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ORIGINAL ARTICLE

A clinical trial of efficacy and safety of inhalation sedation with a 50% nitrous oxide/oxygen premix (Kalinox™) in general practice

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Abstract The current study aimed to verify if the safety and effectiveness of inhalation sedation with 50% nitrous oxide in oxygen (N_2O/O_2) is maintained when the premix is administrated by trained general practitioners in their dental surgeries compared to its use in the hospital. Success (completion of planned treatment), cooperation (modified Venham scale), and adverse events were recorded. The acceptability of the technique to the patients, the level of patient cooperation, the ease of use, and the satisfaction of the dentist were also evaluated. Thirty-three general practitioners included 549 patients and recorded 638 sessions of N_2O/O_2 sedation for dental treatment. Of the sessions, 93.7% were successful in terms of both sedation and treatment. Patient cooperation was seen to improve under N_2O/O_2 sedation, and for 91% of the sessions, the patients declared that they would like future treatment to be undertaken in the same way. No serious adverse events were recorded. Minor adverse events were noted for 10% of the sessions (behavioural, vagal, and digestive disorders). These results were similar to those found for sessions undertaken in hospital practice. The main difference was in the type of patient treated—more patients received N_2O/O_2 sedation in general practice for a one-off indication or for dental phobia, and more patients with intellectual disability and more pre-cooperative children were treated in hospital practice. This study gives strong supporting evidence for the safety and effectiveness of inhalation sedation using 50% N_2O/O_2 in general dental practice for healthy patients.

Keywords Dentistry · Nitrous oxide · Sedation · Safety

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Introduction

The administration of nitrous oxide in oxygen (N_2O/O_2) is indicated to improve cooperation during dental care for patients with behavioural difficulties, such as very young children, patients with dental anxiety or phobia, and persons with intellectual disability. Most studies that have reported the use of inhalation sedation in dentistry have been conducted in the USA, UK, Scandinavia, Australia, Canada, Japan, Israel, Brazil, or France. Restrictions to the use of inhalation sedation in dentistry remain in place in many Central, Southern, and Eastern European countries, partly due to the lack of training of dentists and opposition from anaesthetic colleagues. In order to lift the restrictions in the current evidence-based era, it is extremely important that new studies that follow contemporary research guidelines and report context-specific evidence of safety and effectiveness are undertaken [1, 2].

Conscious sedation with a N_2O/O_2 mixture has been studied extensively in dentistry, and the short-term, perioperative effects of the technique have been well documented for various concentrations of N_2O in O_2 during

administration with both a two-bottle system [3–5] and with a 50% N_2O/O_2 premix [6]. However, despite the high number of studies, the rigorous standards of pharmacological drug testing have not traditionally been applied to the medical gases even though they are also used for therapeutic reasons. For example, these standards imply that evidence for tolerance and efficacy has to be established for a fixed concentration of nitrous oxide, with prospectively defined criteria for efficacy and safety [1]. Administration of nitrous oxide inhalation by titration using a two-bottle system is not compatible with such evaluation as the percentage of N_2O given to each patient is variable. Moreover, there is no consensus between studies on the criteria used to prospectively define either efficacy or adverse events. In this historical context, the majority of studies that have been conducted in dental sedation are not in accordance with the Guidelines for Good Clinical Practice in Clinical Trials [7]. In some countries, the lack of high-quality evidence could be a barrier to the development of inhalation sedation for dental care. The current trend is to change the status of the medical gases to therapeutic drugs in order to better regulate use and improve safety [1, 8]. In the UK, Australia, Canada, Benelux, and France, the 50% N_2O/O_2 premix has recently been recognised as a drug. Other countries and regions, such as Spain, Switzerland, Greece, Portugal, Germany, and Scandinavia, are also likely to change their nomenclature in the near future. In response to this change, a series of clinical trials were performed to produce evidence of the pharmacological effects of a 50% N_2O/O_2 premix when administered as a sedative drug during dental care in the hospital environment [9–11]. No information is available, however, on the ability of dental practitioners to administer conscious inhalation sedation with the same safety and efficacy in their own offices or surgeries rather than in the hospital setting. Good Clinical Practice for clinical trials requires context-specific evidence of safety and effectiveness and thus N_2O/O_2 needed to be tested in general practice.

The current study aimed to verify if the safety and effectiveness of inhalation sedation with 50% N_2O/O_2 is maintained when the premix is administrated by trained general practitioners in their dental surgeries compared to its use in the hospital. The acceptability of the technique to the patients, the level of patient cooperation, the ease of use, and the satisfaction of the dentist are also evaluated. In addition, type of patient, success rate, and incidence of adverse events were compared to the results of the previous clinical trials undertaken in the hospital setting.

Material and methods

This was a prospective, phase III, multicentre, non-randomised, open-label trial. The study protocol, information sheets, and consent forms were approved by the local independent ethics committee (Comité de Protection des Personnes Sud Est 6). Each investigator obtained a freely given written consent for inclusion in the study from each patient and/or his/her parent or legal tutor after explaining the aims, methods, potential hazards, and all other aspects of the study relevant to the patient's decision to participate. Specific information and consent forms were designed for young children, their parents, anxious patients, patients with disability, and their legal tutors.

