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Inhaled methoxyflurane (Penthrox®) sedation for third molar extraction: a comparison to nitrous oxide sedation

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ABSTRACT

Background: The aim of this study was to evaluate the use of inhaled methoxyflurane (Penthrox®) in the reduction of dental anxiety in patients undergoing mandibular third molar removal in a specialist surgical suite and compare it to the conventional nitrous oxide sedation.
Methods: A prospective randomized, non-blinded crossover design study of 20 patients receiving two types of sedation for their third molar extraction who participated in 40 treatment sessions. At first appointment, a patient was randomly assigned to receive either nitrous oxide sedation or intermittent Penthrox® inhaler sedation, with the alternate regimen administered during the second appointment. Peri-procedural vital signs (heart rate and blood pressure) were recorded and any deviations from 20% from the baseline values, as well as any drop in oxygen saturation below 92% were documented. The Ramsay Sedation Scale (RSS) score was recorded every five minutes. Patient cooperation during the procedure, patients' general opinion about the sedation technique, surgeon satisfaction and the occurrence of side effects were all recorded. After the second procedure, the patient was also asked if he or she had any preference of one sedation technique over the other.
Results: Levels of sedation were comparable in nitrous oxide and Penthrox® sedation sessions. However, at 15 minutes of sedation it was significantly lighter ($p < 0.05$) in Penthrox®. No patient in both regimens reached a RSS deeper than a score of 4. Parameters measured for assessment of sedation (patient cooperation, surgeon satisfaction and patient general opinion about sedation technique) were all similarly comparable for both nitrous oxide and Penthrox®. In both sedation sessions, the odour of the inhalational agent was accepted by the patients; half of the patients (10 patients) who received methoxyflurane thought its odour was pleasant. Patients preferred methoxyflurane (Penthrox®) inhalation over nitrous oxide sedation (Fisher's Exact test, $p < 0.05$). Adverse events were minimal. No patient was either deeply sedated or agitated. Blood pressure was within ± 20% from the baseline values. No patient had oxygen saturation less than 92%. Dizziness was the most frequently encountered side effect in both regimens (four patients each). Two patients had bradycardia (HR < 60 beats/minute) when nitrous oxide was used in comparison to one patient with Penthrox® sedation. Paraesthesia of fingers and heaviness of the chest was encountered only with nitrous oxide sedation (four patients). Mild self-limited shivering occurred in one patient with Penthrox® sedation.
Conclusions: The Penthrox® Inhaler can produce a comparable sedation to that of nitrous oxide for the surgical extraction of third molars under local anaesthesia.

Keywords: Inhaled methoxyflurane, Penthrox®, conscious sedation, third molar mandibular extraction.

Abbreviations and acronyms: DAS-R = Dental Anxiety Scale, Revised; MAC = minimum alveolar concentration; PCS = patient controlled sedation; RSS = Ramsay Sedation Scale; VAS = Visual Analogue Scale.

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INTRODUCTION

Surgical removal of third molar teeth is the most common procedure in oral surgery.[1] Studies have revealed that many patients who are about to undergo surgical third molar removal experience high levels of preoperative anxiety.[2–4] This fear and anxiety can deter some patients from consulting, or delaying consultation so that the eventual treatment becomes more urgent and more costly, and often more difficult for the dentist because of anxiety-related patient behaviour during the intervention.[5]

Inhalational sedation has unique advantages. Its onset of action is rapid and the effect can be maintained for as long as administration lasts.[6] The depth of sedation can be titrated and adjusted because the drug

is eliminated through the airway. Instead of a peak effect, a plateau can be reached within a few minutes, and recovery from the state of sedation occurs within minutes of ceasing administration. Currently, nitrous oxide is the only available inhalational agent that meets conscious sedation requirements. However, potential occupational health hazards and the need for equipment limits its use.[6]

Methoxyflurane (Penthrox®) was introduced as a general inhalational anaesthetic agent in the mid 1960s. The unique ability of methoxyflurane to cause effective non-narcotic analgesia and anxiety relief at low (subanaesthetic) concentrations was soon discovered.[7] The Penthrox® Inhaler is a simple plastic hand-held device for methoxyflurane inhalation, often referred to as the 'Green Whistle'. Since 1978, ambulance services throughout Australia have administered methoxyflurane as a first-line analgesic agent.[8] It has been used to progressively relieve anxiety and reduce pain in several clinical settings.[8–12] The product is currently used in the Gulf Area, Eastern Europe, South-East Asia and Latin America. The Penthrox® Inhaler has recently been introduced to the Saudi market for the same purpose, to provide analgesia and anxiety relief.

