A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting?

S C Faddy, S R Garlick

A safe and effective form of pain relief would be an advantage in the prehospital treatment of patients experiencing extreme pain. Although used by many emergency medical services, 50% nitrous oxide (an inhaled analgesic known to have good pain relief properties) is not widely used by volunteer and semiprofessional organisations. This review aimed to determine whether 50% nitrous oxide is safe for use by first responders who are not trained as emergency medical technicians. A thorough search of the literature identified 12 randomised controlled trials investigating the use of 50% nitrous oxide (as compared with placebo or conventional analgesic regimens) in a range of conditions. The outcomes analysed for this review were: adverse events, recovery time, and need for additional medication. None of the studies compared the treatments in the prehospital setting; children were well represented. Adverse effects were rare and significant adverse outcomes such as hypotension and oxygen desaturation could not be attributed to nitrous oxide. Compared with patients receiving conventional analgesia, those receiving 50% nitrous oxide did not require additional medication any more frequently and had a faster recovery from sedative effects. The low incidence of significant adverse events from 50% nitrous oxide suggests that this agent could be used safely by lay responders.

Diffusion hypoxia has been identified as a potential complication of treatment with 50% nitrous oxide, at least theoretically. For this reason, some authors have advocated a period of oxygen therapy immediately following the cessation of nitrous oxide inhalation. Although theoretically a risk, several studies have failed to demonstrate diffusion hypoxia after 50% nitrous oxide inhalation. The safety profile of any analgesic is irrelevant unless it is efficacious in the relief of pain. To this end, we have previously presented data showing remarkable consistency in efficacy of pain relief in studies comparing 50% nitrous oxide with placebo or conventional medication regimens.
FACES rating scale, the Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS), and verbal pain scores to assess the analgesic properties of 50% nitrous oxide. Studies in a variety of patients using a range of scoring systems consistently showed superiority of 50% nitrous oxide over placebo, and equivalence when compared with conventional medication regimens.

The present systematic review assessed the available literature to determine the safety profile of 50% nitrous oxide. We carefully examined the frequency and severity of side effects to determine whether this agent is safe enough to be used by caregivers who are not trained as emergency medical technicians (EMTs).

MATERIALS AND METHODS

Literature search
One reviewer performed all of the literature searches. The Cochrane Database of Systematic Reviews (Issue 2, 2001) was searched for reviews of trials comparing nitrous oxide with placebo or other analgesic agents in the prehospital setting. No such review existed. The database was further searched for a review of similar trials in any setting. There were no reviews specifically involving the use of nitrous oxide in any area of patient care.

The reviewer searched the Medline (1966–Oct 2001) and EMBASE (1985—Oct 2001) databases, using an optimally sensitive search strategy, for relevant studies comparing 50% nitrous oxide with placebo or other analgesic agents in the prehospital setting. Again, no studies in the prehospital setting were found. Consequently, a broader search was performed to find randomised controlled trials from a wide range of clinical settings. Reference lists cited in original articles were examined for relevant studies not identified by the literature search.

Inclusion criteria
Previous studies have demonstrated increasing analgesic and psychomotor effects with increasing concentrations of nitrous oxide. In Australia, the USA, and Europe, 50% nitrous oxide in oxygen is the only premixed concentration commercially available. Therefore, we considered only those randomised controlled studies comparing 50% nitrous oxide with either placebo or another form of analgesia for inclusion in the review.

Outcomes analysed
The main outcomes were adverse effects resulting from treatment with 50% nitrous oxide, compared with either placebo or conventional analgesia. Secondary outcomes included recovery time and the need for additional medication.

Quality assessment and data extraction
Two reviewers independently assessed the quality of each trial. Any disagreement in interpretation of the studies between the reviewers was resolved by discussion. Quality assessment of each study was based on the methodological description of each study, in particular, randomisation, allocation concealment, blinding, and equality of baseline variables.

