An equivalence study comparing nitrous oxide and oxygen with low-dose sevoflurane and oxygen as inhalation sedation agents in dentistry for adults

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IN BRIEF

- Improves knowledge of the efficacy of low-dose sevoflurane and oxygen as an inhalation sedation agent.
- Provides evidence for a viable alternative to nitrous oxide and oxygen.
- Opens the way for further research into higher, sub-MAC, use of sevoflurane and oxygen.

Objective The aim of this study was to examine whether sevoflurane in oxygen was equivalent to near equipotent concentrations of nitrous oxide in oxygen when used as an inhalation sedation agent in terms of patient and user acceptability. **Method** Forty anxious dental patients referred to the sedation suite at Cardiff University School of Dentistry received either nitrous oxide to a maximum concentration of 40% or sevoflurane to a maximum concentration of 0.3% for a routine maxillary plastic restoration with articaine infiltration local analgesia. The inhalation sedation agent to be administered was chosen by a random number allocator. Measurements of blood pressure, oxygen saturation, heart rate, respiratory rate and bispectral index were recorded every 5 minutes. At the end of the treatment episode the patient, the operator and an observer who was unaware of the agent used, recorded their impressions about the episode by completing questionnaires. **Results** In the doses used in this study, sevoflurane was found to be as effective as an inhalation sedation agent as the standard dose of nitrous oxide used in normal inhalation sedation in the treatment of adult anxious dental patients. **Conclusion** Sevoflurane in low concentrations is equivalent in effect to near equipotent concentrations of nitrous oxide. This would suggest that further research, perhaps with slightly higher concentrations of sevoflurane, is needed. If sevoflurane was shown to be acceptable at slightly higher concentrations, there is scope to explore the development of equipment specifically designed to deliver sevoflurane as an inhalation sedation agent in future.

INTRODUCTION

Inhalation sedation is a conscious sedation technique used to manage anxiety that an individual dental patient can feel about dental treatment. During inhalation sedation a gaseous sedative is mixed with oxygen to provide relief of that anxiety. The commonest inhalational sedative agent used in the UK is nitrous oxide. Conscious sedation in the UK is defined as; 'a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation. The drugs and techniques used to provide conscious sedation for dental

treatment should carry a margin of safety wide enough to render loss of consciousness unlikely'.¹⁻³ At present the inhalation sedation agent of choice is nitrous oxide.¹⁻³ During inhalation sedation, nitrous oxide is incrementally introduced to the individual patient's response to produce a feeling of relaxation and anxiolysis.⁴

The success in managing dental anxiety using nitrous oxide inhalation sedation has been confirmed by many clinical studies.⁵⁻⁸ These studies examined the success of inhalation sedation in the management of paediatric dental cases. Successful completion of treatment was found to occur in around 84% of cases.

The use of nitrous oxide, however, is not without local and global environmental effects. Chronic exposure of medical and dental staff to nitrous oxide can lead to adverse effects.^{9,10} These adverse effects can be haematological,^{11,12} neurological,¹³ hepato-renal,⁹ reproductive¹⁴ and ophthalmological.¹⁵ Nitrous oxide is also a drug of misuse by dental professionals¹⁶ and in wider society. Globally nitrous oxide is a 'greenhouse gas'¹⁷ and in the atmosphere can combine

with oxygen to produce the ozone depleting compound nitric oxide.¹⁸ It is good clinical governance to prevent unnecessary exposure of staff to nitrous oxide. In the UK, limits of exposure to staff form part of the Control of Substances Hazardous to Health Regulations (COSHH) in particular the *Occupational exposure standards* (OES) introduced in January 1996.¹⁹ Exposure of staff can be decreased by: efficient scavenging, suitable nosepieces, good technique to reduce mouth breathing and using well-ventilated rooms.

The increased appreciation of the difficulties associated with using nitrous oxide has led to the examination of alternative inhalation sedation agents (Table 1). The agents that have been examined are:

- Isoflurane²⁰⁻²²
- Xenon^{23,24}
- Sevoflurane, both in isolation²⁵⁻²⁷ and with other drugs.²⁸⁻³⁰

From these studies it might be assumed that any of the above agents might be a suitable alternative to nitrous oxide. However, isoflurane³¹ is too irritant and pungent for patients to tolerate; xenon is

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extremely expensive²³ and must be used via a rebreathing circuit; and sevoflurane, while expensive, lacks equipment dedicated for its use an inhalation sedation agent.