Studies have long considered the use of inhaled methoxyflurane (Penthrane®) for conservative dental purposes. Methoxyflurane can produce analgesia and mood modifying properties,[13] and improve operative conditions during dental procedures.[14]

The aim of this study was to evaluate the use of inhaled methoxyflurane (Penthrox®) in the reduction of dental anxiety in patients undergoing mandibular third molar removal in a specialist surgical suite and compare it to conventional nitrous oxide sedation.

Study design

A prospective randomized, non-blinded crossover design was used with each subject serving as his own control. Twenty patients participated in 40 treatment sessions. At first appointment, a patient was randomly assigned to receive either regimen N (nitrous oxide sedation) or regimen P (Penthrox® Inhaler sedation) for the first appointment, with the alternate regimen administered during the second appointment.

METHODS

The study was approved by the Local Ethics Committee and all patients gave informed written consent. Participants included in the study were referred for third molar removal to the Department of Oral and Maxillofacial Surgery, College of Dentistry, King Saud University, Saudi Arabia.

Inclusion criteria were patients who had American Society of Anesthesiologists physical status (ASA) I or II and were between the ages of 18 and 30 years. Patients who were morbidly obese or showed evidence of severe renal impairment, hepatic disorder or obstructive airway disease were excluded from the study. All married women were required to undergo a urine pregnancy test to ensure that they were not pregnant. Patients were discharged into the care of a responsible adult and not permitted to drive or make decisions for 24 hours after the procedure. Patients answered Corah's Dental Anxiety Questionnaire (DAS-R);[15] patients with severe anxiety were excluded. Only those who had a moderate or high level of anxiety according to the DAS-R were selected to take part in the study.[15] Radiological evidence was required to prove that all extractions for all patients (in both procedures) were of comparable difficulty.

Standard preoperative instructions were given. All patients were instructed to not eat or drink after midnight and were scheduled for morning appointments. However, unrestricted clear fluids were allowed for all patients up to two hours before the procedure. All surgery was undertaken in a fully equipped oral and maxillofacial clinic with full resuscitation facilities and conducted by one of two maxillofacial consultants. Local anaesthesia was performed according to a standard protocol using a maximum of two (1.8 ml) carpules of 2% lidocaine with 1:80 000 epinephrine. Patients were monitored via a non-invasive blood pressure cuff, three leads ECG and a pulse oximeter throughout the entire procedure. Initial vital signs and oxygen saturation were recorded and thereafter assessed every five minutes.

Patients were randomly assigned to receive either nitrous oxide sedation or Penthrox® Inhaler sedation for the first session. Before the proposed session, patients were instructed on the use of either the nasal mask for nitrous oxide sedation or the oral inhaler for Penthrox® sedation.

Nitrous oxide sedation session

Nitrous oxide sedation was performed conventionally in accordance with long-standing protocols of the Department of Oral and Maxillofacial Surgery. Initially, 100% oxygen was delivered via a nasal mask, and then nitrous oxide was gradually added, up to 30–50%, titrated to achieve a Ramsay Sedation Scale (RSS) score of 2 to 3 (Table 1).[16] At the end of the procedure, 100% oxygen was given for three minutes before removal of the nasal mask.

The Penthrox® Inhaler is a hand-held green plastic device, 15 cm in length with a mouthpiece at one end and a wick running through the centre. The contents of the 3 ml glass bottle were poured onto the wick. The inhaler was then shaken to dispel any excess liquid and the mouthpiece wiped. The maximum dose of Penthrox® (methoxyflurane) administered via the Penthrox®

Table 1. Ramsay Sedation Scale (RSS)[16]

Score	Description
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

Inhaler was 6 ml of methoxyflurane (two bottles) as recommended.

Initially, two very shallow breaths should be taken to allow the patient to become accustomed to the strong 'fruity' smell. The Penthrox® Inhaler delivers 0.1% to 0.2% of Penthrox® with the 'dilutor' hole uncovered, and 0.2% to 0.4% with the 'dilutor' hole covered during inhalation. The number of puffs was titrated to achieve a RSS of 2 to 3. The maximum amount of puffs allowed initially were 10 as recommended by the manufacturer. Any patient whose requirements for sedation exceeded this number of puffs was excluded from the study. However, patients were allowed later in the procedure to inhale more puffs intermittently if their RSS scores became 1.

Patients returned to the clinic for the second surgical procedure at least four weeks after the initial one and had their third molar extraction exactly under the same set-up, however with the alternate regimen of sedation.