Investigators

General dental practitioners newly qualified in conscious sedation were approached to become investigators in the study. They all held a postgraduate diploma in conscious sedation delivered by one of the dental faculties of Clermont-Ferrand, Strasbourg, Nancy, Marseille, or Bordeaux. The training objectives of the postgraduate course followed guidelines for sedation by non-anaesthetists [12]. This course was designed jointly by academic dentists, anaesthetists, pharmacologists, and pain specialists, all of whom participated actively in teaching the syllabus. Each course lasted 1 year and comprised four 2- to 3-day seminars for theoretical teaching and tutorials and a 10- to 15-day clinical apprenticeship. During the clinical training, the postgraduate student successively observed, assisted, and then performed conscious sedation under supervision using 50% nitrous oxide in oxygen for patients indicated for sedation during dental care. Thirty-eight investigators were recruited but five did not include any patients during the study period and were thus excluded retrospectively. The geographical distribution of the 33 participating general practitioners is shown in Fig. 1.

Patients

In the previous hospital-based clinical trials, the target population was limited to patients unable to accept dental care in the conventional setting for behavioural reasons [3, 13]. It was shown, however, that general practitioners working as trainees in sedation in the hospital had defined an additional indication—patients who required support from sedation for one-off stressful treatment [11]. Consequently, inclusions were classified into four pre-defined groups: (1) patients with intellectual disability, (2) pre-cooperative children (<5 years age), (3) adults or children with dental phobia and/or a marked gag reflex, and (4) patients requiring support for a specific one-off complex dental treatment. All patients requiring sedation were systematically considered for inclusion in the study, whether from the investigators' regular patient base or referred to the practice specifically for inhalation sedation.

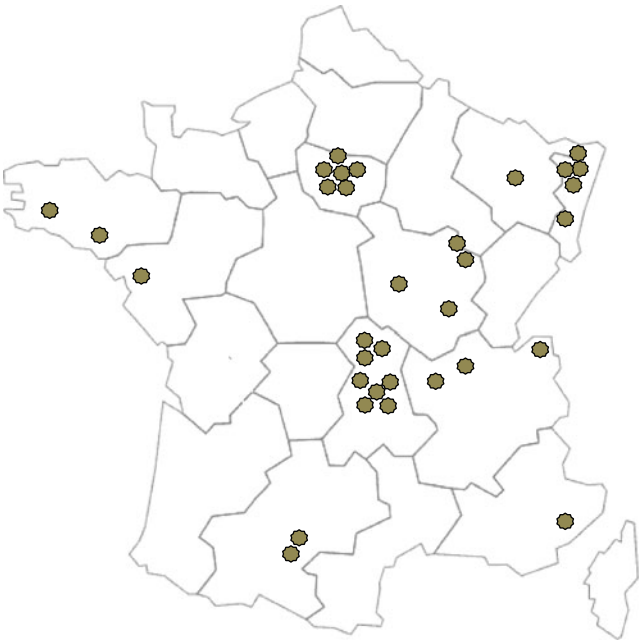

Fig. 1 Geographical distribution of the investigators through the metropolitan French territories

In the absence of the present clinical trial, all these patients would have been left untreated, or treated under restraint, or referred to hospital for management under conscious sedation or general anaesthesia. The exclusion criteria are listed in Table 1.

Material

All investigators were supplied with the premix of 50% N_2O/O_2 in 15-L cylinders at 170 bars pressure (Kalinox™, Air Liquide Santé International, Paris, France). All were provided with modified Bain administration kits and a selection of facial and nasal masks (Fig. 2).

Procedure

A full explanation of the planned treatment and the expected outcome of the sedation was given to each patient in a manner appropriate to his/her level of understanding. A facial or nasal mask was chosen in relation to the age, morphology, and type of spontaneous respiration of the patient (nose or mouth breather). The flow rate for the 50% nitrous oxide in oxygen was between 3 and 15 L/min and was adjusted using visual surveillance of the anaesthetic bag incorporated in the circuit. The induction lasted for a minimum of 3 min. Dental treatment was then performed, with or without local anaesthesia as appropriate. Touch and verbal contact were maintained throughout the treatment, and administration was stopped immediately if communication with the patient was lost. Behaviour management techniques appropriate to the patient's cognitive capacity were used continuously. After completion of treatment, the patients were kept under observation for a period of at least 10 min.

Study criteria

Efficacy

The efficacy of sedation was evaluated by recording the ability to perform dental treatment and the evolution of patient behaviour during the session. For both ethical and psychological reasons, the 'success' of treatment in sedation has to be coupled with an independent evaluation of patient behaviour, in order to avoid situations where completion of treatment is considered successful despite a major physical constraint [14]. For this study, success in performing dental treatment under inhalation sedation was recorded when sedation and dental treatment were performed successfully. Relative failure was recorded when sedation failed to be administered but the planned treatment was completed or when sedation was administered but the dental treatment was not completed. Total failure was recorded when both sedation and treatment failed. Patient behaviour was evaluated using the French-modified Venham scale [15, 16]. This scale is given in Table 2 and goes from 0 (relaxed) to 5 (totally disconnected). Behaviour was scored at first contact with