OBJECTIVE

Clinical trials are used to test the effectiveness of either a new drug, a new formulation of an existing drug or a new means of delivering a drug. Trials can be designed to establish if the effect on a particular outcome measure, perhaps a reduction in the level of cholesterol, is superior to the effect of a placebo. This is referred to as a 'placebo controlled trial'. However, it might be considered unethical to test a new drug against a placebo if an effective treatment for the particular outcome measure already exists. In a 'superiority trial' a new drug might be tested to see if it performs better than the existing therapy. In such trials a 'null hypothesis', that there is no difference between the drugs, is tested using an appropriate statistical test. The trial attempts to demonstrate that the hypothesis can be rejected, by showing a statistically significant difference. Failure to demonstrate a difference does not mean that the drugs are equivalent. Researchers may hope to demonstrate equivalence between a new drug and the standard therapy. The new drug may be cheaper or provide a second line treatment if, or when, the first line treatment has proved ineffective or poorly tolerated. It is not possible to demonstrate exact equivalence between two drugs but the aim of an equivalence trial is to demonstrate that any differences in a particular outcome lie within an accepted range known as the equivalence margin. It is crucial that equivalence trials follow exact methods to prevent false results being produced.³²

In this equivalence trial, the aim was to explore if sevoflurane could be considered equivalent to nitrous oxide as an inhalation sedation agent for dental treatment in adults in terms of patient and user acceptability.

MAIN OUTCOME MEASURES

The outcome measures used to demonstrate equivalence were:

- Effectiveness of the sedative and anxiolytic effect for patients. This was measured using visual analogue scales and a post-operative questionnaire completed by the patient
- Apparent effectiveness of the sedative and anxiolytic effect on the patient recorded by an observer experienced in the management of patients undergoing inhalation sedation and who was blind to the type of agent used. This was recorded using visual analogue scales
- Apparent effectiveness of the sedative

Table 1 A comparison of the ideal inhalation sedation agent with nitrous oxide and sevoflurane

Agent	Ideal	Sevoflurane	Nitrous oxide
Anxiolysis	Yes	Yes	Yes
Ease of titration	Yes	Yes	Yes
Induction	Smooth and rapid	Smooth and rapid	Smooth and rapid
Recovery	Rapid	Rapid	Rapid
Cardio/respiratory stability	Yes	Yes	Yes
Pungent and irritant to airway	No	No	No
Toxicity	No	No	Yes with prolonged or chronic exposure
Metabolism	0%	3%	Less than 1%
Blood gas solubility	Low	0.69	0.47
Ease of altering depth of sedation	Rapid	Rapid	Rapid
Environmental pollutant	No	No	Yes

and hypnotic effect on the patient and working conditions for an operator experienced in treating patients under inhalation sedation. This was recorded via sedation scores and behavioural characteristics scores

- Physiological measurement of blood pressure, oxygen saturation, pulse, respiratory rate and bispectral index at 5 minute intervals.

On statistical advice from colleagues at the Department of Anaesthetics, Intensive Care and Pain Medicine, the 95% confidence interval was calculated for the difference in scores between the two groups of patients (one group receiving sevoflurane and the second group nitrous oxide). The primary outcome measure was the response to the question 'Did you find this form of sedation effective?', recorded on a 100 mm visual analogue scale. Assuming that a difference of less than 10 mm between the groups was unimportant, further calculations with a sample size of 20 patients in each group provided a confidence interval of -6.4 to 6.4 mm for no difference, much less than the acceptable 10 mm.

MATERIALS AND METHODS

Ethical approval for the study was gained from The Cardiff and Vale NHS Trust Research and Development Office and Local Research Ethics Committee.

Patient selection

The study involved the provision of conscious sedation to anxious dental patients who had been referred by either a general dental practitioner (GDP), general medical practitioner (GMP) or community dental

service practitioner to the sedation suite at Cardiff University School of Dentistry. The management strategies utilised in the sedation suite include the use of behavioural management techniques, hypnosis, inhalation sedation using nitrous oxide and oxygen, intravenous sedation using midazolam, oral sedation and intranasal sedation using midazolam. Intravenous sedation using propofol administered by a consultant anaesthetist is used in a separate area as part of an MSc module in conscious sedation. Patients referred to the sedation suite vary widely in their medical status. For safety and ethical reasons only patients who met the American Society of Anaesthesiologists (ASA) rating I were included in the study. Exclusion criteria were:

- Unwillingness to participate in the study
- ASA II or greater
- Patients taking psychoactive medication
- Pregnancy
- Intellectual impairment that may have prevented the patient understanding the aim of the study and therefore not being able to give informed consent
- Inability to arrange an escorting adult
- Participating in other studies
- Anatomical anomalies such as a nasal polyps preventing inhalation of gases
- Allergy to sevoflurane or other volatile gases
- Familial or personal history of malignant hyperthermia
- Patients who had previous experience of inhalation sedation.