Appropriate postoperative pain medication was prescribed and the patient discharged into the care of a responsible adult in accordance with standard department discharge criteria. Amoxicillin 500 mg capsules were prescribed to all patients postoperatively; thrice daily for five days and Ibuprofen 400 mg twice daily when required.

Measurements

The demographic, intraoperative and recovery data were all collected. The number of puffs of Penthrox® received (both initial and intermittent) and time till the intermittent puffs were required in the Penthrox® sedation regimen were all documented. Pre, intra and post-procedural vital signs (heart rate and blood pressure) were recorded every five minutes and any deviation from 20% from the baseline values, as well as any drop in oxygen saturation below 92% were recorded.

The RSS score was recorded every five minutes and the deepest level of sedation attained during each session was recorded by the anaesthetist. Patient cooperation during the procedure was also scored by the anaesthetist using a 0–10 cm Visual Analogue Score (VAS) (0 = uncooperative; 10 = very cooperative). Patients' general opinion about the sedation technique (VAS) (0 = poor; 10 = excellent) and the odour of the inhalational agent used was obtained. The surgeon was also asked to rate his or her satisfaction with the sedation technique using the surgeon satisfaction scale. (Table 2). Any side effects were also reported. After the second procedure, the patient was asked if he or she had any preference of one sedation technique over the other.

Table 2. Surgeon satisfaction scale

Score	Description
1	Dissatisfied
2	Somewhat dissatisfied
3	Neither satisfied nor dissatisfied
4	Somewhat satisfied
5	Satisfied

Statistics

Statistical analyses were made with SPSS® Version 16.0 (SPSS Inc., Chicago, IL, USA). Results are presented as mean and standard deviation (mean ± SD) or in number. Intergroup statistical analyses were performed using Student's *t*-test, and non-parametric data. RSS, patient cooperation, surgeon and patient satisfaction, and depth of sedation were analysed using the Mann-Whitney test, Chi-square test or Fisher's Exact test as appropriate. P-values < 0.05 were considered statistically significant.

RESULTS

Patients' characteristics are shown in Table 3. The duration of surgery recovery time was comparable in

Table 3. Patients characteristics and intraoperative data

Patients characteristics	
Number of patients	20
Age (yr)	23 ± 3.9
Gender (M/F)	8/12
Weight (kg)	64 (range 45–82)
Previous dental history (Y/N)	10/10
ASA classification I/II	18/2
DAS-R	10.7 ± 1.5
Duration of surgery (min) (Nitrous/Penthrox)	19 ± 6.2/20 ± 6.5
Time to sit up unaided (min) (Nitrous/Penthrox)	8.1 ± 3.43/6.8 ± 2.7
Patient requirements of Penthrox	
Initial puffs	
Number of puffs	8.6 ± 1.43
Intermittent puffs	
Number of puffs	4.4 ± 2.96
Number patients required intermittent puffs	15
Time for intermittent puffs (min)	9.8 ± 3.82
Total (initial + intermittent)	13 ± 3.08

Data are expressed as mean ± sd, range and number where appropriate.

both sedation sessions. All patients were able to sit up unaided and transfer themselves unaided from the operating table to the trolley within less than 10 minutes from the end of the procedure. In the Penthrox® session, the initial number of puffs given to achieve a RSS of 2 to 3 was found to be 8.6 ± 1.43. One patient initially required more sedation (more than the recommended maximum 10 puffs) and was excluded from the study. Fifteen patients needed to inhale further Penthrox®; an average of 4.4 puffs after a mean time of 9.8 minutes (Table 3).

The mean RSS was comparable in nitrous oxide and Penthrox® sedation sessions at the measured time points except at 15 minutes of sedation where it was significantly deeper ($p < 0.05$) in nitrous oxide than in Penthrox®; 2.3 ± 1.17 versus 1.6 ± 0.94, respectively (Fig 1). The deepest level of sedation achieved (according to the RSS) was comparable for both regimens (Fig 2). No patient in both regimens reached a RSS beyond a score of 4.

Parameters measured for assessment of sedation (patient cooperation, surgeon satisfaction and patient general opinion about sedation technique) were comparable for both nitrous oxide and Penthrox® as shown in Table 4. In both sedation sessions, the odour of the inhalational agent was accepted by the patients; half of the patients (10 patients) who received methoxyflurane thought its odour was pleasant. Patients preferred methoxyflurane (Penthrox®) inhalation over nitrous oxide sedation (Fisher's Exact test $p < 0.05$). Data were mean ± SD or number of the patients (*$p < 0.05$).

