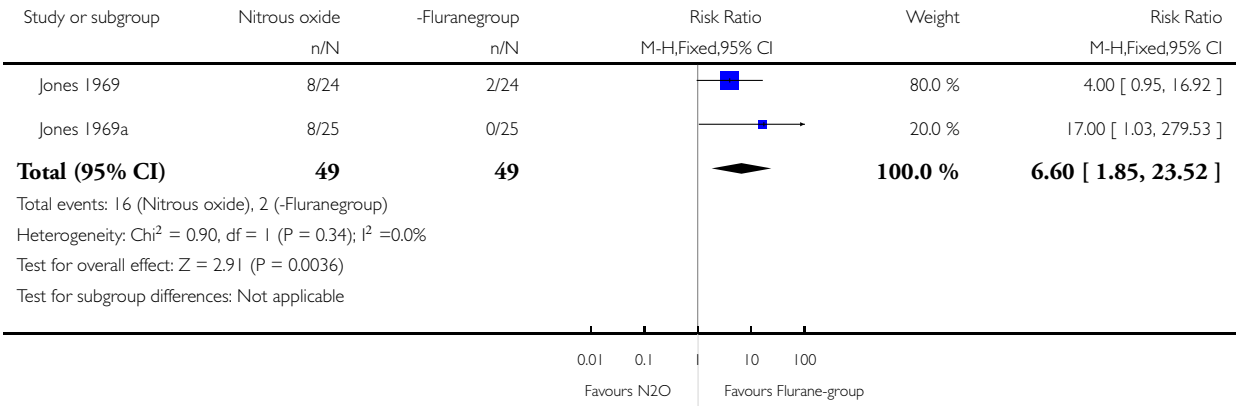


Analysis 1.9. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 9 Nausea.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 9 Nausea

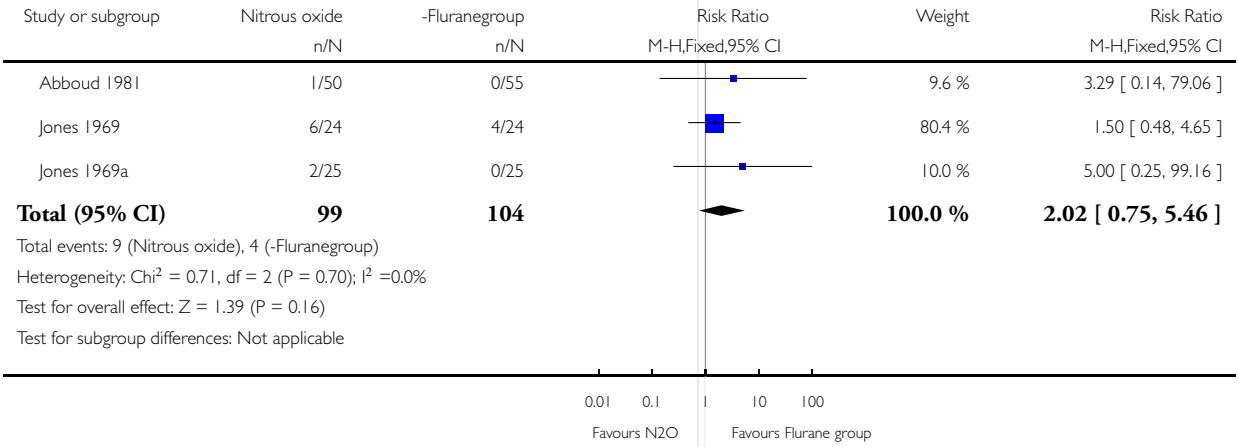


Analysis 1.10. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 10 Vomiting.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 10 Vomiting



Analysis 1.11. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 11 Blood loss in mL.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

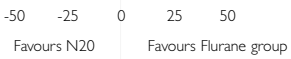
Outcome: 11 Blood loss in mL

Study or subgroup	Nitrous oxide N	Mean(SD)	-Fluranegroup N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Abboud 1981	50	327 (91.92)	55	321 (111.3)		6.00 [-32.91, 44.91]
Abboud 1995	40	364 (0)	40	335 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**90**		**95**			**6.00 [-32.91, 44.91]**

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 12 Apgar score less than seven at five minutes.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 12 Apgar score less than seven at five minutes