Although the presence of an adult escort is not mandatory for inhalation sedation using nitrous oxide, it is a recommendation of the sedation suite that patients who have

not experienced inhalation sedation should attend with an adult escort. To avoid the introduction of bias this recommendation was followed for both patient groups.

Additional considerations

Malignant hyperthermia is a fulminant, life-threatening condition³³ affecting between 1 in 5,000 and 1 in 200,000 of the population and is familial with a dominant pattern of inheritance. It is triggered by exposure to any of the volatile anaesthetic agents such as sevoflurane and all depolarising muscle relaxants. It is characterised by hypermetabolism, muscle rigidity, muscle injury and increased sympathetic nervous system activity. Because of this risk it was necessary to review the protocol regarding management of malignant hyperthermia³⁴ with anaesthetic colleagues and to have a clear procedure in place should such an event occur.

Study design

The study comprised a stratified, randomised equivalence study of 40 adult patients referred to the sedation suite for dental treatment because of their dental anxiety. At their initial presentation for assessment patients were asked to complete a modified dental anxiety score (MDAS),³⁵ a comprehensive medical history questionnaire and to answer questions about their social and dental history. Patients who required a plastic restoration in a maxillary tooth under infiltration local analgesia and inhalation sedation were selected for inclusion in the study. The rationale was that analgesia of maxillary teeth is less operator sensitive and more reproducible. The patient's blood pressure was recorded. Patients were given a full explanation of what the trial would involve. Patients were also given an information sheet about the trial to take home. This included the reassurance that should they choose to withdraw from the trial then their treatment would proceed without delay anyway. No patient opted to withdraw. Written informed consent was gained from the patient using the standard dental hospital consent form.

Sevoflurane cannot be delivered via the same dedicated machinery as nitrous oxide so a Boyle's anaesthetic machine was modified by the Clinical Engineering Department, Cardiff and Vale NHS Trust to deliver the sevoflurane. A possible complication of this was that the Boyle's machine could also deliver nitrous oxide mixed with sevoflurane. The machine was further modified to prevent the delivery of nitrous oxide in this way. The Boyle's machine was fitted with a Bleas Datum anaesthetic vaporiser (Bleas Datum,

Beech House, Chiltern Court, Ashridge Rd, Chesham, HP5 2PX, UK). The machine was calibrated using a gas analyser and the concentration dial on the vaporiser clearly marked at 0.3% sevoflurane.

MAC is the minimum alveolar concentration (in volumes per cent) of an anaesthetic gas at 1 atmosphere absolute that prevents movement of 50% of the population to a standard stimulus.³⁶ The effectiveness of anaesthesia and sedation is related to the partial pressure of an inhalation agent in the brain, as opposed to its alveolar concentration. MAC, because it is measurable, is widely regarded as an index of anaesthetic potency. Sevoflurane is a potent agent with a MAC of 2.0% whereas nitrous oxide is a weak agent with a MAC of 110%. Most inhalation sedation for dental treatment occurs at a concentration of nitrous oxide between 25 and 40%.³⁷ This would equate to a concentration of sevoflurane of 0.25% and 0.4%. In order to maintain a wide margin of safety it was decided, with advice from anaesthetic colleagues, to limit the concentration of sevoflurane to 0.3% during the study.

Use of bispectral index monitoring:

Bispectral analysis (BIS) is a measure of the pharmacodynamic effects of anaesthesia and sedation on the central nervous system (CNS).³⁸ The basis for BIS technology is the surface encephalogram that shows total brain activity as a waveform. This waveform varies during the use of sedatives and anaesthetics. The BIS index is derived from utilising a composite of multiple electroencephalography (EEG) signal processing techniques, including bispectral analysis and time domain analysis. Analysis by multivariate statistical models of EEG data from over 5,000 subjects who had received one or more of the most common hypnotic agents provided the database from which the BIS algorithm could be derived. From this a numerical figure was extrapolated and has been used as a parameter to measure the effects of sedation and anaesthesia.^{39,40} BIS values vary from 100 (fully awake) to 0 (flat line EEG), hence a lower BIS number would indicate reduced brain activity. From the way the BIS value is derived, it can be considered as a statistical function and as an indicator of very recent sedation.⁴¹ BIS monitoring was used during this trial to acquire additional data on each patient's response to the sedative administered.