Adverse events were minimal (Table 5). No patient was either deeply sedated or agitated (Fig 2); blood pressure was within ± 20% from the baseline values. No patient had oxygen saturation less than 92%. However, some patients experienced mild brief self-resolving adverse events. Dizziness was the most frequently encountered side effect in both regimens (four patients each). Two patients had bradycardia (HR < 60 beats/minute) when nitrous oxide was used in comparison to one patient with Penthrox® sedation. Paraesthesia of fingers and heaviness of the chest was encountered only with nitrous oxide sedation (four patients). Mild self-limited shivering occurred in one patient with Penthrox® sedation.

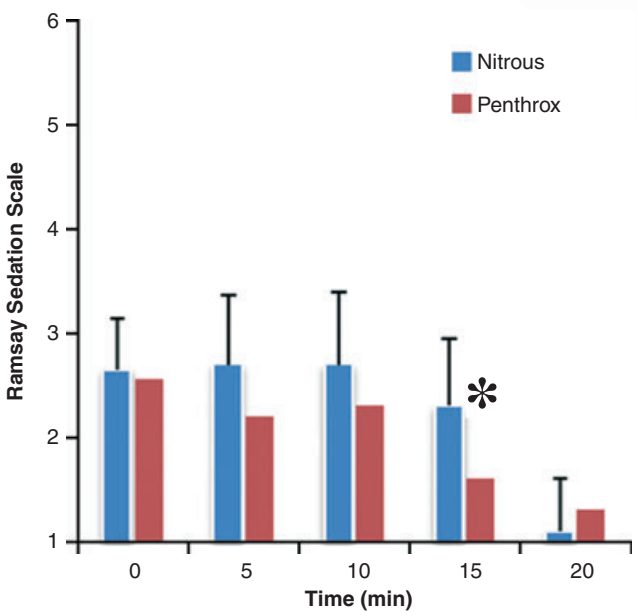

Fig 1. Ramsay Sedation Score (RSS) variables (mean) at the measured time points in the two sedation regimens.

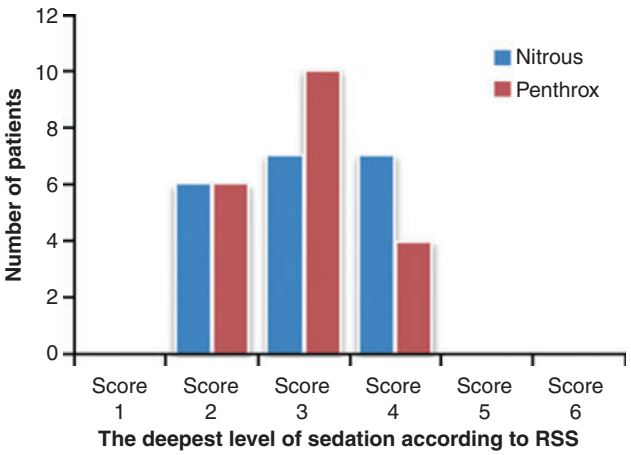

Fig 2. Deepest level of sedation achieved by patients according to Ramsay Sedation Score (RSS).

Table 4. Assessment of sedation technique

Variables	Nitrous	Penthrox®	P value
Patient cooperation (VAS)	5.85 ± 1.95	6.65 ± 1.95	0.546
Surgeon satisfaction (1–5)	3.95 ± 1.19	3.9 ± 1.17	0.841
Patient general opinion (VAS)	5.4 ± 2.79	6 ± 3.14	0.608
Opinion of the odour			
Unpleasant	3	2	
Slightly unpleasant	10	8	
Pleasant	7	10	
No opinion	0	0	
Preferences	7	13*	<0.05

Table 5. Adverse effects

Adverse effects	Nitrous	Penthrox®
Oversedation (RSS over 5)	0 (0%)	0 (0%)
Agitated (RSS less than 2)	0 (0%)	0 (0%)
Dizziness	4 (20%)	4 (20%)
Nausea	2 (10%)	4 (20%)
Bradycardia (HR < 60)	2 (10%)	1 (5%)
Paraesthesia of fingers, heaviness of the chest	4 (20%)	0 (0%)
Headache	1 (5%)	3 (15%)
Shivering	0 (0%)	1 (5%)

Data are expressed as number of patients (percentage).

DISCUSSION

Inhalational sedation is a popular form of sedation, nitrous oxide being the best suited and most frequently used inhalational agent.[6,17] This crossover study has shown that inhaled methoxyflurane (Penthrox®) can produce a comparable sedation to that of nitrous oxide for the surgical extraction of third molars under local anaesthesia with minimal side effects.