Statistical analysis
We used MetaView (Review Manager version 4.1 for Windows, Oxford, England; the Cochrane Collaboration, 2000) to calculate pooled risk differences and assess statistical heterogeneity. Statistical heterogeneity was a strong possibility in this review because of the wide range of patient populations, sources of pain, and control medication regimens employed in the primary studies. We used a random effects model for the pooled analysis because of the clinical heterogeneity in the primary studies.

For each adverse effect, we have given the risk difference (RD) and 95% confidence interval (CI) from studies comparing nitrous oxide and placebo to allow estimation of the rate of events which may be attributed to the nitrous oxide treatment over and above those that would have occurred because of the injury or illness. Test statistics and p values are those reported by each study or, where sufficient data were given, have been independently estimated using Prism version 2.01 (GraphPad Software Inc, San Diego, CA). A p value less than or equal to 0.05 was considered statistically significant.

RESULTS

Literature search
From the electronic search of the Medline and EMBASE databases we identified 1585 citations that matched the search criteria. These were screened for potentially relevant studies. A total of 158 abstracts were retrieved for more detailed evaluation, of which 33 described studies that were potentially relevant to this systematic review. These studies underwent critical appraisal. Twelve studies satisfied all subject and methodology criteria and were subsequently included in the review.

Characteristics of the studies
The characteristics of the studies included in the analysis are shown in table 1; 50% nitrous oxide was compared with control (placebo or conventional analgesia) in a wide variety of patient populations. Importantly, child, adolescent, and adult patients were all well represented. Pain was experienced from a variety of sources, many of which mimic injuries and conditions seen in the prehospital setting. The methodological quality of included studies is described in table 2. As expected from studies with short follow up periods, collection of outcome data was complete in almost all studies.

Adverse effects
Analysis of the pooled risk differences showed that none of the side effects investigated were significantly associated with nitrous oxide analgesia (fig 1).

Nausea
Nausea was assessed in 234 patients from three studies comparing 50% nitrous oxide and placebo. This analysis lacks power, as there were only two reports of nausea in the three studies. The incidence of nausea was 1.7% in all patients treated with nitrous oxide compared with placebo. Once again, this analysis lacked power as there were only two events reported in patients treated with nitrous oxide and no reports in patients treated with placebo (RD 2%, 95% CI −3% to 6%, p = 0.5), and the vomiting could not definitely be attributed
Dizziness

Two studies investigated dizziness in patients treated with 50% nitrous oxide or placebo.16 17 Pooled analysis of risk difference between nitrous oxide and placebo showed no association between nitrous oxide inhalation and dizziness (RD 10%, 95% CI 20% to 41%), but the analysis showed significant statistical heterogeneity ($\chi^2 = 6.13$, df = 1, p = 0.01). Consequently this result should be treated with caution. Notini-Gudmarsson et al18 found that fewer patients treated with nitrous oxide reported dizziness compared with those treated with intramuscular pethidine (10% vs 26%, respectively; p = 0.4).