Before each treatment session the study equipment would be set up and tested. The equipment comprised: a MDM Quantiflex nitrous oxide inhalation sedation apparatus; a modified Boyle's machine with a sample

line to a gas analyser attached to ensure the correct dosage of sevoflurane; an ECG monitor; a pulse oximeter; an automatic sphygmomanometer and a BIS machine.

Screens were placed to obscure the machinery from the observer. The same observer was used for every patient seen, and the same dedicated sedation nurse assisted with each patient. When the reception staff had informed the operator of the patient's arrival a National Examining Board for Dental Nurses (NEBDN) sedation trained dental nurse would give the patient a MDAS questionnaire to complete and also a Gestalt test to perform. Gestalt is a psychological term used to describe an organised 'whole' as being greater than the sum of its parts. Gestalt tests can be used to measure recovery from anaesthesia.⁴²

On attending the appointment the patient was asked if they were experiencing any discomfort away from the planned filling site and also if there had been any change in medical history. The planned procedure was confirmed, preoperative blood pressure taken and ECG leads attached. The patient was then reclined and the BIS and pulse oximeter leads attached. As the gas analyser made a very distinctive sound, it was turned on for every case to try and avoid bias. The type of agent used was allocated from a master list produced by a random number generator.

Inhalation sedation involves the use of 100% oxygen for an initial 2 mins and then the incremental introduction of the sedative agent titrated to the patient's response. During the trial the actions involved in administering both the real agent and the alternative agent were performed so that the observer was unclear as to which agent was being used. Topical anaesthetic gel was applied to the local anaesthetic infiltration site for 1 min and then an infiltration of 2.2 ml 4% articaine and 1:100,000 adrenaline was slowly given. After allowing 5 mins for full analgesia to take place the removal of caries and then restoration of the tooth was completed using conventional dental instruments and materials. On completion of treatment 100% oxygen was administered for 4 mins to prevent possible diffusion hypoxia. The patient was asked to complete another Gestalt test and a post-operative questionnaire. Both the observer and the operator completed questionnaires. To avoid placing undue pressure on the patient the operator would place himself outside of the patient's direct line of vision while being able to still monitor his or her wellbeing. The completed questionnaires were collected and placed in a secured folder and locked in a cabinet.

RESULTS

Forty patients completed the clinical trial. There were 18 male patients and 22 female patients with an average age of 34 years. The age range was 18 to 62 years. On completion of the study, the anonymised raw data was entered onto an Excel spreadsheet and passed for analysis to a statistician in the Department of Anaesthetics, Intensive Care and Pain Medicine of Cardiff University.

Analysis involved chi-squared analysis for all of the question and answer sections except answer seven, 'Do you remember being told the treatment was complete for today', which was analysed using Fischer's exact test because of low numbers. The results from the visual analogue scales were analysed using the Mann-Whitney U-test.

DISCUSSION

Analysis of the results showed that there was equivalence between nitrous oxide and sevoflurane in the domains examined in this trial (Tables 2-6). On reflection there is scope for further study in this area. Sevoflurane was used at a low-dose in this study and this could be increased in further studies, in conjunction with anaesthetic colleagues, while remaining well below the MAC of 2%. Another possible area of future study could be the development of machinery dedicated to the delivery of sevoflurane as a dental inhalation sedation agent.

CONCLUSION

Forty patients who were recruited for treatment in the study completed their planned dental procedure, for many this was their first dental experience for some time due to their anxiety. The technique of administering nitrous oxide inhalation sedation was familiar to the operator and the supporting sedation qualified dental nurses. The technique of administering small percentages of sevoflurane was less easy but by no means difficult, although the use of the gas analyser meant an additional machine to monitor for the assisting dental nurse. In a clinical trial setting in a dental teaching hospital there were fewer time pressures at each treatment episode than would be the case in primary care and so the safe delivery of an agent such as sevoflurane, using non-dedicated machinery, was achieved without any complications. The questionnaires were generally well received and only one patient failed to complete them adequately. The operator and observer both felt that the questions they were expected to answer were reasonable and within their sphere of experience. In a future study it would perhaps be better if the operator also had visual analogue scales to complete, as these proved