Table 1 Criteria for patient exclusion from the study

Medically compromised patients with an American Society of Anesthesiologists (ASA) rating of 3 or above
Patients under 1 year of age
Patients who had successfully received a similar dental treatment without premedication or sedation in the month preceding the consultation (except in the case of traumatic injury)
Patients who had already been included in the study within the last week
Patients with a contraindication relating directly to nitrous oxide
Patients for whom treatment was anticipated to last for over 1 h
Pregnant or breastfeeding patients
Lack of an informed consent form signed by the patient, a parent, or a legal tutor

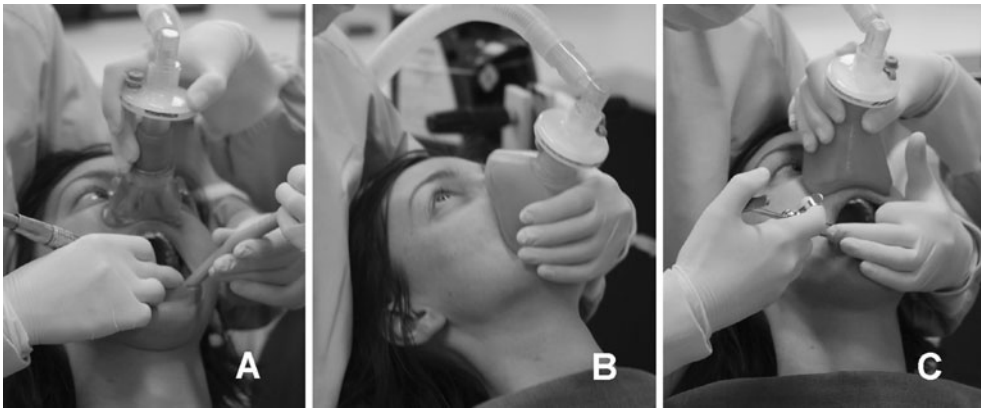

Fig. 2 Nasal (**a**) and full face (**b**, **c**) masks used for administration of 50% N_2O/O_2 premix during dental care

the patient (Ti), on first application of the mask to the face (T_0), at the end of the induction period (T_1), at first injection of local anaesthesia (T_2), and at the end of the session (T_3). The worst behaviour observed for each period was recorded.

Safety

All adverse events were recorded from a prospectively defined list. Investigators were specifically required to record respiratory disorders (hyperventilation, hypoventilation, and hypoxia), digestive disorders (nausea, vomiting), neurological disorders (convulsions, epilepsy), behavioural disorders (euphoria, agitation), and vagal disorders (sweating, pallor).

Patient satisfaction with the session

Patient satisfaction was assessed at the end of the session by the patient himself or herself where possible or by an accompanying carer. Pain and discomfort were reported using separate visual analogue scales (VAS). Patients or their carers were asked which type of management they would prefer for a subsequent treatment session: treatment under inhalation sedation, treatment without sedation, treatment with a different form of conscious sedation, or general anaesthesia. They were also asked what level of consciousness they wished to maintain at a subsequent treatment session in relation to their recent sedation experience: whether they wished to be as conscious, more conscious, or less conscious.

Table 2 English translation of the French-modified version of the Venham scale used in this trial

Score	Behaviour description
0	*Relaxed*, smiling, willing and able to converse, best possible working conditions. Displays the behaviour desired by the dentist spontaneously or immediately upon being asked.
1	*Uneasy*, concerned. Eye contact but tense facial expression. Suspicious of environment. Sits spontaneously back in the chair. Hands remain down or partially raised to signal discomfort. During a stressful procedure, may briefly and rapidly protest to demonstrate discomfort. The patient is willing and able to describe experience as requested. Breathing is sometimes held. Capable of cooperating well with treatment.
2	*Tense*. Tone of voice, questions and answers reflect anxiety. Multiple requests for information. Hands clench armrests or may be tense or raised without interfering with treatment. Sits back spontaneously in chair, but head and neck tense. Accepts hand-holding. Eye contact. During stressful procedure, verbal protest, quiet crying. Patient interprets situation with reasonable accuracy and continues to work to cope with his/her anxiety. Protest more troublesome. Patient still complies with request to cooperate. Continuity is undisturbed.
3	*Reluctant.* Tends to reject the treatment situation, difficulty in assessing situational threat. Frequent sighs. Pronounced protest, crying. Only sits back in chair after being asked several times, the head and neck remain tense. Slight movements of avoidance. Tense hands, avoids eye contact. Accepts hand-holding. Minor attempts to use hands to stop procedure. Wriggling. Protest out of proportion to threat or is expressed well before the threat. Copes with situation with great reluctance. Treatment proceeds with difficulty.
4	*Very disturbed* by anxiety and unable to assess situation. Physically very tense, wrinkled eyebrows, eye contact avoided or eyes shut. General crying not related to treatment. Prominent avoiding movements, needing physical restraint on occasion. Places hands over mouth or on dentist's arm to prevent treatment, but eventually allows care to progress. Pinches lips together but ends up by opening the mouth. Regularly lifts head from chair. Rejects physical contact but may still accept hand-holding. Patient can be reached through oral communication and eventually with reluctance and great effort begins to work to cope. Dissociation is only partial. Protest regularly disrupts procedure.
5	*Out of contact*, fails to grasp the reality of the threat. Inaccessible to oral and visual communication. Rejects physical contact. Clenches mouth and lips. Closes mouth and clenches teeth whenever possible. Violent head movements. Screaming, shouting, swearing, fighting, aggressive. Regardless of age, reverts to primitive flight responses. Actively involved in escape behaviour. Physical restraint required.