### Table 1: Characteristics of trials of 50% nitrous oxide for pain relief

<table>
<thead>
<tr>
<th>Study</th>
<th>No analysed</th>
<th>Participants*</th>
<th>Pain source</th>
<th>Comparative intervention</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castera et al, 200115</td>
<td>100</td>
<td>44.4 (12.5) years†</td>
<td>Percutaneous liver biopsy</td>
<td>Placebo: oxygen</td>
<td>AE: nausea, headache</td>
</tr>
<tr>
<td>Forbes and Collins, 200013</td>
<td>102</td>
<td>60% male</td>
<td>Colonoscopy</td>
<td>IV sedation: midazolam + meperidine</td>
<td>Recovery</td>
</tr>
<tr>
<td>Castera et al, 200115</td>
<td>22</td>
<td>31 (8.9) years†</td>
<td>Migraine</td>
<td>Placebo: 100% oxygen</td>
<td>AE: vomiting, additional medication</td>
</tr>
<tr>
<td>Burton et al, 199812</td>
<td>30</td>
<td>3.7 (1.6) years†</td>
<td>Laceration repair</td>
<td>Placebo: 100% oxygen</td>
<td>AE: vomiting, dizziness, oxygen desaturation</td>
</tr>
<tr>
<td>Notini-Gudmarsson et al, 199616</td>
<td>38</td>
<td>60 (29–83) years</td>
<td>Colonoscopy</td>
<td>IM sedation: pethidine</td>
<td>Recovery: beginning of procedure to discharge Additional medication</td>
</tr>
<tr>
<td>Saunders et al, 199514</td>
<td>91</td>
<td>63.9 (53–75) years‡</td>
<td>Colonoscopy</td>
<td>Placebo: oxygen</td>
<td>AE: nausea, vomiting, dizziness, drowsiness, headache</td>
</tr>
<tr>
<td>Evans et al, 19951</td>
<td>30</td>
<td>10 (4–15) years</td>
<td>Fracture reduction</td>
<td>IM sedation: meperidine + promethazine</td>
<td>AE: nausea, vomiting</td>
</tr>
<tr>
<td>Saunders et al, 199410</td>
<td>89</td>
<td>63% male</td>
<td>Colonoscopy</td>
<td>Placebo: air</td>
<td>Recovery: time in outpatient area Additional medication</td>
</tr>
<tr>
<td>Lindblom et al, 199411</td>
<td>50</td>
<td>43 (30–56) years</td>
<td>Colonoscopy</td>
<td>IV sedation: ketobemidone + midazolam</td>
<td>Recovery: Patient chose to leave recovery area Additional medication</td>
</tr>
<tr>
<td>Henderson et al, 199014</td>
<td>165</td>
<td>52% male</td>
<td>Venous cannulation</td>
<td>Placebo: 100% oxygen</td>
<td>Additional medication</td>
</tr>
<tr>
<td>Harrison et al, 198719</td>
<td>170</td>
<td>Adult women</td>
<td>Labour</td>
<td>IM sedation: pethidine + promazine</td>
<td>AE: nausea, additional medication</td>
</tr>
<tr>
<td>Kerr et al, 197516</td>
<td>81</td>
<td>56 (31–72) years 88% male</td>
<td>Chest pain</td>
<td>Placebo: air</td>
<td>AE: vomiting, drowsiness</td>
</tr>
</tbody>
</table>

AE: adverse effects, IM, intramuscular; IV, intravenous.
*Values are median (range) unless otherwise stated: †mean (SD); ‡mean (range); *median (interquartile range).

### Table 2: Methodological quality of trials of 50% nitrous oxide for pain relief

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to follow up (n/N [%])</th>
<th>Method of randomisation and allocation concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castera et al, 200115</td>
<td>0/100 (0)</td>
<td>Random numbers. Allocation concealment not stated</td>
<td>Nurse and patient</td>
</tr>
<tr>
<td>Forbes and Collins, 200013</td>
<td>0/102 (0)</td>
<td>States randomised. Allocation concealment not stated</td>
<td>None</td>
</tr>
<tr>
<td>Castera et al, 200115</td>
<td>0/22 (0)</td>
<td>Computer-generated sequence, sealed envelopes</td>
<td>Investigators and patient</td>
</tr>
<tr>
<td>Burton et al, 199812</td>
<td>0/30 (0)</td>
<td>Computer sequence generated by nurse not involved in study</td>
<td>Investigators and patient</td>
</tr>
<tr>
<td>Notini-Gudmarsson et al, 199616</td>
<td>2/40 (5)</td>
<td>Randomly assigned. Allocation concealment not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Saunders et al, 199514</td>
<td>0/131 (0)</td>
<td>Randomly allocated. Allocation concealment not stated</td>
<td>Investigators and patient</td>
</tr>
<tr>
<td>Evans et al, 19951</td>
<td>0/30 (0)</td>
<td>Sealed unmarked envelopes from box</td>
<td>Not stated</td>
</tr>
<tr>
<td>Saunders et al, 199410</td>
<td>0/89 (0)</td>
<td>Stratified block randomisation</td>
<td>Investigators and patient</td>
</tr>
<tr>
<td>Lindblom et al, 199411</td>
<td>0/50 (0)</td>
<td>Block randomisation, blocks of 10. Closed envelopes</td>
<td>Investigators and patient</td>
</tr>
<tr>
<td>Henderson et al, 199014</td>
<td>Not stated</td>
<td>Patient’s choice of analgesia</td>
<td>Outcome assessor</td>
</tr>
<tr>
<td>Harrison et al, 198719</td>
<td>0/70 (0)</td>
<td>Block randomisation. Sequentially numbered cylinders</td>
<td>unclear investigator and patient</td>
</tr>
<tr>
<td>Kerr et al, 197516</td>
<td>35/116 (30)</td>
<td>Block randomisation. Sequentially numbered cylinders</td>
<td></td>
</tr>
</tbody>
</table>
Drowsiness

