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Systematic review: The use of nitrous oxide gas for lower gastrointestinal endoscopy

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KEY WORDS

Sigmoidoscopy, Colonoscopy, Nitrous Oxide

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CONFLICTS OF INTEREST

None

For Peer Review

ABSTRACT

Background

Nitrous oxide gas (N₂O) has been proposed as an alternative to intravenous (iv) analgesia in patients undergoing lower gastrointestinal endoscopy.

AIMS

We performed a systematic review of randomized studies where N₂O had been compared against control in patients undergoing either flexible sigmoidoscopy or colonoscopy.

Methods

Electronic databases were searched; reference lists checked and letters sent to authors requesting data. Methodological quality was assessed. Data was tabulated on the duration and difficulty of the procedure, quality of sedation and speed of patient recovery.

Results

11 studies were identified containing 623 patients. No differences were seen between groups for duration, difficulty of procedure or complications. Patient reported pain was similar for N₂O when undergoing flexible sigmoidoscopy vs no sedation and when undergoing colonoscopy vs iv sedation. Differences in delivery of N₂O were identified. In all studies N₂O was associated with a more rapid recovery than iv sedation.

Conclusion

For patients undergoing colonoscopy N₂O provides comparable analgesia to iv sedation. The rapid psychomotor recovery with N₂O enables quicker patient discharge, and removes the need for a patient to be chaperoned. Benefit was not seen from N₂O in

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3 patients undergoing flexible sigmoidoscopy possibly because it was delivered on
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5 demand rather than continuously.
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INTRODUCTION

Flexible sigmoidoscopy is often performed without analgesia or sedation. The potential for pain and discomfort are the main limitations^{1, 2} and can deter patients from returning for repeat procedures, which may decrease their compliance in a bowel cancer-screening program. Colonoscopy is less well tolerated than flexible sigmoidoscopy.

Pain and vasovagal reactions are common, such that the standard practice is to provide intravenous analgesia and sedation to patients. This usually allows completion of the procedure but at the risk of oxygen desaturation, prolonged recovery time in the endoscopy department and the need for continued chaperoning at home.

Conscious sedation describes the physical state that allows patients to tolerate pain and discomfort while maintaining adequate cardiorespiratory function and the ability to respond purposefully to verbal commands³. The therapeutic goal of conscious sedation may be better described as a combination of sedation and analgesia⁴.

Nitrous Oxide (N₂O) is an inert gas that since 1844 has been valued in anaesthetic practice for its analgesic, amnesic and sedative properties. It can be combined with oxygen in equal volumes (Entonox®) and is widely used in this form as an analgesic in obstetric and dental practice. It is fast acting (effect noted within 60 seconds on inhalation) and has a short recovery time (being eliminated unchanged by the lungs in 1-5 minutes). This potentially makes it an ideal agent outpatient procedures like lower gastrointestinal endoscopy.

The purpose of this review is to consider the current evidence base for the use of nitrous oxide gas for sedation in patients undergoing flexible sigmoidoscopy or colonoscopy.

METHODS

Eligibility criteria

Clinical trials were eligible if adult patients undergoing either colonoscopy or flexible sigmoidoscopy were randomly allocated to receive either sedation with nitrous oxide or control.

Search strategy and trial identification

We performed computerised searches of PubMed, Embase, the Cochrane library using the search terms, “nitrous oxide”, “Entonox”, “sedation”, “analgesia”, “inhalational”, “colonoscopy”, “sigmoidoscopy”. **Following this the same search terms were entered into Google® for additional information.** Reference lists from eligible trials were checked in an attempt to locate any further publications. Authors were contacted to request data or information on trial methodology, which had not been reported. We also approached the Linde group (Munich, Germany), owners of the British oxygen company (BOC) to ask if they were aware of any unpublished data on the use of nitrous oxide in endoscopy departments.

The titles of the articles located by the searches were scanned (SJL and SW) and where the title was thought to be relevant the abstract was read (SJL and SW), and if the article still appeared relevant a copy of the full manuscript was obtained. Full manuscripts were reviewed (SJL and SW) and a final decision made about inclusion.

Data extraction and outcomes

Two authors (SJL and SW) extracted and tabulated data for each study, and crosschecked for consistency. Disagreements were resolved by consensus.