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Abboud 1981	0/50	2/55		0.22 [0.01, 4.47]
Abboud 1995	0/40	0/40		0.0 [0.0, 0.0]
Belfrage 1974	0/51	0/47		0.0 [0.0, 0.0]
Cheng 2001	0/25	0/25		0.0 [0.0, 0.0]
Stefani 1982	0/18	0/22		0.0 [0.0, 0.0]
Total (95% CI)	**184**	**189**		**0.22 [0.01, 4.47]**

Total events: 0 (Nitrous oxide), 2 (-Fluranegroup)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Nitrous oxide versus flurane derivatives, Outcome 13 NACS < 35 at 2 hours after delivery.

Review: Inhaled analgesia for pain management in labour

Comparison: 1 Nitrous oxide versus flurane derivatives

Outcome: 13 NACS < 35 at 2 hours after delivery

Study or subgroup	Nitrous oxide n/N	-Fluranegroup n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abboud 1995	7/40	4/40		20.8 %	1.75 [0.56, 5.51]
Cheng 2001	11/25	8/25		41.7 %	1.38 [0.67, 2.83]
Stefani 1982	9/18	8/22		37.5 %	1.38 [0.67, 2.83]
Total (95% CI)	**83**	**87**		**100.0 %**	**1.45 [0.91, 2.33]**

Total events: 27 (Nitrous oxide), 20 (-Fluranegroup)

Heterogeneity: $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 1 Satisfaction with pain relief (first stage, good to complete).

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 1 Satisfaction with pain relief (first stage, good to complete)

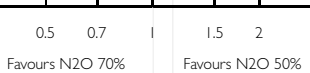
Study or subgroup	N2O 50% n/N	N2O 70% n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
MRC 1970	194/259	173/242		100.0 %	1.05 [0.94, 1.17]
Total (95% CI)	**259**	**242**		**100.0 %**	**1.05 [0.94, 1.17]**

Total events: 194 (N2O 50%), 173 (N2O 70%)

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable



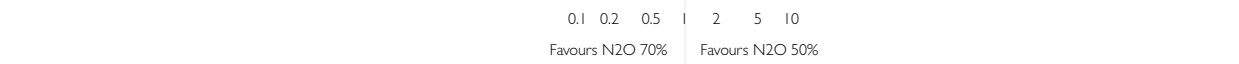
Analysis 2.2. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 2 Satisfaction with pain relief (second stage, good to complete).

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 2 Satisfaction with pain relief (second stage, good to complete)

Study or subgroup	N2O 50% n/N	N2O 70% n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
MRC 1970	184/259	177/242		100.0 %	0.97 [0.87, 1.08]
Total (95% CI)	**259**	**242**		**100.0 %**	**0.97 [0.87, 1.08]**
Total events: 184 (N2O 50%), 177 (N2O 70%)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Not applicable					

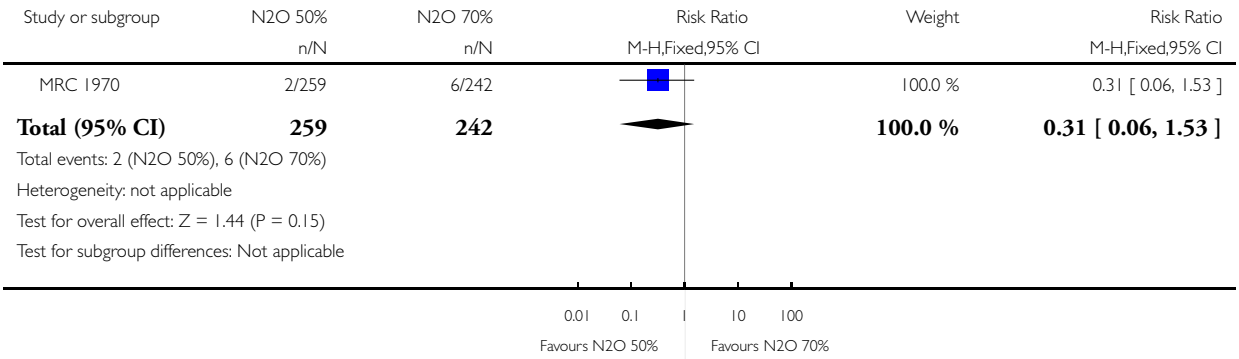


Analysis 2.3. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 3 Caesarean section.

