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

Welchman S, Cochrane S, Minto G, Lewis S

CRD summary
The review concluded that N_2O was comparable to intravenous sedation for colonoscopy patients and offered quicker recovery. Trials of flexible sigmoidoscopy revealed no benefits for N_2O over oxygen; this may have been due to differences in administration. The basic synthesis did not consider trial quality and other trial characteristics, so these conclusions should be considered with caution.

Authors' objectives
To review the evidence base for use of nitrous oxide (N_2O) gas for sedation in patients undergoing flexible sigmoidoscopy or colonoscopy.

Searching
PubMed, EMBASE and The Cochrane Library databases and Google were searched. Search terms were reported. Reference lists of any retrieved papers were checked for potentially eligible articles. Authors of eligible studies and a pharmaceutical manufacturer were contacted for unpublished data. It was not reported whether language restrictions were applied to the search.

Study selection
Clinical trials that compared N_2O to control as sedation for adult patients who underwent colonoscopy or flexible sigmoidoscopy were eligible for inclusion.

Participant age ranged from 40 to 64 years. The intervention in all trials was use of Entonox. Investigational techniques included colonoscopy and flexible sigmoidoscopy. In trials that administered colonoscopy, N_2O was compared to an intravenously administered opiate with or without Midazolam. Trials that employed flexible sigmoidoscopy used oxygen (effectively a placebo) as the comparator treatment. In flexible sigmoidoscopy, the depth of insertion ranged from 18cm to 60cm from the anus. Across all trials, procedure duration ranged from nine to 47 minutes (where stated). The time between scope withdrawal and discharge home ranged from zero to 80 minutes for patients who underwent colonoscopy. Most trials employed visual analogue scales to assess patient experience.

Two reviewers assessed study eligibility.

Assessment of study quality
Two reviewers assessed allocation sequence generation, allocation concealment, method of randomisation generation, inclusion and exclusion criteria and adherence to intention-to-treat analysis of included trials. Any disagreements were resolved by consensus.

Data extraction
Two authors extracted data on patient experience, psychomotor recovery, length of post-procedural stay and adverse events. Any disagreements were resolved by consensus.

Methods of synthesis
Studies were summarised by means of a narrative synthesis.

Results of the review
Nine randomised trials were included (623 participants). Sample sizes ranged from 27 to 131. Three trials assessed flexible sigmoidoscopy. Six trials assessed colonoscopy. The authors stated insufficient reporting of methodological details in most trials, especially for generation of allocation sequence, allocation concealment and power calculations. In most trials patients and/or outcome assessors were blinded to the intervention. Six trials used intention-to-treat analysis.

Patient experience: Three colonoscopy trials reported no differences in pain scores between the N_2O group and control for pre-procedural anxiety. Six studies reported on procedural pain. One colonoscopy study reported significantly lower...
pain scores for the N\textsubscript{2}O group compared to control (16.7 points and 40.1 points) and one colonoscopy study reported higher pain scores in the N\textsubscript{2}O group compared to control (33 points and 3 points).

The other trials (three flexible sigmoidoscopy and one colonoscopy) reported no significant differences between groups. One flexible sigmoidoscopy trial reported lower levels of procedural discomfort in the N\textsubscript{2}O group compared to control (30 points and 71 points). Two trials (one flexible sigmoidoscopy, one colonoscopy) reported no significant differences between groups for procedural discomfort. No significant differences were reported for the for extra intravenous sedation between groups in five colonoscopy trials.

**Adverse effects** (five trials): One colonoscopy trial reported more adverse events in the N\textsubscript{2}O group (15 events) compared to control (five events). Four trials (one sigmoidoscopy and three colonoscopy) reported no significant differences between groups.

**Psychomotor recovery** (four trials): Two colonoscopy trials reported better psychomotor recovery in the N\textsubscript{2}O group compared to control immediately after procedures. One colonoscopy trial reported mixed results for psychomotor recovery. Results were not reported for one trial.

**Length of post-procedural stay** (seven trials): Five colonoscopy trials and one sigmoidoscopy trial reported significantly shorter time-periods for post-procedural stay for N\textsubscript{2}O. One colonoscopy trial reported no differences between groups.

**Authors’ conclusions**

N\textsubscript{2}O was comparable to intra-venous sedation for patients who underwent colonoscopy and offered the benefit of a quicker recovery after the procedure. Trials of flexible sigmoidoscopy revealed no benefits for N\textsubscript{2}O over oxygen; this may have been due to differences in administration.

**CRD commentary**

The review question and inclusion criteria were clear. Several relevant sources were searched. Attempts were made to reduce publication bias by searching for unpublished material. It was unclear whether language restrictions were applied and so the risk of studies being missed was uncertain. The risk of reviewer bias was reduced by use of duplicate independent review processes for study selection, quality assessment and data extraction.

The use of a narrative approach rather than a meta-analysis to synthesise studies was appropriate given reported differences in study design and non-normal distribution of most data. However, the synthesis merely classified and grouped trials by the significance level of any reported differences and did not take into account effect sizes, study quality and sample size, which hindered interpretation of the results.

Despite transparent and systematic review methodology, the basic synthesis and the possibility of language bias mean that the authors conclusions need to be considered with caution.

**Implications of the review for practice and research**

**Practice**: The authors suggest that N\textsubscript{2}O given proactively to flexible sigmoidoscopy patients may improve outcomes.

**Research**: The authors stated that it was difficult to comment on the practicality of patient-administered N\textsubscript{2}O sedation as no economic evaluation data were included in the review. The authors recommended that future studies investigate multimodal sedation regimens that combined minimal sedation techniques with approaches such as distraction, variable stiffness scopes, other sedation and magnetic imaging devices (to provide more accurate warnings to the patient about which parts of the procedure were likely to cause pain and/or discomfort).

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