1
2
3 Data was extracted on inclusion criteria, exclusion criteria, control regime, endoscopists
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5 experience, study methodology (including randomization and blinding), age, sex and
6
7 baseline patient anxiety. Procedural data was recorded (depth of insertion, duration of
8
9 procedure, technical difficulty, length of stay after the procedure until fit for discharge
10
11 (recovery time)). Outcomes recorded included: pain, discomfort, requirement for
12
13 'breakthrough' analgesia, satisfaction with the procedure and psychomotor recovery.
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17 Adverse events were also recorded.
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19 **Assessment of methodological quality**

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21 Several aspects of trial design have been shown to be associated with a reduction in
22
23 estimated bias of treatment effects^{5, 6}: these include generation of the allocation
24
25 sequence and concealment of allocation from participants and outcome assessors. Both
26
27 authors (SJL and SW) independently assessed the methodological quality of the
28
29 included trials. We considered generation of allocation sequence and concealment of
30
31 allocation to be adequate if the resulting sequences were random and if participants and
32
33 enrolling investigators could not predict the assignment. In addition we also recorded
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35 method of randomization generation, criteria for inclusion and exclusion and intention to
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37 treat analysis. Any differences were resolved by consensus (SL and SW).
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RESULTS

We identified 154 references through electronic data base searches. After exclusion of duplicates this was reduced to 102 abstracts. Twelve abstracts appeared relevant and the full papers were assessed. A further three studies were rejected for being non-randomised⁷, inclusion of paediatric patients⁸ or using nitrous oxide in addition to sevoflurane (an inhalational anaesthetic agent)⁹.

Nine publications¹⁰⁻¹⁸ were deemed by both authors to be original research and to fit the search criteria. One of the three groups (placebo) in the study by Trojan *et al*¹⁸ was excluded, as patients were not allocated randomly. No further articles were identified from reference lists or correspondence.

Characteristics of trials, patients and interventions

Nine randomized trials published between 1994 and 2009 were identified with a total of 623 patients (216 undergoing flexible sigmoidoscopy, 407 undergoing colonoscopy, table 3). Additional unpublished data were obtained for five studies^{12-14, 16, 17} (these data comprised of methodology, patient characteristics and outcomes). Most trials were small (table 3, range 27¹⁸ to 131¹⁵ patients) with five studies having less than 60 patients randomised^{10, 14, 16-18}. Trials excluded patients who were considered to be physically frail or whose procedures were likely to be technically difficult.

In three studies of patients undergoing flexible sigmoidoscopy¹⁰⁻¹² nitrous oxide gas was compared against a control gas (effectively placebo) of oxygen alone (table 1). In six studies where patients underwent colonoscopy¹³⁻¹⁸, nitrous oxide gas was compared against an intravenously administered opiate with or without midazolam.

Methodological quality of trials

1
2
3 Reporting of generation of randomisation sequences, concealment of allocation and
4
5 power calculations was poor (table 2). In five trials allocation was concealed using
6
7 sealed envelopes^{11, 13-16}. Where explicit, four trials were double blinded^{11, 12, 14, 17}. Three
8
9 trials were not analysed on an intention to treat basis^{11, 12, 18}.

13 Procedure

14
15 Nitrous oxide gas was taken 'on demand' by the patients participating in the three
16
17 studies of flexible sigmoidoscopy (table 1). There were six studies where patients
18
19 underwent colonoscopy: in three patients were 'pre-loaded' with nitrous oxide for one to
20
21 two minutes^{13, 15, 18} (table 1). From the start of colonoscopy nitrous oxide was given
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23 continuously for a period then on demand in three studies^{13, 15, 17} and throughout the
24
25 whole procedure in one study¹⁶ (table 1). No data was presented on the time required to
26
27 train patients to use the nitrous oxide gas. Little data was presented on the
28
29 endoscopist's technical experience (table 1).
30
31 The difficulty of procedure was only recorded in the studies where colonoscopy was
32
33 used; no differences between groups were noted (table 3). No differences were seen
34
35 between groups for depth of insertion at sigmoidoscopy or caecal intubation (table 3).
36
37 The duration of procedure or where measured, the time taken to reach the caecum was
38
39 not different between the groups (table 3). However, the duration of colonoscopic
40
41 examination varied widely from a median of 16 min¹⁶ to 32 min¹⁵. Only the two studies
42
43 by Saunders *et al* reported on the number of polypectomies done during endoscopic
44
45 examination with nitrous oxide vs placebo gas 29 vs 27¹² and nitrous oxide vs
46
47 intravenous sedation 2 vs 2¹⁷ in the 'placebo' group. No data was presented on other
48
49 procedures done during endoscopic examination. Patients received more midazolam
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2
3 (mean dose 4.7mg) in the study by Forbes *et al*¹³ than in other studies. Additional
4
5 intravenous sedation was not commonly given, and no difference between groups was
6
7 noted (table 4).
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10 11 **Patient experience**