Dentist satisfaction with the session

Dentists were also asked which type of management they would prefer for a subsequent treatment session with the patient: treatment under inhalation sedation, treatment without sedation, treatment with a different form of conscious sedation, or general anaesthesia. Dentists reported what level of consciousness they wished for the patient at a subsequent treatment session in relation to the recent session: whether they wished the patient to be as conscious, more conscious, or less conscious. Dentists also scored the ease of use of the procedure as: easy, not easy, very difficult, or impossible.

Comparison with previous hospital-based studies

The following outcomes were compared to the results of three previous studies undertaken in the hospital setting: professional profile of the sedationists (hospital or private practitioner), their experience in sedation (either experts, trainees, or novices), type of patient, success rate, and safety.

Statistical analysis

Given the number of investigators, the high range of different types of treatment likely to be performed, and the four different patient groups, it was estimated that at least 480 sessions of inhalation sedation should be recorded in order to allow analysis of success according to the different categories.

The analysis of a successfully completed treatment under sedation was performed in relation to incidence of adverse events, gender, type of patient, previous experience of inhalation sedation, investigator, and type of treatment. In addition, type of patient, success rate, and incidence of adverse events were compared to the results of the previous similar studies undertaken in the hospital setting. The Fisher's exact test, the Pearson chi-square test, or the Wilcoxon test was used as appropriate.

Results

Descriptive data

Among the study period, 638 administrations of N_2O/O_2 were indicated for 549 patients. The distribution of the patient groups is shown in Table 3. Forty-four percent of sessions involved female patients, and the median age was 15 years (mean, 22.8 years; range, 1–80 years). Six of the investigators each recruited 5% to 9% of total inclusions, and all the other investigators recruited 1% to 4% of total inclusions. The median number of inclusions per patient was 1 (range, 1 to 10), corresponding to 75.4% of patients with a single sedation session. For those patients with more than one inclusion (24.6%), the median number of sedation sessions was 2.

The mean duration and the median duration of administration of inhalation sedation were 22.13 min and 20 min, respectively (range, 3 to 80 min). The mean and median flow rates were 7.38 L/min and 6 L/min, respectively (range, 3 to 15 L/min). Of the sessions, 67.4% involved a restorative or periodontal treatment or an oral surgery under local anaesthesia.

Success in performing dental treatment under inhalation sedation

The session was a success (both sedation and treatment were performed successfully) for 93.7% of the 638 sessions. Of the 40 failed sessions, 37.5% were a total failure (sedation and treatment), 37.5% resulted in a partial failure where treatment could not be completed despite adequate sedation, and 25% were sessions where treatment was performed despite failure to induce an appropriate level of sedation. Figure 3 gives success rates according to type of patient group. The percentage of failures ranged from 3.7% for patients requiring support for specific one-off dental treatment to 12.7% for patients with intellectual disability.

The failure rate was not affected by gender (5.7% males; 6.8% females; Pearson chi-square, $P=0.57$) nor by previous experience of inhalation sedation (6.3% failure for both those with and without previous experience). There was no statistical difference in failure rate between the different types of patient group (Fisher's exact test $P=0.09$). Figure 4 shows success rates according to type of dental care performed. Of those sessions that failed, planned dental treatment and failure rate (FR) were: acclimatisation to inhalation sedation (FR, 16.4%), endodontic treatment under local anaesthesia (FR, 11.5%), extraction or oral surgery under local anaesthesia (FR, 10.5%), scaling

Table 3 Distribution of sessions according to patients group

Patients groups	Number of sessions	(%)
Pre-cooperative children (≤5 years old)	85	13.32
Patients with intellectual disability (>5 years old)	71	11.13
Patients with dental fear or phobia (>5 years old)	269	42.16
Patients with a one-off indication (>5 years old)	213	33.39

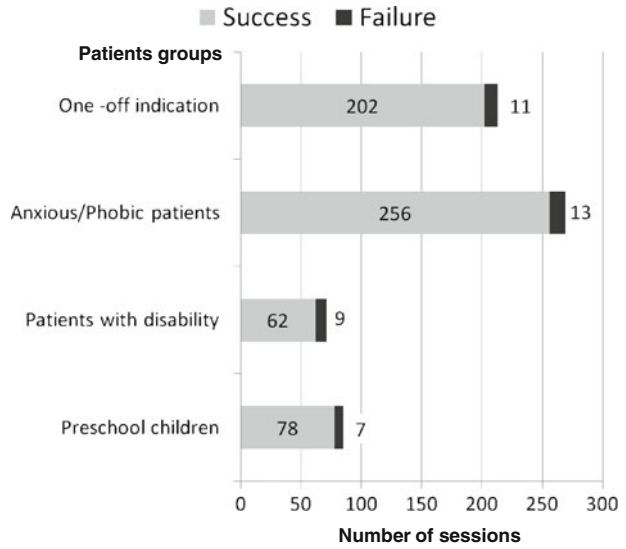

Fig. 3 Distribution of successful and failed sessions of dental care under N_2O/O_2 inhalation among the different patients groups

without local anaesthesia (FR, 8.6%), clinical examination (FR, 8.3%), and restorative treatment under local anaesthesia (FR, 5.0%).