Two studies assessed drowsiness in 135 patients treated with 50% nitrous oxide or placebo. The pooled result of these studies showed that 3% of patients treated with nitrous oxide analgesia and 4% of patients treated with placebo experienced drowsiness, indicating that drowsiness was probably unrelated to nitrous oxide inhalation (RD –1%, 95% CI –7% to 5%, p = 0.8).

Headache

Saunders et al. found no occurrences of headache in a group of 47 patients treated with 50% nitrous oxide or placebo. Although Castera et al. demonstrated a higher incidence of headache in patients treated with 50% nitrous oxide or placebo, there was no difference in the incidence of headache between their two groups (Fig 1). Similarly, Notini-Gudmarsson et al. did not receive any reports of headache in 38 patients treated with 50% nitrous oxide or intramuscular pethidine.

Hypotension

Saunders et al. reported hypotensive episodes in only 2 of 30 patients (7%) treated with 50% nitrous oxide compared with 4 of 30 patients (13%) given placebo during colonoscopy. Hence, episodes of hypotension appeared to be due to the colonoscopy rather than the nitrous oxide therapy (RD –7%, 95% CI –22% to 8%). Furthermore, the incidence of hypotension in patients who were treated with nitrous oxide was lower than in patients treated with intravenous midazolam and pethidine (14%).

Oxygen desaturation

Only one study compared episodes of oxygen desaturation in patients treated with 50% nitrous oxide or placebo. There were no significant oxygen desaturation events in any of the patients. Two studies compared episodes of oxygen desaturation in patients treated with either 50% nitrous oxide or conventional analgesia. There were no episodes of oxygen desaturation in 49 patients who were treated with nitrous oxide, compared with nine episodes in 48 patients treated with pethidine, with or without midazolam (RD –10%, 95% CI –1% to –78%, p = 0.03).

Recovery time

Table 3 summarises the results from studies measuring recovery times in patients treated with 50% nitrous oxide or either placebo or conventional analgesic medication. All of the studies comparing 50% nitrous oxide with conventional analgesia showed a significantly shorter recovery time for patients treated with nitrous oxide. One of these studies also compared recovery time in patients treated with 50% nitrous oxide and those treated with placebo. There was no significant difference in recovery times after the two treatments.

Additional medication

Table 4 compares the number of patients treated with 50% nitrous oxide requiring additional medication with those given either placebo or conventional analgesia. Two studies compared the need for additional medication in patients receiving either nitrous oxide or placebo. Significantly fewer patients treated with nitrous oxide required additional medication.
medication compared with those who received placebo.19–26 Four studies compared the need for additional medication in patients receiving either nitrous oxide or conventional medication. There was no significant difference between the groups in the need for additional medication in three of the studies.19–23,26 In contrast, Harrison et al10 found that patients treated with pethidine and promazine during labour needed additional medication more often than patients who were treated with nitrous oxide. In this study, pethidine and promazine were administered intramuscularly in doses similar to in other studies in which similar drugs were administered intravenously.