Table 2 Responses to MDAS, observer and patient VAS questionnaire (median [IQR] range)

	Nitrous oxide	Sevoflurane	P value
Modified dental anxiety score	20 [17 to 24] (7 to 25)	18 [14 to 21] (6 to 25)	p = 0.14 (NS)
Degree of patient relaxation	84 [57 to 88] (7 to 95)	80 [67 to 86] (45 to 92)	p = 0.62 (NS)
Effectiveness of sedation	85 [59 to 88] (5 to 94)	82 [68 to 86] (38 to 93)	p = 0.64 (NS)
Degree of anxiety	81 [56 to 85] (1 to 93)	79 [66 to 84] (42 to 87)	p = 0.64 (NS)
Patient visual analogue scale 1	79 [59 to 92] (18 to 99)	72 [46 to 92] (9 to 100)	p = 0.46 (NS)
Patient visual analogue scale 2	88 [51-95] (0 to 100)	84 [66 to 94] (12 to 100)	p = 0.94 (NS):

Table 3 Responses to patient questionnaires. Missing data reflects non-completion of questionnaire by some participants

Question		Yes	No	Not sure	A little	Total
Do you remember having an injection	Nitrous oxide	14(73.7%)	2 (10.5%)	3 (15.8%)		19
	Sevoflurane	17(85.0%)	2 (10.0%)	1 (5.0%)		20
	Total	31(79.4%)	4(10.25%)	4(10.25%)		39
Do you remember the fast hand piece being used?	Nitrous oxide	9 (47.4%)	4 (21.1%)	6 (31.6%)		19
	Sevoflurane	13(65.0%)	3 (15.0%)	4 (20.0%)		20
	Total	22(56.4%)	7(17.95%)	10(25.6%)		39
Did it bother you	Nitrous oxide	10(52.6%)	2 (10.5%)		7 (36.8%)	19
	Sevoflurane	10(52.6%)	0 (0%)		9 (47.4%)	19
	Total	20(52.6%)	2 (5.3%)		16(42.1%)	38
Do you remember the slow hand piece being used?	Nitrous oxide	12(63.2%)	1 (5.3%)	6 (31.6%)		19
	Sevoflurane	15(75.0%)	1 (5.0%)	4 (20.0%)		20
	Total	27(69.2%)	2 (5.1%)	10(25.6%)		39
Did it bother you?	Nitrous oxide	10(52.6%)	1 (5.3%)		8 (42.1%)	19
	Sevoflurane	12(60.0%)	1 (5.0%)		7 (35.0%)	20
	Total	22(56.4%)	2 (5.1%)		15(38.5%)	39
Do you remember a filling being placed in your tooth	Nitrous oxide	14(73.7%)	2 (10.5%)	3 (15.8%)		19
	Sevoflurane	18(90.0%)	2 (10.0%)	0		20
	Total	32(82.1%)	4 (10.3%)	3 (7.7%)		39
Do you remember being told that treatment is complete for today?	Nitrous oxide	19 (95%)	1 (5%)			20
	Sevoflurane	20 (100%)	0			20
	Total	39 (97.5)	1 (2.5%)			40
Do you remember if the gas smelled?	Nitrous oxide	6 (30.0%)	8 (40.0%)	6 (30.0%)		20
	Sevoflurane	15(75.0%)	5 (25.0%)	0		20
	Total	21(52.5%)	13(32.5%)	6 (15.0%)		40
Was it pleasant or not?"	Nitrous oxide	6 (30.0%)	1 (5.0%)	13(65.0%)		20
	Sevoflurane	10(50.0%)	4 (20.0%)	6 (30.0%)		20
	Total	16(40.0%)	5 (12.5%)	19(47.5%)		40

to be a very valuable tool for recording subjective experiences. In a trial such as this the use of the Trieger test to assess recovery from conscious sedation might be regarded

as being excessive but because of the lack of experience in using sevoflurane it was considered prudent to be able to assess recovery at the end of the treatment session.