Patient behaviour

Figure 5 shows the distribution of Venham scores at each point in time during the sedation session. The percentage of patients with a Venham score of 0 or 1 at initial contact with the dentist was 56%. This percentage rose to 92% after induction and was maintained at 87% during actual treatment. For 11% of patients, behaviour was slightly poorer during treatment than at the end of induction, but was still more favourable than before sedation.

Safety

No serious adverse events were reported during the study. A total of 567 sessions (88.9%) were carried out without any adverse event. Table 4 shows the distribution of sessions among the reported adverse events. The most frequently reported adverse events were behavioural, vagal, and digestive disorders (respectively in 5.3%, 4.4%, and 2.8% of the sessions).

Patient satisfaction

For 91% of the sessions, the patients desired to be treated with inhalation sedation in the same manner for subsequent treatment sessions. In 82% of cases, they wished for a similar level of consciousness and would have wished to be 'less conscious' during treatment in 13% of cases. The mean pain reading on VAS was 10.8 mm for patients providing an auto-evaluation and 16.1 mm for patients for whom the parent or carer gave the score. In terms of discomfort, the mean VAS scores were 15.9 mm and 24.6 mm for auto- and hetero-evaluation respectively.

Dentist satisfaction

For 92% of the sessions, the dentists wished to manage their patients using inhalation sedation for subsequent treatment sessions. In 82% of cases, they wished for a similar level of consciousness and would have wished for

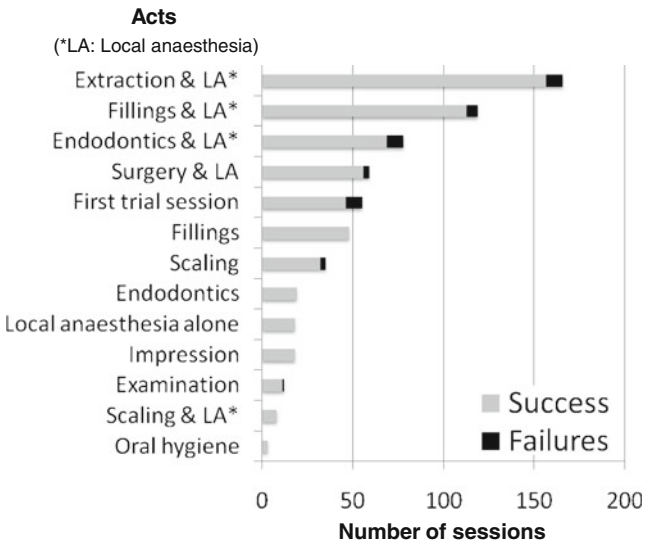

Fig. 4 Distribution of successful and failed sessions of dental care under N_2O/O_2 inhalation according to type of dental treatment

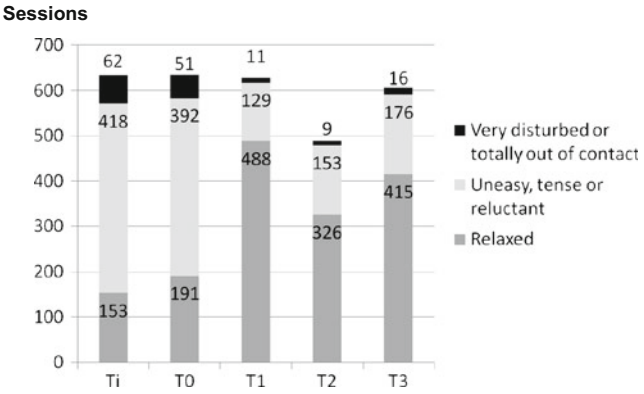

Fig. 5 Proportion of sessions of dental care under N_2O/O_2 inhalation for each Venham score category, at each of the five points in time during the sedation session. *Ti* at the beginning of the session during the first contact with the patient, before starting any care; *T0* on application of the mask to the face; *T1* at the end of the induction period, at least 3 min after the beginning of inhalation; *T2* during the first injection of local anaesthesia; *T3* during dental treatment (for *Ti* and *T3*, if changes in behaviour appeared, the highest score was recorded)

Table 4 Distribution of number of sessions in relation to the prelisted categories of adverse events

Adverse events		Number of sessions	%
Respiratory (n=638)		0	0
Digestive (n=636)	Nausea	11	1.73
	Vomiting	7	1.10
Behavioural (n=635)	Euphoria	22	3.46
	Hyperexcitability	12	1.89
Neurological (n=635)	Convulsions	3	0.47
Vagal (n=636)	Sweating	7	1.10
	Pallor	11	1.23
	Vertigo	10	1.57

the patient to be 'less conscious' during treatment for 13% of sessions. These results are almost identical to those reported by the patients.

The technique of inhalation sedation was considered easy to use by 80.6% of dentists, not very easy by 15.3%, very difficult by 3.9%, and impossible by 0.2%.