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 3 Caesarean section

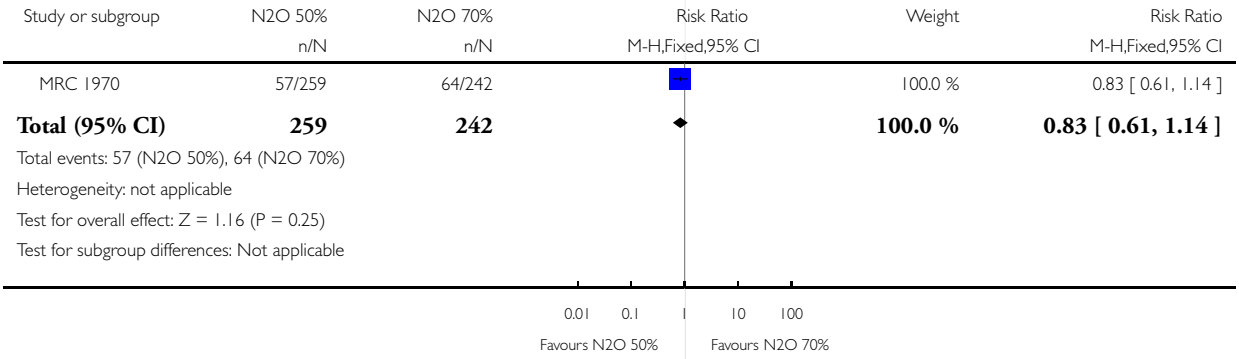


Analysis 2.4. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 4 Assisted vaginal birth.

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 4 Assisted vaginal birth

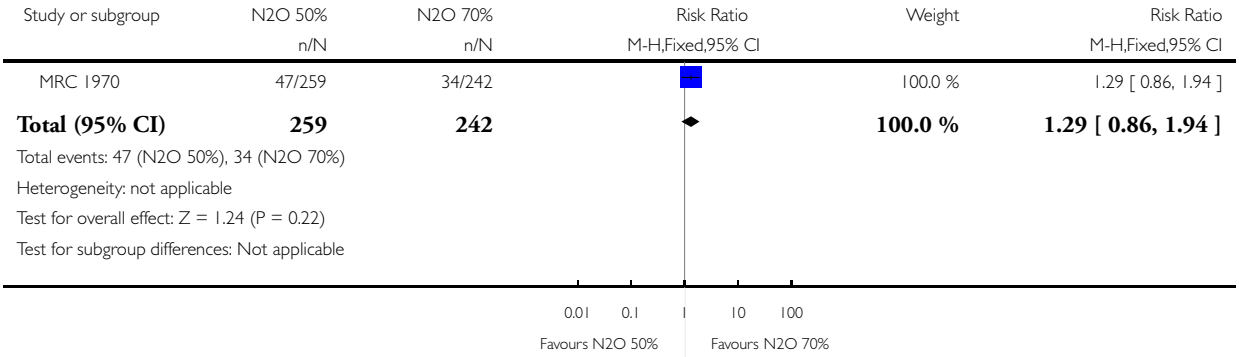


Analysis 2.5. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 5 Vomiting.

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 5 Vomiting

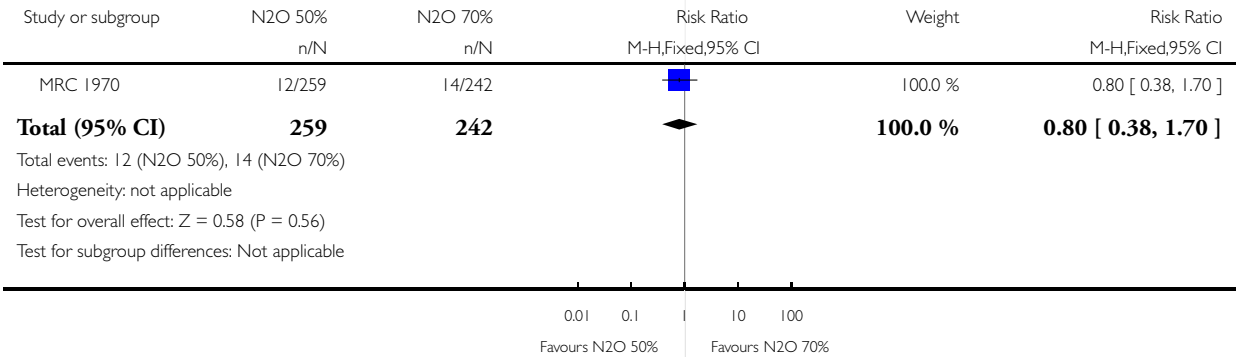


Analysis 2.6. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 6 Postpartum haemorrhage.