Table 4 Physiological results for patients given sevoflurane

Patient	1	3	5	8	9	13	14	15	17	18	19	23	26	30	31	32	34	35	36	37	40
% Sevoflurane	0.3	0.2	40	0.3	0.3	0.3	0.2	0.3	0.1	0.3	0.3	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.3
Modified dental anxiety score	13	18	21	20	17	9	21	18	18	20	21	18	23	13	6	25	19	19	22	13	17
Sedation score	1	2	2	1	1	2	2	2	2	1	2	1	2	2	1	2	1	1	2	2	1
Ellis score	1	2	1	2	1	1	1	1	1	1	1	1	2	2	1	1	2	1	1	1	4
Reproduced Trieger test at end	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum systolic BP	148	127	125	145	119	136	122	133	144	140	126	156	143	117	134	108	119	135	149	137	124
Maximum diastolic BP	97	63	61	88	56	71	58	80	78	75	66	91	58	62	78	58	62	72	83	70	74
Minimum systolic BP	130	105	112	134	85	129	108	111	116	122	94	147	124	102	124	100	110	114	129	119	101
Minimum diastolic BP	70	55	40	66	23	64	45	62	59	54	54	74	58	46	59	45	48	45	66	54	48
Maximum respiratory rate (breaths/min)	14	17	23	24	20	22	23	19	26	31	23	24	22	21	28	17	27	24	19	27	14
Minimum respiratory rate (breaths/min)	8	9	12	10	16	13	10	12	16	12	17	14	12	11	11	11	15	14	13	14	8
Minimum oxygen saturation (%)	97	100	100	100	100	100	100	100	97	97	100	100	99	100	98	100	100	100	100	99	100
Maximum heart rate	87	87	99	76	109	67	80	107	104	96	89	103	86	82	108	86	76	79	98	76	76
Minimum heart rate	71	71	63	66	82	53	62	93	84	74	73	95	64	57	80	72	56	64	84	59	63
Minimum BIS reading	96	97	84	97	96	90	96	97	97	90	98	97	96	93	83	98	91	88	97	95	97

Table 5 Physiological results for patients given nitrous oxide

Patient	2	4	6	7	10	11	12	16	20	21	22	24	25	27	28	29	33	38	39
Nitrous oxide%	30	35	30	40	40	35	30	40	30	40	30	35	30	40	35	35	35	35	35
Modified dental anxiety score	23	19	24	23	25	17	9	15	24	24	23	19	14	19	7	20	25	18	18
Sedation score	1	3	2	1	1	2	2	2	2	1	1	1	2	1	2	1	2	1	1
Ellis score	2	2	2	3	1	2	1	1	1	3	1	1	1	2	1	2	1	1	1
Reproduced Trieger test at end	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum systolic BP	139	133	104	149	122	163	114	125	130	143	109	107	122	119	131	131	156	135	101
Maximum diastolic BP	80	69	88	83	73	84	66	79	68	75	59	59	63	72	63	68	77	81	52
Minimum systolic BP	120	114	93	125	110	136	102	115	119	121	99	99	110	107	123	119	135	117	89
Minimum diastolic BP	72	44	50	61	52	72	47	57	56	57	48	54	53	38	47	54	61	63	44
Maximum respiratory rate (breaths/min)	17	15	20	25	16	20	20	16	52	24	18	24	24	*	21	24	17	18	21
Minimum respiratory rate (breaths/min)	13	9	14	20	9	18	10	13	17	16	16	15	15	*	12	13	10	13	13
Minimum oxygen saturation	97	100	99	100	97	100	99	100	100	100	98	100	100	100	100	99	99	99	100
Maximum heart rate	89	87	56	83	87	120	60	82	58	129	88	72	66	89	78	76	100	79	90
Minimum heart rate	74	71	46	71	72	89	49	65	49	94	73	60	48	57	59	54	86	70	64
Minimum BIS reading	98	97	92	95	98	97	92	96	96	98	92	95	88	98	85	97	96	97	95

*denotes data not collected during session

The selection criteria for this type of study had to be rigid and correctly applied to avoid introducing any bias. During screening of patients to try and find a suitable participant

it was not uncommon to see 10 or 12 patients before anyone who fitted the criteria was examined. For the operator, who was a part-time student working mostly in primary care,

this proved worryingly time consuming. Fortunately, many patients appreciated that they were attending a dental teaching hospital and that participation in a study