Comparison with previous hospital-based studies

Table 5 compared categories of patient, success rate, and percentage of adverse events reported in previous similar studies in relation to the professional profile of the administrators, their experience of sedation, and the setting in which the administrations were undertaken. The distribution of patient subgroups, the success rate, and the percentage of adverse events differed significantly between the studies (Chi-square analysis, $P<0.001$). In particular, patients with one-off indications and those with dental fear represented the majority of patients treated in general practice, whilst the proportion of pre-cooperative children and patients with intellectual disability was lower than that in hospital practice. The success rate for experts working in the hospital and for general practitioners working independently in their surgeries was similar. The success rate was lower for trainees during their sedation training. The percentages of minor adverse events increased slightly when general dentists administered inhalation sedation compared to experts, whether working as trainees in the hospital or as newly qualified sedationists in their general practices.

Discussion

This clinical trial offers a wide range of arguments, collected according to the high standard of pharmacological research, that could be used to encourage the development of inhalation sedation in countries that still have restrictions to the use of N_2O/O_2 in dental care. It demonstrated that conscious sedation with a premix of 50% N_2O/O_2 can be administered safely and effectively by general dentists in their surgeries. This study also reveals original data regarding the differences in type of indication and rate of adverse events between general and hospital practice.

In terms of effectiveness, the 93.7% success rate found here is very similar to that reported in previous studies of experienced hospital dental sedationists using the same criteria for success [9, 10, 17] and is better than that previously reported for trainee dental sedationists in the hospital setting [11]. Improvement in patient cooperation on inhalation of N_2O/O_2 is also clearly demonstrated. The percentage of patients that were relaxed prior to induction was 24% and reached 68% during the actual dental treatment. Only 2.6% of patients presented a behaviour that was detrimental to the continuity of treatment during the act (Venham scores of 4 or 5). Treatment was thus undertaken in comfortable conditions for both the patient and the dentist. Patient and operator satisfaction confirmed this with over 90% of patients and dentists opting for the same type of anxiety management for subsequent visits, a result similar to that found in other studies of inhalation sedation [18, 19].

In terms of safety, tolerance of the 50% N_2O/O_2 was extremely good, with only 10.6% of sessions reporting minor adverse events. Control of nausea and vomiting during dental sedation is a specific challenge. Nitrous oxide may cause emesis by stimulation of the sympathetic system through catecholamine release [20], pressure-volume changes in the middle ear [21, 22], and alteration of gastric myoelectrical activity [23]. A previous prospective survey which analysed the factors affecting tolerance of the 50% N_2O/O_2 premix in a wide range of clinical situations reported that the main factors associated with adverse events were age, concomitant drug administration, and longer duration of inhalation [24]. The low rate of adverse effects reported in this study is in accordance with previous studies with the system [4, 25, 26]. It is, however, slightly higher than that found for experienced hospital practitioners using the premix [9, 10, 17]. Table 4

Table 5 Efficacy and tolerance of 50% N_2O/O_2 premix (Kalinox™) administered during dental care in relation to patient group, experience of sedationist, and setting

References	Hennequin et al. (2004) [9]	Collado et al. (2006) [10]	Collado et al. (2008) [11]	Current study
Setting	Hospital	Hospital	Hospital	Dental office
Investigators' experiences	Hospital dentists, experts	Hospital dentists, experts	Hospital and general dentists, trainees	General dentists, novices
Number of care sessions	1,205	1,221	826	638
Number of patients	661	543	662	549
Patients in subgroups (%)				
Pre-cooperative children (<5 year old)	349 (29%)	219 (18%)	124 (15%)	83 (13%)
Patients with learning disabilities (≥5 year old)	602 (50%)	635 (52%)	330 (40%)	77 (11%)
Patients with dental fear or phobia (≥5 year old)	254 (21%)	367 (30%)	306 (37%)	268 (42%)
Patients with specific one-off indication (≥5 year old)	None	None	66 (8%)	210 (33%)
Number of successful sessions (successful sedation and treatment) (%)	1123 (93.2%)	1157 (94.8%)	740 (89.6%)	593 (93.6%)
Number of sessions with at least one adverse event (%)	74 (6.2%)	79 (6.5%)	107 (13%)	71 (11%)
Number of sessions with at least one severe adverse event (%)	None	None	None	None

The degree of competence in sedation was classified by: Experts, teachers in dental sedation who had routinely administered sedation in the hospital over the last 3 years; Trainees, general dentists who administered sedation during their postgraduate training in sedation in the hospital; Novices, general dentists, newly qualified in conscious sedation, holding a university diploma in conscious sedation

shows a higher incidence of adverse events for trainees and those newly qualified in sedation. The adverse events that are expected during sedation are very similar to those induced by stressful stimuli. It is thus unknown if the increase in adverse events is related to the gas itself or to the ability of the sedationist to use cognitive and behavioural management techniques. It may be hypothesised that general dentists have difficulty applying techniques for the deconditioning of fear, as these are time-consuming, require specific competence, and a high level of experience. This hypothesis is also supported by the differences in the selection of the patients for sedation between the current study in general practice and previous studies in the hospital setting. Table 4 reports a far greater proportion of patients with a one-off indication and of anxious patients in general practice than in hospital practice. Communication with these patients requires less specific skills than communication with pre-cooperative children or patients with intellectual disability. It seems probable that the rate of adverse events could be reduced if dentists were given specific training in the adaptation of behaviour management to different patient groups. Moreover, the use of a pulse oximeter for monitoring the patient during the session could help the practitioners to improve their confidence for the treatment of American Society of Anesthesiologists Classification 2 (ASA 2) patients.

