Nitrous oxide for relief of labor pain: a systematic review

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Authors' objectives
To determine the efficacy and safety of nitrous oxide (N2O) for labour analgesia.

Searching
MEDLINE (up to October 2000) and the Cochrane Controlled Trials Register in the Cochrane Library (Issue 3, 2000) were searched. The search terms included 'nitrous oxide', 'inhalation', 'childbirth', 'labor' and 'labour'. The reference lists of the retrieved studies were also searched. Articles written in languages other than English were excluded.

Study selection
Study designs of evaluations included in the review
It would appear that the efficacy studies had to be randomised controlled trials (RCTs), although this was not directly stated as a condition. It was stated that the studies were excluded on the grounds of not being randomised or controlled. Studies had to have 'low to moderate risk of bias' to be included, while studies with self-selected participants or other selection bias were excluded. All of the included efficacy trials were RCTs.

The design of the studies evaluating side-effects were not subject to inclusion criteria. Controlled and uncontrolled trials, observational studies and case reports were eligible. Some observational studies were subsequently excluded on the grounds of bias. Unpublished data were excluded. In addition, some other studies on occupational exposure were reported but not systematically reviewed.

Specific interventions included in the review
The criterion for inclusion was analgesia using N2O. Some studies assessed continuous administration of N2O through a nasal catheter; some assessed intermittent administration, titrated by an anesthesiologist in two studies but with the mode of delivery and control not stated for others. The mean duration of use, where stated, varied from 10 to 137 minutes. The concentrations of N2O varied from 30 to 80%, with the majority of studies using 50%. Four studies compared N2O concentrations (50 to 80%). N2O was also compared with other analgesics, including methoxyflurane, enflurane, isoflurane, desflurane, trichloroethylene and non-inhaled analgesics, including epidurals. Some studies allowed prior and concurrent use of opioids, while others excluded such use.

Participants included in the review
The participants included were women in labour. Three studies only included women in second stage labour, and three only women in first stage when labour was established; the remainder of the studies were in both first and second stage labour, or unspecified.

Outcomes assessed in the review
The outcomes assessed were a measure of efficacy for pain relief or a measure of side-effects on the labour, the mother, and/or the foetus or newborn baby. Studies in which the efficacy assessment was delayed, or the assessment was not by the parturient woman, were excluded. Pain relief was measured by a categorical scale or by a visual analogue score. The side-effects experienced by the women were self-reported after labour, and concerned experiences such as nausea, vomiting, consciousness and memory. Effects on labour were measured by haemodynamic changes, oxygen saturation levels, diffusion hypoxia, intra-uterine pressure and contraction frequency. Effects on the baby were measured using the Neurologic and Adaptive Capacity Score (NACS) and Early Neonatal Neurobehavioral Scale (ENNS) score at points from birth to 24 hours of life, and the 1-minute Apgar scores.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection. Since there is only a single author, it would appear that only one person was involved.
Assessment of study quality
The author does not report a method for assessing validity, other than stating that studies were assessed for low to moderate risk of bias. This included an assessment of the methods used to select and randomise participants, and an assessment of the adequacy of the control groups; blinding was not a criterion. Since there is only a single author, it would appear that only one person performed the validity assessment.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Since there is only a single author, it would appear that only one person was involved. The data items extracted are listed in the article. These included details of the following: N2O administration; the percentages of nulliparous women in each group; the use of other analgesics before or during the study period; the stage and progress of labour; the methods used to assess maternal analgesia; and adverse outcomes.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken, but no categorisation or weighting was employed to synthesise the efficacy results. The individual studies were described in tabular format and in the text. The side-effects were categorised as: progress of labour and maternal side-effects; neonatal outcomes; maternal oxygen saturation. In addition, selected studies on occupational pollution and contamination, and on equipment and hygiene, were summarised. The excluded observational studies were discussed as they provided supporting evidence on efficacy and safety.

How were differences between studies investigated?
Differences between the studies were not investigated and can only be elicited by reference to the tables and text.

Results of the review
Eleven RCTs of efficacy (total n=709) were included, with sample sizes ranging from 34 to 130. Six were crossover trials. Eight studies of adverse outcomes were included, whose designs were not fully specified. There was one double-blind RCT (n=400), four others were described as non-randomised (two of which were large multicentre studies) and one was observational. The sample sizes ranged from 24 to 659 in the studies of side-effects.

The studies did not provide clear, quantitative, objective evidence of efficacy, although it appears that N2O benefits many parturient women. In 7 of the 11 studies, women described significant analgesia with N2O use. However, the comparator analgesics were preferred or rated more effective by more women in 6 studies; N2O was preferred in 2 studies. As no statistical analyses were reported, it is unclear if any of these results reached statistical significance. Two studies that assessed labour progress found no adverse effects. The incidence of nausea and vomiting with N2O was reported in 8 studies, and ranged from 5 to 36%, but there were no unmedicated controls for comparison. The only RCT amongst these studies was one that compared different concentrations of N2O (from 50 to 80%). It found no effect of increasing N2O concentration on labour duration; no significant effect on nausea or vomiting or on hazy memory of labour; a significant increase in dreams and on memory of delivery with increased concentration; increased unconsciousness from 1 to 5%; and no effect on 1-minute Apgar scores.

A large non-randomised trial comparing concentrations found broadly similar results. There did not appear to be evidence of any serious adverse effects on the mother and child, or on labour, amongst those evaluated. No studies were found that evaluated the effect on breast-feeding. The reported data on occupational exposure were mixed in terms of exceeding the recommended US exposure levels of 100 ppm, but the evidence review was not systematic.

Authors' conclusions
N2O is not a potent labour analgesic, but it is safe for parturient women, their newborns, and health care workers in attendance. It appears to provide adequately effective analgesia for many women.
CRD commentary
The review question was reasonably clear. However, the author's criteria for including the studies, and the validity assessment method which determined inclusion, require further clarification. The search strategy was reasonable, but the exclusion of the non-English language papers found could have affected the conclusions. It would appear that the review processes were probably carried out by the single author as no other reviewer was named; this leaves the selection and extraction of the data open to potential errors.

The reported details of the individual studies were generally thorough but details of the study designs were lacking. It was unclear whether this is because the original studies did not fully report their designs. The chosen method of synthesis was appropriate for the data. However, there was little attempt at any systematic synthesis on the basis of, for example, trials with or without opioids, or with continuous or intermittent use of N2O, or by stage of labour, or by trial size or quality.

The statistical significance of the individual trial results was not reported, and this made it difficult to assess the robustness of the conclusions. The conclusion regarding the safety for health workers is not justified because a systematic review of this topic was not carried out.

Most of the conclusions appear to follow from the results. However, the opportunity was not taken to fully interpret the available quantitative data on either N2O or on comparisons with other methods of analgesia used in the studies.

Implications of the review for practice and research
Practice: The author states that N2O appears to provide analgesia that is comparable to that of paracervical block and probably better than that of opioids, but which is limited in comparison with epidural. It is relatively benign. When applied properly, it can provide significant pain relief for at least 50% of the patients. More sophisticated delivery devices may improve its continued use; a suggested technique was described in the article.

Research: The author states that the efficacy of more precise timing, to achieve more optimal concentrations at contraction peaks, could be investigated. Studies without confounding factors are required, particularly co-administered opioids. The efficacy and safety of combining N2O with opioids and other methods of analgesia require investigation, and the required features for safe administration need to be determined. The effects on breast-feeding should also be studied.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.