Patients can feel nervous or phobic about tooth extraction. The degree of dental anxiety can vary widely, whether it be because of negative childhood experience, injection anxiety (needle phobia) or dental pain. In this study, patients with moderate to high levels of anxiety according to Corah's Dental Anxiety Scale, Revised (DAS-R) were selected; these levels of anxiety have proved to be managed satisfactorily with inhalational sedation. Patients who have severe anxiety (or phobia) cannot be managed by inhalational sedation, particularly conscious sedation, and are best managed under general anaesthesia.[5,18]

Subanaesthetic doses of potent inhalational agents have long been thought to produce inhalational conscious sedation.[19–21] However, the need for anaesthetic equipment limits their use, particularly in office based settings. Therefore, Penthrox® is a revolutionary alternative inhaled agent in this respect. It is ideal for office based dental sedation because of the ease of administration, and eliminates the need for nasal masks and cumbersome anaesthesia equipment. It can also be considered an additional simple treatment option for patients requiring rapid non-injectable, non-narcotic sedation and/or analgesia in dental practice.

In the present study, methoxyflurane has shown to generally provide satisfactory sedation similar to that of nitrous oxide in third molar extraction with local anaesthesia. However, there are two exceptions. Firstly, although clinically insignificant, sedation levels were lighter after 15 minutes from administration of Penthrox®. This can be attributed to the divergence of the techniques used for both agents as in nitrous oxide there was a continuous administration of the agent, whilst Penthrox® was administered intermittently to allow its sedative effect to gradually wear off.[19,22] Secondly, it was obvious that most patients preferred Penthrox® over nitrous oxide. Thirteen of our patients considered methoxyflurane a better sedation option than nitrous oxide. Patients preferred to have control of their anxiety relief by simply inhaling Penthrox® through the inhaler; a concept which may be similar to that of patient controlled sedation (PCS).[23] The odour of the inhalational agent was a strong determinant for acceptance or rejection of a sedation technique. The strong 'fruity' smell of methoxyflurane appeared to not bother patients, as long as the first two puffs were taken slowly. This held true in our study as most of our patients accepted the odour of methoxyflurane and half considered it pleasant. In dental sedation, pain should be effectively controlled by local anaesthesia. However, if pain is encountered during sedation, methoxyflurane is the preferred choice over nitrous oxide.[24]

Methoxyflurane (Penthrox®) is the most potent inhalational agent ever used for general anaesthesia (MAC% 0.16). However, its high solubility (blood/gas partition coefficient 12) and low vapour pressure at room temperature limits its rate of induction.[24] In the context of sedation, these limitations are not clinically noticeable but rather allow patients to ease gradually into sedation. Rapid recovery is essential for sedation techniques, especially when performed in an office based environment. This is one of the advantages of inhalational sedation with nitrous oxide and other potent inhalational anaesthetic agents with low solubility.[20,21] In contrast, methoxyflurane has a characteristic gradual offset action. This is beneficial because it preserves some of its effect, especially analgesia, for some time after administration has ceased.[19,22] In this study, the recovery profile of methoxyflurane competes with nitrous oxide in this respect. The recovery profile achieved when Penthrox® was used may be attributed to the intermittent pattern of its administration.

Penthrox® sedation resulted in very mild, brief self-resolving adverse events in the present study. Although it is outside the scope of the present study, nephrotoxicity associated with methoxyflurane administration has been quite a concern. It has been extensively studied and demonstrated to be dose related.[25] It was concluded that no toxicity was expected at exposures of less than 2.5 MAC-hours (minimum alveolar concentration of the anaesthetic times hours of administration). Clinical nephrotoxicity generally occurred at exposures of greater than 5 MAC-hours. When used as directed and administered via the Penthrox® Inhaler, it is not possible to reach methoxyflurane dosage levels that can produce nephrotoxicity. The maximum recommended dose of Penthrox® (methoxyflurane) administered via the Penthrox® Inhaler is 6 ml of methoxyflurane which represents 0.59 MAC-hours. Clinical evidence and a practical usage history of the Penthrox® Inhaler over 30 years confirms the safety of methoxyflurane.[8,14] However, data on repeated exposure of patients and clinical personnel to methoxyflurane are outdated and scarce,[26–28] and should be further investigated if Penthrox® is to be used frequently in dental clinics.

One limitation of the study design may be the inevitable unblinded nature of the study. However, the fact that many parties shared in the assessment (patients, anaesthetist and surgeons) may have reduced the bias that could have occurred due to the absence of blindness.

CONCLUSIONS

The Penthrox® Inhaler can produce a comparable sedation to that of nitrous oxide in a specialist surgical suite for the surgical extraction of third molars under local anaesthesia. Most patients prefer the inhaler because of its ease of use, minimal side effects and lack of cumbersome anaesthetic equipment.

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