12
13 In most studies visual analogue scales were used to assess patient experience. Pre-
14
15 procedure anxiety was recorded in three studies where colonoscopy was used. No
16
17 differences were noted between groups (table 4).
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21 For patients undergoing sigmoidoscopy no differences in abdominal pain were reported,
22
23 although discomfort was reduced in the nitrous oxide group compared to the control arm
24
25 in one study (table 4). Saunders *et al*¹² found that in the patients who actually used the
26
27 gas (nitrous oxide 23, control 24 patients) pain was reduced with nitrous oxide (median
28
29 score 10 vs 30 respectively) $p=0.045$. In patients undergoing colonoscopy three
30
31 studies^{14, 16, 17} found no differences in pain scores between groups; one study did not
32
33 report pain outcomes¹⁸. Forbes *et al*¹³ found that median pain score was higher where
34
35 nitrous oxide was used, while Maslekar *et al*¹⁵ showed the reverse (table 4).
36
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40 41 **Side effects**

42
43 No serious side effects or procedural complications were reported in any study (table 4).
44
45 The commonest side effect of nitrous oxide reported was headache. Nausea was noted
46
47 in some patients receiving opioid analgesia. Oxygen desaturation and post procedural
48
49 hypotension were noted in two studies^{13, 17} with no obvious differences between groups.
50
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52 53 **Psychomotor recovery**

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55 Four studies examined aspects of psychomotor recovery following colonoscopy.
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57 Lindblom *et al*¹⁴ assessed patients ability to recall ten objects shown to them before the
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3 procedure and then immediately after. Patients receiving nitrous oxide gas had better
4
5 recall than those receiving intravenous therapy (median number of items correctly
6
7 recalled were, 9 and 8.5 before the procedure and 9 and 7 after, respectively $p=0.025$).
8
9 Trojan *et al*¹⁸ asked patient to undergo assessments 20 min before their colonoscopy,
10
11 immediately after, then again 15, 30 and 45 min later. Only seven patients receiving
12
13 nitrous oxide and six receiving intravenous therapy were fit enough to undergo testing
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15 immediately after their procedure due to drowsiness or dizziness. No differences were
16
17 noted for reaction times between groups. Tests of complex psychomotor co-ordination
18
19 (tracking test) improved after the procedure in both groups but no difference in degree of
20
21 improvement was seen between groups. Manual dexterity was not altered by nitrous
22
23 oxide gas but was impaired with intravenous therapy up to 45 min post colonoscopy.
24
25 Letter cancellation (a test used to assess visual perception) was only impaired in those
26
27 receiving intravenous therapy immediately after their procedure ($p=0.04$). Maslekar *et*
28
29 *al*¹⁵ showed with letter cancellation tests that patients receiving nitrous oxide had
30
31 returned to median of 92% of their pre-colonoscopy value in tests done immediately on
32
33 return to the recovery room, by 15 min after the procedure to 94% and at discharge (28
34
35 min post colonoscopy) to 100%: where as for those patients receiving intravenous
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37 therapy scores were 68% 15 min post procedure ($p=0.001$) and 87% at discharge (51
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39 min post colonoscopy) ($p=0.003$).
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48 **Length of post-procedural stay**

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50 For patients who had undergone colonoscopy, the time between scope withdrawal and
51
52 readiness for home discharge varied from a median of 0 min¹⁴ to 80 min¹³. This time
53
54 period was shorter for patients receiving nitrous oxide than control in all of the six
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3 studies (table 4). Little difference was seen for patients undergoing flexible
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5 sigmoidoscopy.
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DISCUSSION

There was no difference in patient reported discomfort between nitrous oxide and control groups for patients undergoing either flexible sigmoidoscopy or colonoscopy. Nitrous oxide gas was well tolerated and had no impact on the duration, quality or difficulty of examination. Following colonoscopy the use of nitrous oxide for sedation was associated with a more rapid recovery when compared to intravenous sedative and analgesia. No differences in complications were seen between groups. Unfortunately because of differences in study design and because most data was not normally distributed it is inappropriate to combine results for meta-analysis.