Table 6 Results of the physiological measurements

Variable	Group	Median [IQR] (range)	P value (Mann-Whitney U test)
BIS min	nitrous oxide	96 [92 to 97] (84 to 98)	0.81
	sevoflurane	96 [92 to 97] (83 to 98)	
DY MAX	nitrous oxide	71 [63 to 80] (52 to 88)	0.98
	sevoflurane	72 [62 to 80] (56 to 97)	
DY MIN	nitrous oxide	54 [47 to 60] (38 to 72)	0.45
	sevoflurane	55 [47 to 64] (23 to 74)	
MAX HR	nitrous oxide	85 [73 to 97] (56 to 129)	0.52
	sevoflurane	87 [77 to 102] (67 to 109)	
MIN HR	nitrous oxide	65 [55 to 74] (46 to 94)	0.24
	sevoflurane	71 [62 to 82] (53 to 95)	
RESPMAX	nitrous oxide	20 [17 to 24] (15 to 52)	0.32
	sevoflurane	23 [19 to 26] (14 to 31)	
RESPMIN	nitrous oxide	13 [12 to 16] (9 to 20)	0.20
	sevoflurane	12 [10 to 14] (8 to 17)	
SPO2 MIN	nitrous oxide	100 [99 to 100] (97 to 100)	0.52
	sevoflurane	100 [99 to 100] (97 to 100)	
SYS MAX	nitrous oxide	128 [115 to 138] (101 to 163)	0.22
	sevoflurane	135 [123 to 144] (108 to 156)	
SYS MIN	nitrous oxide	115 [103 to 121] (89 to 136)	0.66
	sevoflurane	115 [103 to 128] (85 to 147)	

such as this was to be expected and so once the process was explained only two patients declined to take part.

Patients who took part in the study were accepting of the monitoring and recording equipment used and many were interested in what the equipment was there to do. This distraction provided a useful way of introducing the patient into the treatment session.

In summary, the statistical analysis and experience gained within the limits of the study showed that sevoflurane was equivalent to nitrous oxide when administered at low doses for inhalation sedation in this study.

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- General Dental Council. *Maintaining standards: Guidance to dentists on professional and personal conduct*. London: GDC, 2001.
- Department of Health. *Conscious sedation in the provision of dental care*. London: DH, 2003.
- National Dental Advisory Committee for Scotland. *Conscious sedation in dentistry*. Edinburgh: National Dental Advisory Committee for Scotland, 2006.
- Meehan R, Robb N, Seymour R. *Pain and anxiety control in dentistry*. Oxford: Oxford University Press, 1999.
- Shaw A, Meehan J, Kilpatrick N, Welbury R. The use of inhalation and local anaesthetic instead of general anaesthesia for extractions and minor oral surgery in children: A prospective study. *Int J Paediatr Dent* 1996; **53**: 213–215.