Developing sedation for dental care supports public health goals. It is important to bear in mind that all the patients included in this study would have been referred to the hospital, been treated with more restraint, or have been left untreated if the general practitioner did not have access to inhalation sedation within the surgery. The impact of a high number of healthy, if anxious, patients on waiting lists and saturation of specialist services is considerable, particularly as these patients potentially represent 10% to 14% of the population in an industrialised country [13]. If these patients with "simple needs" fill hospital services, then access to care is reduced for the more complex patients, for whom hospital care is a necessity (ASA 3 and above). In France, there are currently only approximately 20 hospital centres proposing dental treatment under conscious sedation. The majority of patients that are unable to cooperate with dental care in general practice are thus treated under general anaesthesia or left untreated. This study shows that 90% of these patients could potentially be treated in general practice with inhalation sedation—the financial impact of the extension of this technique to general practice should not therefore be ignored.

Ease of access to sedation techniques is also important in the potential prevention of dental anxiety and phobia. Of the patients treated in the current study,

33% needed support for specific one-off complex dental treatment, such as oral surgery. Although dental anxiety is multifactorial [27–29], many patients report that their dental phobia was triggered during a particularly stressful episode of treatment [30–32]. It is not unreasonable to assume that the better the control of anxiety during stressful procedures, the less iatrogenic the dentist is in the aggravation of dental anxiety [31]. In addition, the use of inhalation sedation has been shown to be beneficial in the reduction of dental anxiety over the long term in comparison to both behaviour management techniques alone and to general anaesthesia [15, 33]. Unlike general anaesthesia or other types of conscious sedation, nitrous oxide has very little amnesic effect [34]. During inhalation sedation, patients are exposed to dental care while nitrous oxide induces relaxation. The association of relaxation and exposition to the stressor is the foundation of cognitive and behavioural therapies. It has previously been demonstrated that these conditions improve the ability to cope with dental treatment over time in a controlled setting [10].

Another major advantage of providing access to inhalation sedation in general practice setting is to allow local access to simple care for the most challenging patients [17]. Even if complex restorative treatment were impossible, inhalation sedation might enable the general dental practitioner to undertake a simple examination or a scale and polish for the majority of such patients. This would allow practitioners to address their patients to specialist services appropriately, with some estimation of the treatment required, and also to maintain oral health on return to the primary health care system after management under general anaesthesia or other sedation in the hospital setting.

In conclusion, this study gives strong supporting evidence for the safety and effectiveness of inhalation sedation using 50% N_2O/O_2 in general dental practice for ASA 1 or 2 patients. The results suggest that approximately 90% of patients who have failed to access care in the conventional setting could be successfully treated using this technique in general practice, including persons with intellectual disability, children under 5 years of age, and anxious and phobic adults and children. In addition, patients requiring support for specific one-off complex dental treatment, such as oral surgery, may also benefit from this technique safely.