**DISCUSSION**

This systematic review demonstrates that 50% nitrous oxide, when used by trained personnel in a medical setting, is a safe form of analgesia. When viewed in conjunction with previous studies on efficacy, 50% nitrous oxide provides effective analgesia for a range of injuries with minimal side effects. Serious adverse effects such as hypotension and oxygen desaturation have not been shown to occur during treatment with nitrous oxide. In addition, patients treated with 50% nitrous oxide recover faster and do not require additional medication any more frequently than patients treated with intravenous analgesia.

For a number of years, many organisations throughout the world, including some employing caregivers not trained as emergency medical technicians, have made use of 50% nitrous oxide analgesia. Until now there has not been a summary evidence base for the safety of this form of analgesia. The results of this review suggest that 50% nitrous oxide may be safe even when used by caregivers who do not possess medical, nursing, or EMT qualifications. This review reinforces the ongoing use of 50% nitrous oxide by these groups.

Primary care organisations currently allowing lay responders to use 50% nitrous oxide have strict criteria for certification. In most cases, caregivers must possess advanced first aid and advanced resuscitation certification, and often require a mandatory period of experience before training to use analgesic gases. This ensures the carer has adequate underlying knowledge to rule out contraindications and deal with any complications that may arise. In addition, there are strict controls on security to avoid illicit abuse, as well as guidelines to ensure adequate ventilation of exhaled gas and environmental safety. The method of self-administration is itself a safety feature of 50% nitrous oxide. If a patient loses consciousness, the mask falls away from the face allowing inhalation of ambient air. The patient then rapidly regains consciousness.

As with any intervention in any area of patient care, some injuries and conditions preclude the safe use of nitrous oxide in the prehospital setting. Nitrous oxide diffuses rapidly into gas filled cavities, actually diffusing in faster than nitrogen can diffuse out.19 As a consequence, air filled cavities will increase in volume, pressure, or both. Nitrous oxide is therefore contraindicated in patients who are suspected of having a pneumothorax, bowel obstruction, or decompression sickness. Fifty percent nitrous oxide has a disproportionately stronger effect in patients who are intoxicated, or under the influence of sedatives or opioids,27 or who have a depressed level of consciousness. Nitrous oxide may induce unconsciousness in these patients. It should not be given to patients with head injury as it is known to increase intracranial pressure.28 It has also been suggested that a patient who is hypovolaemic may lose consciousness more readily while inhaling 50% nitrous oxide.29 Nitrous oxide/oxygen mixtures separate when stored below 5°C and must be rewarmed and remixed before use. There are, therefore, a number of important contraindications to nitrous oxide therapy.

Although this review advocates the use of nitrous oxide by members of the community who are not trained as EMTs, it is important that a major focus of training this group is the

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Study population</th>
<th>Pain source</th>
<th>50% N2O</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% nitrous oxide vs placebo</td>
<td>60 Adult</td>
<td>Colonoscopy</td>
<td>32*</td>
<td>36*</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Saunders et al, 1994</td>
<td>102 Adult</td>
<td>Colonoscopy</td>
<td>30 (30–45)</td>
<td>60 (30–110)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>50% nitrous oxide vs conventional medication</td>
<td>38 Adult</td>
<td>Colonoscopy</td>
<td>49 (28–148)</td>
<td>83 (29–300)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Evans et al, 1995</td>
<td>30 Children</td>
<td>Fracture reduction</td>
<td>30 (15–60)†</td>
<td>83 (60–150)†</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Saunders et al, 1994</td>
<td>59 Adult</td>
<td>Colonoscopy</td>
<td>32*</td>
<td>60*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lindblom et al, 1994</td>
<td>50 Adult</td>
<td>Colonoscopy</td>
<td>0 (0–5)††</td>
<td>37.5 (10–75)††</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Recovery time stated as median (range) unless stated otherwise: *median; †mean (range); ‡median (interquartile range).