In the three studies where patients underwent flexible sigmoidoscopy around 50% experienced enough discomfort to use sedation (nitrous oxide or control gas). Nitrous oxide gas appeared to reduce patient reported procedural discomfort in one study¹¹ and pain scores in another¹², but overall it was not obviously superior to placebo gas (oxygen alone).

Patients undergoing colonoscopy commonly experienced pain and discomfort whether receiving nitrous oxide or intravenous sedation. Maslekar *et al*¹⁵ found nitrous oxide superior to intravenous sedation in terms of pain score, patient satisfaction and greater willingness to undergo another procedure using the same sedation regimen, while the smaller study by Forbes *et al*¹³ found the reverse, perhaps because they used larger doses of midazolam. Overall, little difference in patient reported pain or discomfort was seen between groups (table 4), suggesting that for colonoscopy, nitrous oxide sedation may be equivalent to intravenous opioid and benzodiazepine. The apparently conflicting findings (that nitrous oxide is an effective sedative for colonoscopy but no better than placebo for flexible sigmoidoscopy) may be related to differences in the manner in which

1
2
3 the nitrous oxide was administered. Patients undergoing flexible sigmoidoscopy were
4
5 not 'loaded' with nitrous oxide gas prior to their procedure, whilst patients undergoing
6
7 colonoscopy usually received a preprocedural loading dose followed by continuous use
8
9 for the initial part of the examination. The onset of analgesic effect of nitrous oxide gas
10
11 occurs approximately 60 seconds following inhalation. It is therefore likely that when
12
13 taken in response to pain it will not be as effective as when taken prophylactically. Pain
14
15 and discomfort occur predominantly during insertion of the endoscope. If nitrous oxide
16
17 gas were to be given proactively to patients undergoing flexible sigmoidoscopy then an
18
19 improved outcome may be apparent.
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24 Overall a reasonable number of patients were recruited to the nine studies. Most trials
25
26 were not of high quality and few were large. There was little evidence of randomization
27
28 bias between groups. The main message of these studies was to show similar patient
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30 satisfaction for colonoscopy using nitrous oxide compared with intravenous sedation and
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32 analgesia, but with more rapid recovery times and almost immediate return of
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34 psychomotor function. Nitrous oxide therefore has potential to improve patient flow
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36 through the endoscopy department and also benefit patients who otherwise would
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38 require assistance with transportation or care at home following colonoscopy. No data
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40 was presented on the cost involved in nursing/personnel time required to educate
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42 patients on how to self-administer the nitrous oxide gas, so it is difficult to comment on
43
44 the overall practicality of this approach.
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50 Six of the nine studies reported adverse effects, which were uncommon and mild with
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52 any sedation regimen. Nitrous oxide irreversibly inactivates methionine synthetase
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54 resulting in raised plasma homocysteine concentrations. Homocysteine is implicated in
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56 myocardial ischaemia, immunodeficiency and impaired wound healing¹⁹. Prolonged use
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3 of nitrous oxide during surgery is associated with postoperative nausea, vomiting, poorer
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5 wound healing and possibly increased cardiac complications²⁰. A large study currently
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7 recruiting, is examining the safety profile of high dose nitrous oxide (70% N₂O in oxygen
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9 for maintenance of anaesthesia in major surgery, www.enigma2.org.au). In view of the
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11 short duration and the relative lack of tissue damage caused during endoscopy, it is
12
13 unclear whether these concerns apply when 50% nitrous oxide in oxygen is used as a
14
15 sedative for such procedures. Because of small participant numbers, exclusion of
16
17 patients with significant comorbidity, lack of standardization of nitrous oxide dosing
18
19 regimens and inconsistent reporting of outcomes the studies within this review are
20
21 unable to address any of these safety concerns. **None of the included studies**
22
23 **addressed the possibility of teratogenic risk to staff secondary to environmental**
24
25 **contamination by nitrous oxide, however, endoscopy suites are generally well ventilated**
26
27 **and we know of no case reports of miscarriage attributable to nitrous oxide in midwives.**
28
29 **In practice this is unlikely to be a consideration.**