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References

1. Collado V, Nicolas E, Faulks D, Hennequin M (2007) A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. Expert Opin Drug Saf 6:559–571
2. Matharu LL, Ashley PF (2007) What is the evidence for paediatric dental sedation? J Dent 35:2–20
3. Nathan JE, Venham LL, West MS, Werboff J (1988) The effects of nitrous oxide on anxious young pediatric patients across sequential visits: a double-blind study. ASDC J Dent Child 55:220–230
4. Hallonsten AL, Koch G, Schröder U (1983) Nitrous oxide sedation in dental care. Community Dent Oral Epidemiol 11:347–355
5. Peretz B, Katz J, Zilburg I, Shemer J (1998) Response to nitrous oxide and oxygen in dental phobic patients. Int Dent J 48:17–23
6. Warren VN, Crawford AN, Young TM (1983) The use of Entonox as a sedation agent for children who have refused operative dentistry. J Dent 11:306–312
7. European Agency For The Evaluation of Medicinal Products (1995) Note for guidance on clinical safety data management: definitions and standards for expedited reporting. ICH Technical Coordination, London. CMP/ICH/377/95
8. Boulland P, Favier JC, Villevieille T, Allanic L, Plancade D, Nadaud J, Ruttiman M (2005) Premixed 50% nitrous oxide and oxygen: theoretical recalls and practical modalities. Ann Fr Anesth Rèanim 24:1305–1312
9. Hennequin M, Manière MC, Albecker-Grappe S, Faulks D, Berthet A, Tardieu C, Droz D, Wolikow M, Koscielny S, Onody P (2004) A prospective multicentric trial for effectiveness and tolerance of a N_2O/O_2 premix as a drug. J Clin Psychopharmacol 24:552–554
10. Collado V, Hennequin M, Faulks D, Mazille MN, Nicolas E, Koscielny S, Onody P (2006) Modification of behaviour with 50% nitrous oxide/oxygen conscious sedation over repeated visits for dental treatment: a three year prospective study. J Clin Psychopharmacol 26:474–481
11. Collado V, Nicolas E, Faulks D, Tardieu C, Maniere MC, Droz D, Onody P, Hennequin M (2008) Evaluation of safe and effective administration of nitrous oxide after a postgraduate training course. BMC Clin Pharmacol 8:3. doi:10.1186/1472-6904-8-3
12. Knape JT, Adriaensen H, Van Aken H, Wp B, Carlsson C, Dupont M, Pasch T (2007) Board of Anaesthesiology of the European Union of Medical Specialists. Guidelines for sedation and/or analgesia by non-anaesthesiology doctors. Eur J Anaesthesiol 24:563–567
13. Chanpong B, Haas DA, Locker D (2005) Need and demand for sedation or general anaesthesia in dentistry: a national survey of the Canadian population. Anesth Prog 52:3–11
14. Vargas KG, Nathan JE, Qian F, Kupietzky A (2007) Use of restraint and management style as parameters for defining sedation success, a survey of pediatric dentists. Pediatr Dent 29:220–227
15. Veerkamp JSJ, Gruythuysen RJM, Hoogstraten J, van Amerongen WE (1993) Dental treatment of fearful children using nitrous oxide. Part 4: anxiety after two years. ASDC J Dent Child 60:372–376
16. Hennequin M, Faulks D, Collado V, Thellier E, Nicolas E (2007) French versions of two indices of dental anxiety and patient cooperation. Eur Cell Mater 13:38
17. Faulks D, Hennequin M, Albecker-Grappe S, Manière MC, Tardieu C, Berthet A, Wolikow M, Droz D, Koscielny S, Onody P (2007) Sedation with 50% nitrous oxide/oxygen for outpatient dental treatment in individuals with intellectual disability. Dev Med Child Neurol 49:621–625
18. Wilson KE, Welbury RR, Girdler NM (2007) Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. A randomised cross-over clinical trial. Acta Anaesthesiol Scand 51:1062–1067

19. Arcari S, Ferro R (2008) Preschool children and relative analgesia: satisfactory grading through a verbal questionnaire. Eur J Paediatr Dent 9:18–22
20. Pohjavaara P, Telaranta T, Vaisanen E (2003) The role of the sympathetic nervous system in anxiety: is it possible to relieve anxiety with endoscopic sympathetic block? Nord J Psychiatry 57:55–60
21. Nader ND, Simpson G, Reedy RL (2004) Middle ear pressure changes after nitrous oxide anesthesia and its effect on postoperative nausea and vomiting. Laryngoscope 114:883–886
22. Karabiyik L, Bozkirli F, Celebi H, Goksu N (1996) Effect of nitrous oxide on middle ear pressure: a comparison between inhalational anaesthesia with nitrous oxide and TIVA. Eur J Anaesthesiol 13:27–32
23. Muth ER, Thayer JF, Stern RM, Friedman BH, Drake C (1998) The effect of autonomic nervous system activity on gastric myoelectrical activity: does the spectral reserve hypothesis hold for the stomach? Biol Psychol 47:265–278
24. Onody P, Gil P, Hennequin M (2006) Safety of inhalation of a 50% nitrous oxide/oxygen premix: a prospective survey of 35 828 administrations. Drug Saf 29:633–640
25. Berge TI (1999) Acceptance and side effects of nitrous oxide oxygen sedation for oral surgical procedures. Acta Odontol Scand 57:201–206
26. Jastak JT, Paravecchio R (1975) An analysis of 1331 sedations using inhalation, intravenous or other techniques. JADA 91:1242–1249
27. Skaret E, Berg E, Kvale G, Raadal M (2007) Psychological characteristics of Norwegian adolescents reporting no likelihood of visiting a dentist in a situation with toothache. Int J Paediatr Dent 17:430–438
28. Locker D, Thomson WM, Poulton R (2001) Psychological disorder, conditioning experiences and the onset of dental anxiety in early adulthood. J Dent Res 80:1588–1592
29. Poulton R, Waldie KE, Thomson WM, Locker D (2001) Determinants of early vs late onset dental fear in a longitudinal epidemiological study. Behav Res Ther 39:777–785
30. Averly PA, Hobman R, Bond S, Girdler NM, Steele J (2008) Investigating the lived experiences of children and their parents who have been referred to a primary care sedation service. SAAD Dig 24:3–11
31. Klages U, Ulusoy O, Kianifard S, Wehrbein H (2004) Dental trait anxiety and pain sensitivity as predictors of expected and experienced pain in stressful dental procedures. Eur J Oral Sci 112:477–483
32. Locker D, Shapiro D, Liddell A (1996) Negative dental experiences and their relationship to dental anxiety. Community Dent Health 13:86–92
33. Arch LM, Humphris GM, Lee GT (2001) Children choosing between general anaesthesia or inhalation sedation for dental extractions: the effect on dental anxiety. Int J Paediatr Dent 11:41–48
34. File SE, Easton P, Skelly AM (1991) Amnesia for dental procedures and mood change following treatment with nitrous oxide or midazolam. Int Clin Psychopharmacol 6:169–178