### Table 4

Need for additional medication in patients receiving 50% nitrous oxide (N2O) compared with placebo or conventional analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Study population</th>
<th>Pain source</th>
<th>Additional medication (n (%)</th>
<th>50% N2O</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% nitrous oxide vs placebo</td>
<td>22 Adult</td>
<td>Migraine headache</td>
<td>2 (20)</td>
<td>10 (83)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triner et al, 1999</td>
<td>60 Adult</td>
<td>Colonoscopy</td>
<td>3 (10)</td>
<td>13 (43)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saunders et al, 1994</td>
<td>38 Adult</td>
<td>Colonoscopy</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% nitrous oxide vs conventional medication</td>
<td>50 Adult</td>
<td>Colonoscopy</td>
<td>3 (10)</td>
<td>5 (17)</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notini-Gudmarsson et al, 1996</td>
<td>59 Adult</td>
<td>Colonoscopy</td>
<td>1 (4)</td>
<td>5 (20)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans et al, 1995</td>
<td>70 Adult</td>
<td>Labour</td>
<td>1 (5)</td>
<td>40 (80)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ability to suspect or identify conditions in which the use of nitrous oxide may be dangerous. In a recent study of continuous positive airway pressure for cardiogenic pulmonary oedema, EMTs failed to identify the presence of contraindications in four of 17 patients.9 The authors of that study stressed the need to focus attention during training on identifying important contraindications when introducing new techniques.10

All of these factors should be encompassed in a clear protocol, supervised and regularly revised by a medical director, before members of a first aid or primary care organisation are accredited to provide analgesia with 50% nitrous oxide. The National Association of Emergency Medical Service Physicians (NAEMSP) position statement on the use of nitrous oxide in prehospital emergency care states that nitrous oxide is within the scope of practice of EMS medical directors and can be used by EMS field personnel following appropriate education and training.11

Our review suggests that with appropriate training, non-EMS care providers can also safely use the analgesic benefits of 50% nitrous oxide.

Randomised studies included in this review included a variety of patient populations and a broad spectrum of pain sources. Application of the findings of this review to prehospital care is appropriate because of the consistency of the results across such a heterogeneous group of studies.

Although our aim was to demonstrate the safety of 50% nitrous oxide in prehospital care, there are no randomised controlled studies investigating adverse effects from 50% nitrous oxide in this setting. Numerous case series exist, but this study design excludes investigation of cause and effect (that is, which adverse effects are due to nitrous oxide inhalation and which effects would have occurred anyway).

Our analysis was confined to randomised controlled studies comparing 50% nitrous oxide analgesia with either placebo or conventional medication. As a result, comparisons between nitrous oxide and conventional medication regimens are based on a small number of studies for most of the adverse outcomes considered. Even when pooled analysis of multiple studies was possible, the evidence for equivalence is good, but not always definitive.

A potential weakness of this review is the methodological quality of the primary studies. As shown in table 2, only seven of the 12 randomised studies included in this review gave adequate information on the method of randomisation. Five of these studies gave information on allocation concealment. Eight studies gave adequate information on the methods of blinding. However, collection of outcome data was complete in nearly all studies.

CONCLUSIONS

Fifty per cent nitrous oxide has previously been shown to have similar efficacy for pain relief for a range of procedures compared to conventional analgesia with intravenous analgesic regimens, including opioid analgesia. This review has shown that side effects are uncommon and major adverse events such as hypotension and oxygen desaturation could not be attributed to nitrous oxide inhalation. Recovery from sedative effects of nitrous oxide is faster compared with intravenous analgesia.

Nitrous oxide at a concentration of 50% is an effective and safe form of analgesia. The side effect profile of this agent suggests that it could be used safely by adequately trained lay persons in the prehospital setting.

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