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 6 Postpartum haemorrhage

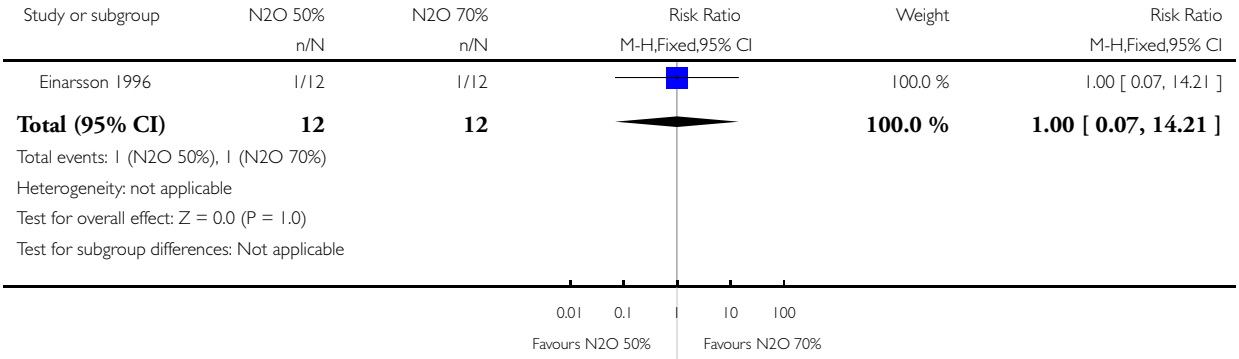


Analysis 2.7. Comparison 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength, Outcome 7 Hypoxaemia mother.

Review: Inhaled analgesia for pain management in labour

Comparison: 2 Inhaled analgesia of one strength versus inhaled analgesia of different strength

Outcome: 7 Hypoxaemia mother

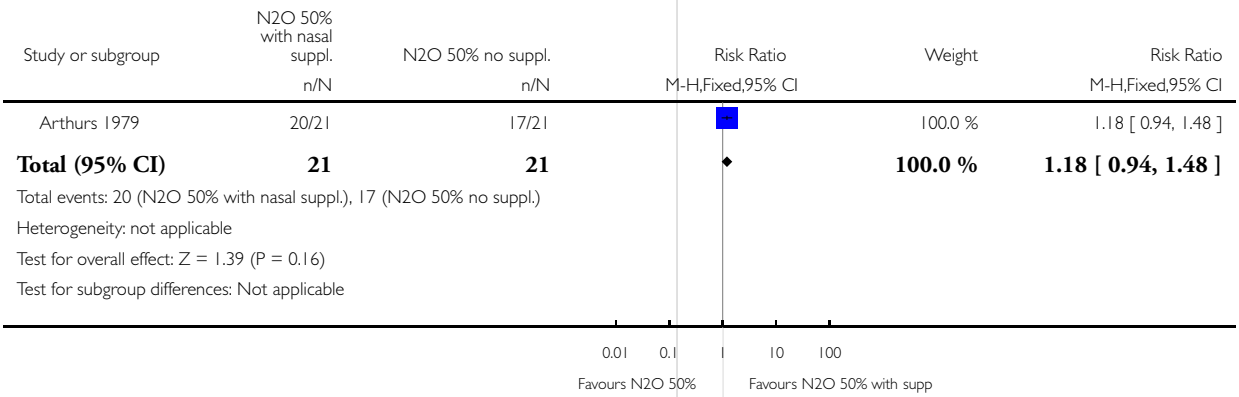


Analysis 3.1. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 1 Satisfaction with pain relief (first stage, considerable to complete).