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36 Significant numbers of patients experience pain and discomfort when undergoing lower
37
38 gastrointestinal endoscopy thus there is considerable potential for improving patients`
39
40 experience. Few studies have examined patients` expectations and the usefulness of
41
42 simple visual analogue scales for pain as an end-point for patient satisfaction. For
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44 patients undergoing colonoscopy it appears that intravenous sedation is only marginally
45
46 superior to placebo²¹. In line with this observation colonoscopy is performed without
47
48 sedation in many countries²². The magnitude of discomfort a patient should be
49
50 expected to tolerate is subjective, and there are large variations in practice across the
51
52 world. Patient satisfaction appears to be is considerably higher if sedation with
53
54 propofol[®] is used instead of light conscious sedation with a benzodiazepine and an
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3 opioid²³ however, this drug is easy to overdose, increasing the risk of apnoea and
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5 hypoxia. In many countries, including the United Kingdom and the USA, the use of
6
7 propofol infusions mandates the continuous presence of anaesthetic trained personnel,
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9 which considerably increases cost. Such economic considerations generally preclude
10
11 more than light conscious sedation for the majority of patients.
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15 On the evidence presented in this review, it has not been conclusively shown that self
16
17 administered nitrous oxide gas improves patients` experience. This may relate to the
18
19 dosing regimen: during endoscopic procedures the operator is often poor at predicting
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21 which manoeuvres are likely to be painful²⁴ such that it may be difficult to instruct when a
22
23 patient should self administer. Patients taking the gas in reaction to pain may fail to
24
25 achieve adequate concentrations, since there is a lag time prior to the onset of effect.
26
27 The low solubility of nitrous oxide gas results in rapid eliminated with minimal residual
28
29 analgesic effect.
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33 Further studies may wish to examine the benefits of a 'multi-modal' approach
34
35 complementing minimal sedation techniques in patients undergoing lower
36
37 gastrointestinal endoscopy with for example the use of CO₂ insufflation (rapid absorption
38
39 reduces discomfort from intestinal distension), magnetic imaging devices, variable
40
41 stiffness scopes and distraction²⁵. Regimens that achieve a background level of nitrous
42
43 oxide or the role of nitrous oxide in combination with intravenous analgesics and
44
45 sedatives or subanaesthetic doses of agents such as sevoflurane⁹ may be worth
46
47 exploring in further studies, but the safety of such regimens in the absence of a trained
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49 anaesthetist remains untested.
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53 Sedation with nitrous oxide appears to offer little benefit to patients undergoing flexible
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55 sigmoidoscopy, though this may well reflect the way the gas was administered in the
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3 studies examined. The main message of these studies was to show similar patient
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5 satisfaction for colonoscopy using nitrous oxide gas compared with intravenous sedation
6
7 and analgesia, but with more rapid recovery times and an almost immediate return of
8
9 psychomotor function. Nitrous oxide gas has the potential to improve patient flow
10
11 through the endoscopy department. No data was presented on the nursing time taken
12
13 to educate patients to the use of nitrous oxide pre-procedure so it is difficult to state
14
15 overall benefit. Patients who live alone or who wish to drive home may in particular
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17 benefit from the rapid recovery of psychomotor function seen when nitrous oxide gas is
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19 used⁷.
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Table 1
Study design