- Blain K, Hill F. The use of inhalation sedation and local anaesthetic as an alternative to general anaesthesia for dental extractions in children. *Br Dent J* 1998; **12**: 608–611.
- Berge T I. Acceptance and side effects of nitrous oxide oxygen sedation for oral surgery procedures. *Acta Odontol Scand* 1999; **57**: 201–206.
- Bryan R. The success of inhalation sedation for comprehensive dental care within the Community Dental Service. *Int J Paediatr Dent* 2002; **12**: 410–414.
- Cohen E N, Gift H C, Brown B W *et al*. Occupational disease in dentistry and chronic exposure to trace anaesthetic gases. *J Am Dent Assoc* 1980; **101**: 21–31.
- Whitcher C, Cohen E, Trudell J. Chronic exposure to anaesthetic gases in the operating room. *Anaesthesiology* 1971; **35**: 348–353.
- Nunn J F. Clinical aspects of the interaction between nitrous oxide and vitamin B12. *Br J Anaesth* 1987; **59**: 3–13.
- Shaw A, Morgan M. Nitrous oxide: time to stop laughing? *Anaesthesia* 1998; **53**: 213–215.
- Layzer R. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978; **2**: 1227.
- Roland A S, Baird D D, Shore D L, Weinberg C R, Savitz D A, Wilcox A J. Nitrous oxide and spontaneous abortion in female dental assistants. *Am J Epidemiol* 1995; **141**: 531–538.
- Lockwood A, Yang F. Nitrous oxide inhalation anaesthesia in the presence of intraocular gas can cause irreversible blindness. *Br Dent J* 2008; **204**: 247–248.
- Brilliant J. Nitrous oxide as a psychedelic drug. *New Engl J Med* 1970; **283**: 1522.
- Maskell K, Callander B, Mintzer I. Basic science of climate change. *Lancet* 1993; **342**: 1027–1031.
- Logan M, Farmer J. Anaesthesia and the ozone layer. *Br J Anaesth* 1989; **63**: 645–647.
- Health Services Advisory Committee. *Anaesthetic gases: controlling exposure under COSHH*. London: HMSO 1995.
- Parbrook G D, James J, Braid D P. Inhalation sedation with isoflurane: an alternative to nitrous oxide. *Br Dent J* 1987; **163**: 88–92.
- Mc Menemin M, Parbrook G. Comparison of the effects of sub anaesthetic concentrations of isoflurane or nitrous oxide in volunteers. *Br J Anaesth* 1988; **60**: 56–63.
- Ho E, Parbrook G, Still D, Parbrook E. Memory function after IV midazolam or inhalation of isoflurane for sedation during dental surgery. *Br J Anaesth* 1990; **64**: 337–340.
- Dingley J, King R, Hughes L *et al*. Exploration of xenon as a potential cardiostable sedative: a comparison with propofol after cardiac surgery. *Anaesthesia* 2001; **56**: 826–835.
- Bedi A, McCarroll C, Murray J M, Stevenson M A, Fee J P. The effects of subanaesthetic concentrations of xenon in volunteers. *Anaesthesia* 2002; **57**: 233–241.
- Tomi K, Mashimo T, Tashiro C *et al*. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70**: 684–686.
- Haraguchi N, Furusawa H, Takezaki R, Oi K. Inhalation sedation with sevoflurane: a comparative study with nitrous oxide. *J Oral Maxillofac Surg* 1995; **53**: 24–26.
- Carpenter R, Descamps M, Morley C, Leary T, Jones J. The effect of low dose sevoflurane on saccadic eye movement latency. *Anaesthesia* 2002; **57**: 855–859.
- Lahoud G, Averley P, Hanlon M. Sevoflurane inhalation conscious sedation for children having dental treatment. *Anaesthesia* 2001; **56**: 447–484.
- Lahoud G, Averley P. Comparison of sevoflurane and nitrous oxide mixture with nitrous oxide alone for inhalation conscious sedation in children having dental treatment: a randomized controlled trial. *Anaesthesia* 2002; **57**: 446–450.
- Averley P, Girdler N, Bond S, Steen N, Steele J. A randomised controlled trial of paediatric conscious sedation for dental treatment using intravenous midazolam combined with inhaled nitrous oxide or nitrous oxide/sevoflurane. *Anaesthesia* 2004; **59**: 844–852.
- McLeod D D, Ramayya G P, Tunstall M E. Self-administered isoflurane in labour. A comparative study with entonox. *Anaesthesia* 1985; **60**: 56–63.
- Jones B, Jarvis P, Lewis J, Ebbutt A. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996; **313**: 36–39.
- Denborough M, Forster J, Lovell R, Maplestone P, Villiers J. Anaesthetic deaths in a family. *Br J Anaesth* 1962; **34**: 395–396.
- Gemmell L. Management of a malignant hyperthermia crisis. *Anaesthesia News* 2011; **289**: 27.
- Humphris G M, Clarke H M, Freeman R. Does completing a dental anxiety questionnaire increase dental anxiety? A randomised controlled trial with adults in dental practice. *Br Dent J* 2006; **201**: 33–35.
- Aitkenhead A, Rowbotham D, Smith G (eds). *Textbook of anaesthesia*. 4th ed. London: Churchill Livingstone, 2001.
- Roberts G J. Inhalation sedation (relative analgesia) with oxygen/nitrous oxide gas mixtures: 1. Principles. *Dent Update* 1990; **17**: 139–142, 145–146.
- Company overview of Aspects Medical Systems Inc, One Upland road, Norwood, MA 02062 USA*. Bloomberg Businessweek, 2014. Online overview available at <http://investing.businessweek.com/research/stocks/private/snapshot.asp?privcapId=25134> (accessed June 2014).
- Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting depth of anaesthesia induced by sevoflurane. *Anaesthesiology* 1998; **88**: 642–650.
- Hall D L, Weaver J, Ganzberg, Rashid R, Wilson S. Bispectral EEG index monitoring of high-dose nitrous oxide and low-dose sevoflurane sedation. *Anaesth Prog* 2002; **49**: 56–62.
- Chan M T, Gin T. What does the Bispectral EEG index monitor? *Eur J Anaesthesiol* 2000; **17**: 146–148.
- Newman M G, Trieger N, Miller J C. Measuring recovery from anaesthesia—a simple test. *Anaesth Analg* 1969; **48**: 136–140.