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 1 Satisfaction with pain relief (first stage, considerable to complete)

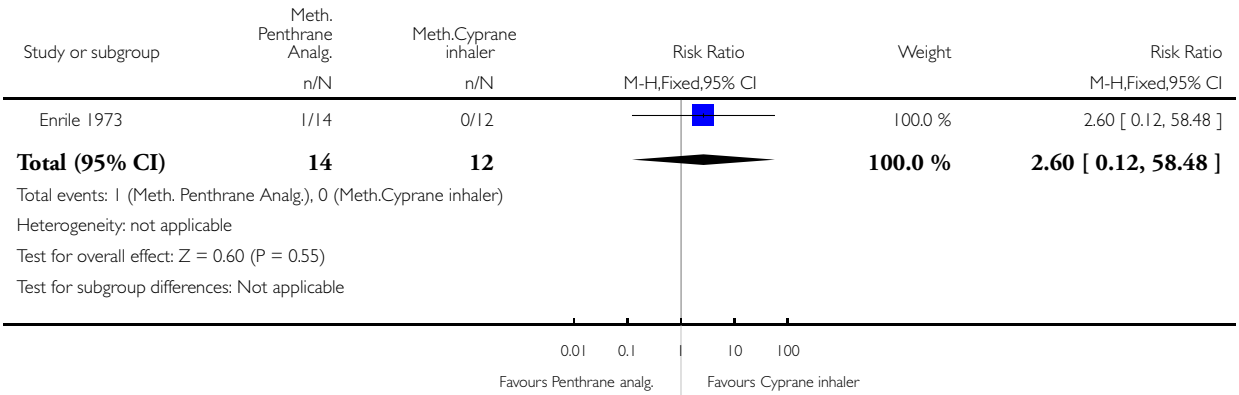


Analysis 3.2. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 2 Caesarean section.

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 2 Caesarean section

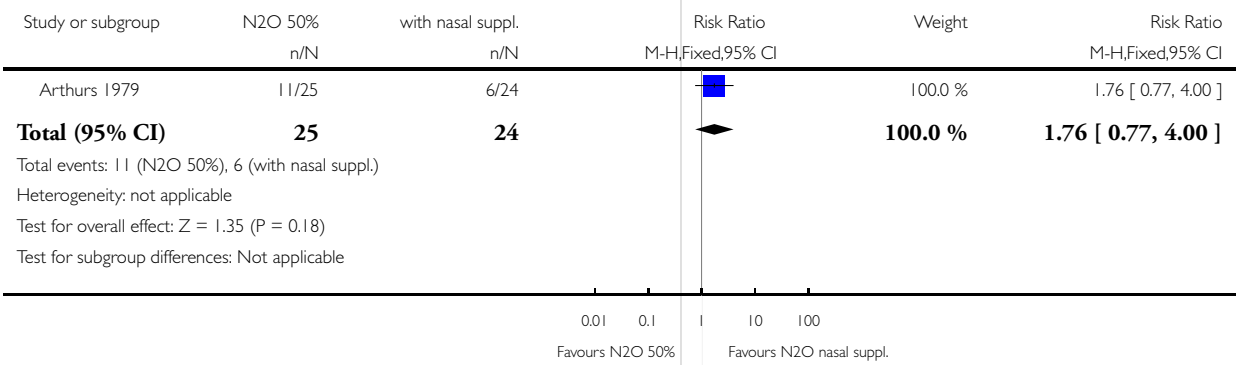


Analysis 3.3. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 3 Vomiting (N2O + nasal).

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 3 Vomiting (N2O + nasal)



Analysis 3.4. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 4 Vomiting dichotomous Penthr./Cypr..

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 4 Vomiting dichotomous Penthr./Cypr.

Study or subgroup	Penthrane analgizer n/N	Cyprane inhaler n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Enrile 1973	0/14	0/12		0.0 [0.0, 0.0]
Total (95% CI)	**14**	**12**		**0.0 [0.0, 0.0]**

Total events: 0 (Penthrane analgizer), 0 (Cyprane inhaler)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 5 Postpartum haemorrhage.