Study	Year	Procedure	Inclusion criteria	Exclusion criteria	Nitrous oxide regime	Control regime	Endoscopist experience	No of endoscopists
Saunders	1995	Sigmoidoscopy	55-75yrs, screening program	COPD, pneumothorax, bowel obstruction, glaucoma, obstructive uropathy, autonomic dysfunction unstable angina tachyarrhythmias, anticholinergic medication.	Patient administered 'on-demand'	Oxygen	> 50 procedures	1
Fich	1997	Sigmoidoscopy	Screening and non-screening	Chronic lung disease, Severe chronic illness	Anaesthetist assisted 'on demand'	Oxygen	Fellow >1year experience	ND
Harding	2000	Sigmoidoscopy	All	Patients driving	Nurse assisted 'on demand'	Oxygen	Not stated	5
Lindblom	1994	Colonoscopy	20-70yrs	Previous colonic resection, drug abuse, intolerance to drugs used, inability to speak swedish	Nurse assisted	Ketobemidone 2.5mg + midazolam 2.5mg	'Considerable'	6
Saunders	1994	Colonoscopy	All cases	COPD, Pneumothorax, bowel obstruction, malignant hyperpyrexia	Patient administered, continuous for first 1 min then 'on-demand'	Pethidine 50mg + midazolam 2.5mg + hyoscine 20mg	> 500 procedures	2
Notini-Gudmarsson	1996	Colonoscopy	All cases	COPD, Pneumothorax, bowel obstruction, malignant hyperpyrexia	Patient administered, continuous throughout with deeper breaths if required	Pethidine 1mg/kg IM	'Experienced'	2
Trojan	1997	Colonoscopy	All routine, ASA grade 1 or 2	Not stated	Patient administered Pre-load given 1 min then 'on-demand'	Pethidine 25-50mg + midazolam 2.5mg + hyoscine 20mg	Not stated	3
Forbes	2000	Colonoscopy	All cases	Not stated	Patient administered Pre-load given 1 min, continuous to caecum then 'on-demand'	Midazolam 0.06mg/kg + Meperidine 0.76mg/kg	Not stated	2
Maslekar	2009	Colonoscopy	All outpatients	Severe chronic illness, colonic resection, combined gastroscopy, chronic respiratory illness, mechanical impediment, non-english speakers	Patient administered Pre-load 2 min, continuous to caecum then 'on-demand'	Midazolam + fentanyl	Not stated	ND

Table 2

Methodological quality

Study	Generation of allocation sequence	Concealment of allocation	Power calculations	Blinding of intervention from		Analysed as ITT
				Patient	Assessor	
Saunders	Computer (in blocks)	No	None	Yes	Yes	No
Fich	Not stated	Not stated	Not stated	Yes	No	Yes
Harding	Not stated (in blocks)	Sealed envelopes	Not stated	Yes	Yes	No
Lindblom	Not stated (in blocks)	Sealed envelopes	Not stated	Yes	Yes	Yes
Saunders	Computer (in blocks)	Not stated	None	Yes	Yes	Yes
Notini-Gudmarsson	Not stated	Sealed envelopes	Yes	Yes	Yes	Yes
Trojan	Not stated	Not stated	Not stated	Not stated	Yes	No
Forbes	Tables	Sealed envelopes	Not stated	No	No	Yes
Maslekar	Not stated (in blocks)	Sealed envelopes	Yes	No	No	Yes

Table 3

Baseline and procedural data (means, unless otherwise stated^m)

Study	Number		Age (years)		Male:Female		Depth of insertion (cm from anus)				Procedure duration (min)		Procedural difficulty	
	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control
Saunders	48	43	64	64	30:18	27:16	60 ^m	60 ^m	-	-	15 ^{m p}	18 ^{m p}	ND	ND
Fich	18	20	58	59	9:9	12:8	51	48	-	-	9.4	9	ND	ND
Harding	45	42	52	53	24:16	15:22	29 ¹	28 ¹	-	-	ND	ND	ND	ND
							Caecal intubation		Time to caecum					
Lindblom	25	25	46 ^m	40 ^m	14:11	12:13	25	25	ND	ND	47 ^m	45 ^m	ND	ND
Saunders	30	29	46 ^m	42 ^m	14:16	11:18	30	29	13 ^m	14 ^m	ND	ND	E2A21D7	E1A22D6
Notini-Gudmarsson	19	19	59 ^m	60 ^m	ND	ND	17	17	ND	ND	17	16	6.4	6.2
Trojan	12	15	52	53	6:6	11:4	12	15	ND	ND	28	30	E0A7D5	E0A13D2
Forbes	56	46	48	49	26:30	29:17	54	46	9.8	7.5	17.4	16.6	26	17
Maslekar	65	66	56 ^m	60 ^m	29:36	34:32	61	61	18 ^m	20 ^m	26.5 ^m	31.9 ^m	17 ^M	14 ^M
ND = No data, ^m = Median * = p<0.05, ¹ = Time to descending colon, ^p = excluding patients who had polypectomies, E = Easy, A = Average, D = Difficult														

Table 4

Quality of sedation, recovery times and side effects (means, unless otherwise stated^m)

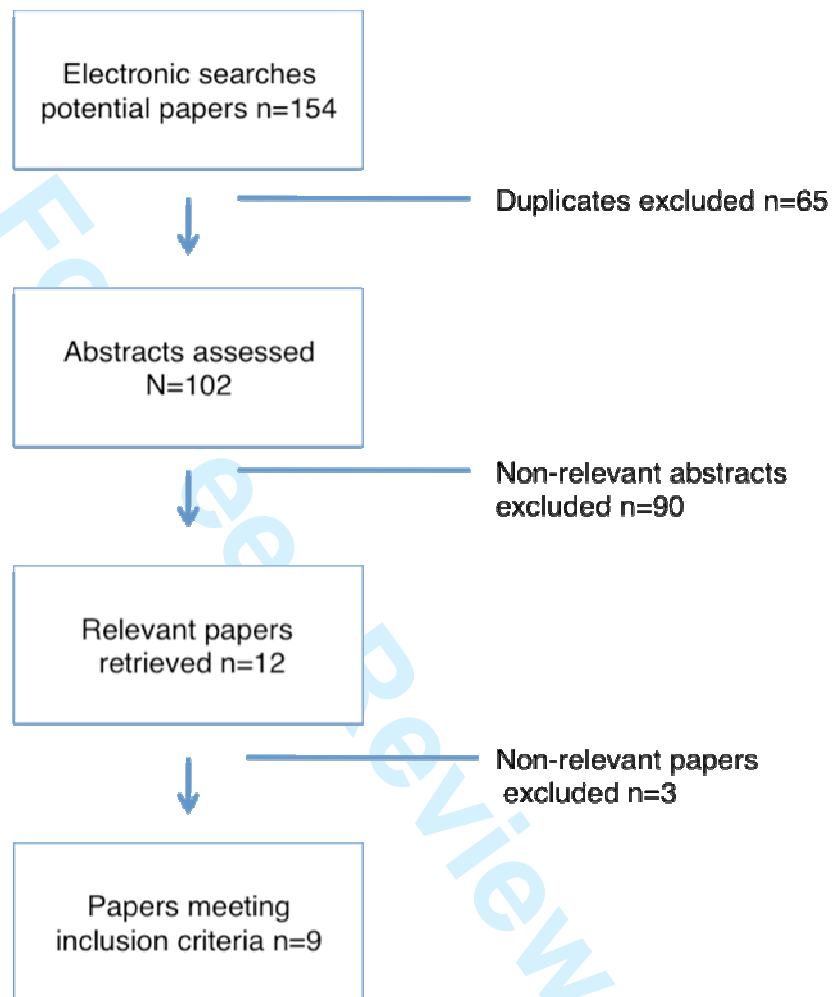
Study	Pre-procedure VAS anxiety (0-100)		Procedural VAS pain (0-100)		Procedural VAS discomfort (0-100)		Extra iv sedation given		Fit for discharge following scope withdraw (min)		Adverse events during procedure		
	Entanox	Entanox	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control	Entanox	Control	Comment
Saunders	ND	ND	24 ^m	42 ^m	ND	ND	-	-	ND	ND	0	0	None
Fich	ND	ND	47	37	16	18	-	-	3.3	0.5*	ND	ND	None
Harding	ND	ND	ND	ND ¹	30	71*	-	-	ND	ND	ND	ND	ND
Lindblom	ND	ND	- ^T	- ^T	51 ^m	54 ^m	1	5	0 ^m	37.5 ^{m*}	ND	ND	ND
Saunders	42 ^m	42 ^m	15 ^m	10 ^m	ND	ND	5	3	32 ^m	60 ^{m*}	2	10	Desaturation, hypotension, nausea, headache, drowsiness, dizzy, parathesia
Notini-Gudmarsson	ND	ND	44	58	ND	ND	0	1	39	80*	ND	ND	Nausea, tachycardia, dizziness
Trojan	ND	ND	ND	ND	ND	ND	ND	ND	9	16	0	0	None
Forbes	27 ^m	27 ^m	33 ^m	3 ^{m*}	ND	ND	ND	5	30 ^m	60 ^{m*}	15	5*	Desaturation, hypotension, sweating, bradycardia
Maslekar	7.5 ^M	7.5 ^M	16.7	40.1*	ND	ND	0	0	28	51*	0	0	Nausea

VAS 1-100 (or converted to if 1-10), ND = No data, ^T = pain and discomfort are the same when translated into Swedish, ¹ = a different scale was used with no difference between groups, ^m = Median * = p<0.05

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For Peer Review

Figure 1

Study selection

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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