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 5 Postpartum haemorrhage

Study or subgroup	Penthrane analgizer meth. n/N	Cyprane inhaler meth. n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Enrile 1973	0/14	1/12		100.0 %	0.29 [0.01, 6.50]
Total (95% CI)	**14**	**12**		**100.0 %**	**0.29 [0.01, 6.50]**

Total events: 0 (Penthrane analgizer meth.), 1 (Cyprane inhaler meth.)

Heterogeneity: not applicable

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 6 Mild pre-eclampsia.

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 6 Mild pre-eclampsia

Study or subgroup	Penthrane inhaler meth n/N	Cyprane inhaler meth n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Enrile 1973	1/14	1/12		100.0 %	0.86 [0.06, 12.28]
Total (95% CI)	**14**	**12**		**100.0 %**	**0.86 [0.06, 12.28]**

Total events: 1 (Penthrane inhaler meth), 1 (Cyprane inhaler meth)

Heterogeneity: not applicable

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

Analysis 3.7. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 7 Apgar score (continuous, at 5 min.Penthr/Cypr).

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 7 Apgar score (continuous, at 5 min.Penthr/Cypr)

Study or subgroup	Penthrane analgizer meth N	Mean(SD)	Cyprane inhaler meth N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Enrile 1973	14	9 (0.4)	10	9 (0.5)		100.0 %	0.0 [-0.37, 0.37]
Total (95% CI)	**14**		**10**			**100.0 %**	**0.0 [-0.37, 0.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 3.8. Comparison 3 Inhaled analgesia using one type of delivery system versus a different delivery system, Outcome 8 Apgar score (continuous N2O/N2O with nasal suppl.).

Review: Inhaled analgesia for pain management in labour

Comparison: 3 Inhaled analgesia using one type of delivery system versus a different delivery system

Outcome: 8 Apgar score (continuous N2O/N2O with nasal suppl.)

Study or subgroup	N2O		N2O with nasal suppl.		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Arthurs 1979	25	9.3 (1.1)	24	9.6 (0.7)		100.0 %	-0.30 [-0.81, 0.21]
Total (95% CI)	**25**		**24**			**100.0 %**	**-0.30 [-0.81, 0.21]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 1 Pain intensity (first stage, clear/severe to intense/extreme).

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 1 Pain intensity (first stage, clear/severe to intense/extreme)

Study or subgroup	nitrous oxide 50% n/N	no analgesia n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ji 2002	9/100	100/100		72.4 %	0.09 [0.05, 0.17]
Zhang 2001	0/60	30/50		27.6 %	0.01 [0.00, 0.22]
Total (95% CI)	**160**	**150**		**100.0 %**	**0.06 [0.01, 0.34]**

Total events: 9 (nitrous oxide 50%), 130 (no analgesia)

Heterogeneity: $Tau^2 = 1.08$; $Chi^2 = 2.03$, df = 1 (P = 0.15); $I^2 = 51\%$

Test for overall effect: Z = 3.14 (P = 0.0017)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 2 Pain intensity (first stage, VAS 0-10 after 1 hour).

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

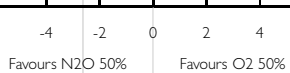
Outcome: 2 Pain intensity (first stage, VAS 0-10 after 1 hour)

Study or subgroup	nitrous oxide 50% N	Mean(SD)	O2 50% N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Talebi 2009	260	4.8 (1.6)	249	8.3 (1.3)		100.0 %	-3.50 [-3.75, -3.25]
Total (95% CI)	**260**		**249**			**100.0 %**	**-3.50 [-3.75, -3.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 27.14 (P < 0.00001)

Test for subgroup differences: Not applicable

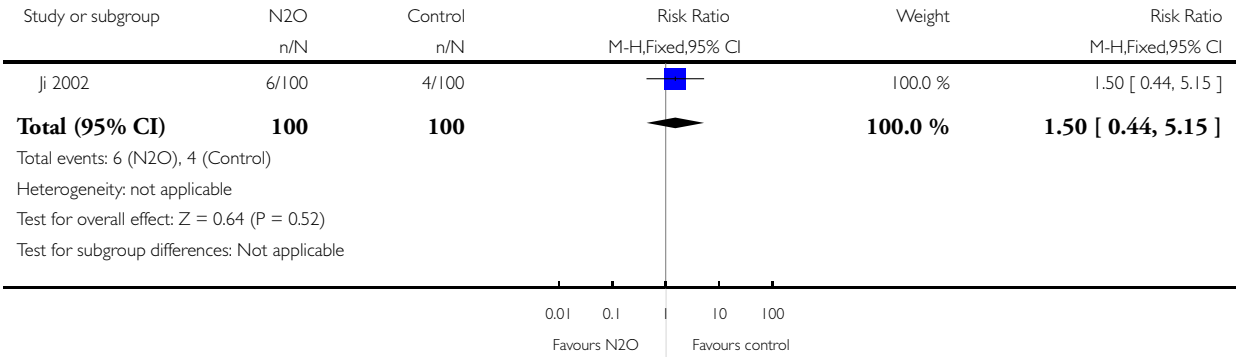


Analysis 4.3. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 3 Assisted vaginal birth.

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 3 Assisted vaginal birth

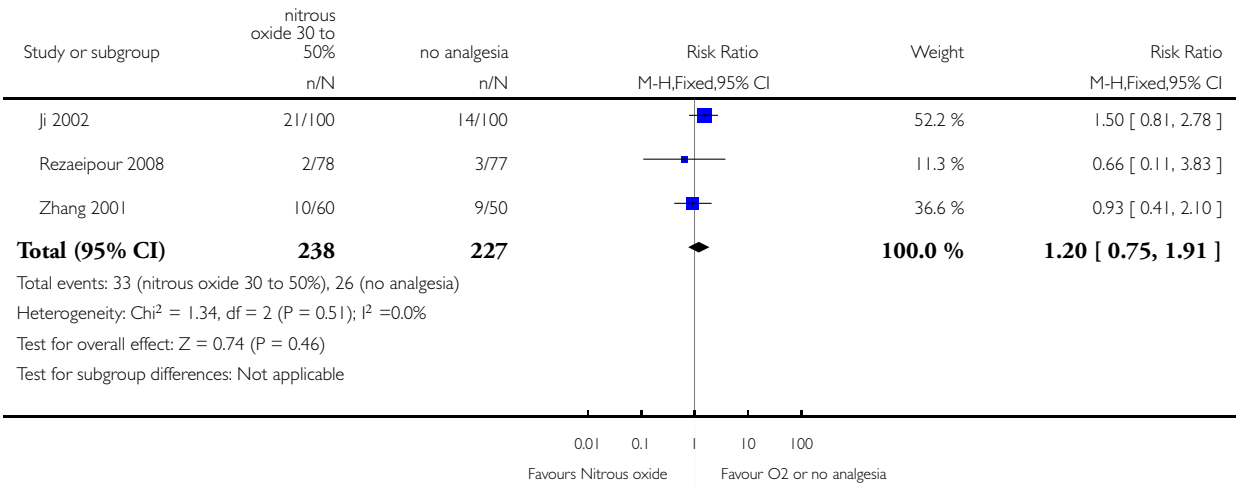


Analysis 4.4. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 4 Caesarean section.

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 4 Caesarean section

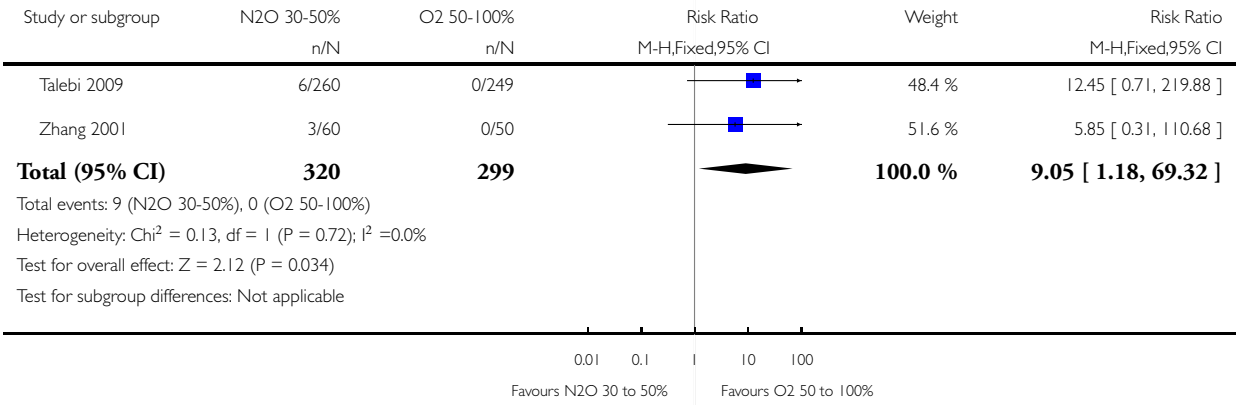


Analysis 4.5. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 5 Vomiting.

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 5 Vomiting



Analysis 4.6. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 6 Nausea.

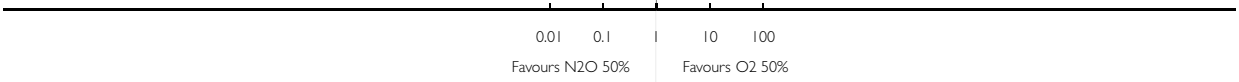
Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 6 Nausea

Study or subgroup	N2O 50% n/N	O2 50% n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Talebi 2009	22/260	0/249		100.0 %	43.10 [2.63, 706.74]
Total (95% CI)	**260**	**249**		**100.0 %**	**43.10 [2.63, 706.74]**

Total events: 22 (N2O 50%), 0 (O2 50%)
Heterogeneity: not applicable
Test for overall effect: Z = 2.64 (P = 0.0084)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 7 Dizziness.

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 7 Dizziness

Study or subgroup	N2O 50% n/N	O2 50% n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Talebi 2009	59/260	0/249		100.0 %	113.98 [7.09, 1833.69]
Total (95% CI)	**260**	**249**		**100.0 %**	**113.98 [7.09, 1833.69]**

Total events: 59 (N2O 50%), 0 (O2 50%)
Heterogeneity: not applicable
Test for overall effect: Z = 3.34 (P = 0.00083)
Test for subgroup differences: Not applicable

Analysis 4.8. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 8 Drowsiness.

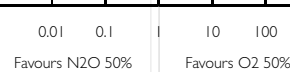
Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 8 Drowsiness

Study or subgroup	N2O 50% n/N	O2 50% n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Talebi 2009	40/260	0/249		100.0 %	77.59 [4.80, 1254.96]
Total (95% CI)	**260**	**249**		**100.0 %**	**77.59 [4.80, 1254.96]**

Total events: 40 (N2O 50%), 0 (O2 50%)
Heterogeneity: not applicable
Test for overall effect: Z = 3.06 (P = 0.0022)
Test for subgroup differences: Not applicable

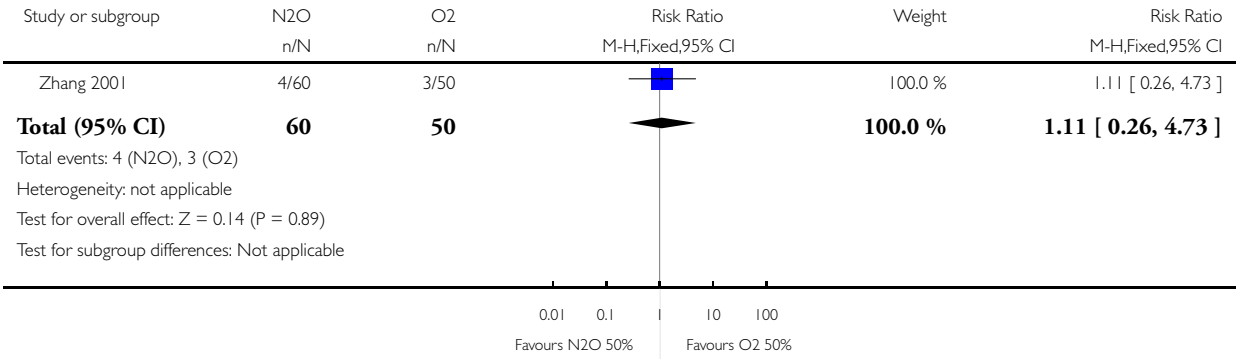


Analysis 4.9. Comparison 4 Inhaled analgesia versus placebo control/no treatment, Outcome 9 Neonatal asphyxia.

Review: Inhaled analgesia for pain management in labour

Comparison: 4 Inhaled analgesia versus placebo control/no treatment

Outcome: 9 Neonatal asphyxia



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