

Clinical Paper  
Randomized Trial Dentoalveolar Surgery

# Improved sedation for oral surgery by combining nitrous oxide and intravenous Midazolam: a randomized, controlled trial<sup>☆</sup>

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**Abstract.** The objective is to investigate whether sedation techniques for oral surgery can be improved by combining the use of inhalation of nitrous oxide/oxygen with intravenous Midazolam.

*Prospective, randomized controlled clinical trial:* Patients requiring extractions or surgery were randomly allocated to subgroups receiving either intravenous Midazolam or nitrous oxide/oxygen or a combined technique using nitrous oxide/oxygen and intravenous Midazolam. Safety parameters, amount of sedative agents administered, recovery time and co-operation scores were recorded. Patients receiving the combined sedation technique were initially titrated with 10% nitrous oxide, increasing by increments of 10% up to a maximum of 40% nitrous oxide and 60% oxygen. Midazolam was then titrated (initially 2 mg wait 2 min with increments of 1 mg every minute until appropriately sedated) whilst still administering 40% nitrous oxide.

When a combined technique of N<sub>2</sub>O/O<sub>2</sub> and Midazolam was used there was a statistically significant reduction in the amount of Midazolam required to achieve effective sedation ( $P < 0.001$ ), an overall significant reduction in recovery time ( $P < 0.001$ ) and a significant improvement in co-operation ( $P < 0.01$ ) and arterial oxygen saturation ( $P < 0.001$ ).

This combined technique was found to be safe and reliable, requiring reduced doses of Midazolam and demonstrable improvement in patient recovery and co-operation.

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Oral surgery procedures are often associated with fear of pain and preoperative anxiety<sup>13,15,17</sup>. Dentistry has developed a number of pharmacological and non-pharmacological methods of fear and anxiety control<sup>8,15,23</sup>, and the GENERAL DENTAL COUNCIL<sup>8</sup> and the ROYAL COLLEGE OF ANAESTHETISTS<sup>22</sup> encourage conscious sedation as a safe alternative to other techniques. There has been considerable recent interest in the issue of optimal conscious sedation<sup>1</sup> and the principle of minimum intervention<sup>7,8</sup>.

The two main techniques of conscious sedation used in the U.K. are inhalation nitrous oxide/oxygen and intravenous Midazolam. There have been no major adverse effects reported in dentistry and both techniques are considered safe when guidelines are properly adhered to<sup>1,6,8,9,22,23</sup>. Both techniques, however, have certain disadvantages. The main disadvantage of inhalation nitrous oxide/oxygen is that many patients are not adequately sedated by this and hence it is not often used for oral surgery procedures. Conversely, it has numerous advantages such as rapid onset of action, drug dose is titratable, the depth of sedation is easily changed, duration is variable, there is rapid recovery, no injection is required, there are very few reported side effects, it is inherently safe and it has good analgesic properties which is beneficial during oral surgical procedures<sup>1,10,11,15,18,20,24</sup>.

Intravenous Midazolam is a standard technique in dentistry and oral surgery practice. Advantages include a rapid onset, anterograde amnesia, easy titration to patient response and hence avoiding overdose, few side effects and the fact that a reversal agent Flumazenil is available. Disadvantages include the fact that Midazolam, even though it has minimal effects on the cardiovascular and respiratory systems, lowers blood pressure, increases heart rate and respiratory depression. It has no recognized analgesic properties, venepuncture can be a problem for needle phobics, recovery is not always complete when the dental or surgical procedure is over, and in some cases intravenous Midazolam sedation with local anaesthetic may be insufficient for more protracted surgical procedures and patient co-operation can be poor<sup>2,15,16,19</sup>.

The aim of this study was to investigate if sedation techniques for oral surgery could be improved by combining the use of inhalation nitrous oxide/oxygen and intravenous Midazolam. The potential advantages of such a combined technique over intravenous Midazolam alone were judged to be as follows:

- Improved safety.
- A possible reduction in the amount of Midazolam required to achieve effective sedation.
- A shortened recovery time.
- Improved patient co-operation.
- Effective sedation and pain control for more invasive oral surgical procedures, which might otherwise have required a general anaesthetic.
- The elderly and medically compromised may be more suited to this technique where higher doses of Midazolam are undesirable and where supplemental oxygen may be beneficial.
- The possibility of lengthening the period of effective sedation by increasing the concentration of nitrous oxide when the effect of Midazolam is wearing off.
- Flexibility, by increasing or decreasing the level of sedation at any point during treatment by altering the concentration of nitrous oxide.
- The possibility of rapidly reversing sedation by turning off nitrous oxide and administering 100% oxygen. The antagonist Flumazenil may still be used if required.
- Nitrous oxide/oxygen administration prior to intravenous cannulation and local anaesthesia may make the combined technique more acceptable to needle phobic patients.

The objectives of the study were thus to determine:

1. whether the combined technique is safe;
2. whether there is a reduction in the amount of Midazolam required to achieve effective sedation when a combined technique is used compared to intravenous Midazolam alone;
3. whether there is a reduction in recovery time when a combined technique is used compared to intravenous Midazolam alone;
4. whether patient co-operation is improved when a combined technique is used compared to intravenous Midazolam alone.

## Methodology

### The combined sedation technique of nitrous oxide/oxygen and intravenous Midazolam

Patients administered the combined technique were initially titrated with 10% nitrous oxide, increased by increments of 10% up to a maximum of 40% nitrous

oxide and 60% oxygen. After 2 min of continuous inhalation, if the patients were not adequately sedated, intravenous Midazolam was then titrated: initially 2 mg slowly over 30 s. If the patients were not appropriately sedated after 2 min, increments of 1 mg were given every minute until the desired level of sedation was reached, whilst still administering 40% nitrous oxide and 60% oxygen.

If the patient became less sedated during surgery, when the effect of Midazolam was wearing off, the combined technique offered the possibility of lengthening the period of effective sedation by increasing the concentration of nitrous oxide by increments of 5% up to a maximum of 55% nitrous oxide and 45% oxygen.

Similarly, if required, the level of sedation could be lightened by decreasing the concentration of nitrous oxide or even terminating the inhalation of nitrous oxide and administering 100% oxygen. The benzodiazepine antagonist Flumazenil could be used if required for rapid sedation reversal.

### Study design

This prospective, randomized and controlled study was approved by the Joint Ethics Committee of the Newcastle and North Tyneside Health Authority, the University of Newcastle upon Tyne and the University of Northumbria at Newcastle.

The study was designed to include 60 patients attending for oral surgery procedures using local anaesthesia, supplemented with sedation. Thirty patients were allocated to group 1 and 30 patients to group 2. Group 1 was for patients who required dental extractions only, whilst group 2 patients required surgical removal of teeth and/or roots. Each group had 3 subgroups.

Subgroup A patients received inhalation nitrous oxide/oxygen as the sole sedation agent. The patient was initially titrated with 10% nitrous oxide, increased by increments of 10% up to a maximum of 40% nitrous oxide and 60% oxygen. If the patient was not adequately sedated at 40% nitrous oxide, further increments of 5% nitrous oxide was given up to a maximum of 55% nitrous oxide.

Subgroup B patients received intravenous Midazolam as the sole sedative agent (technique: initially 2 mg slowly over 30 s. If the patients were not appropriately sedated after 2 min, increments of 1 mg every minute were given until the desired level of sedation was reached).

In subgroup C, patients received a combined sedation technique with nitrous

Table 1. Planned allocation of patients

Subgroup	Number of patients	Number of visits	Sedation technique
Group 1 (dental extractions only)			
1A	10	1	Inhalation of N <sub>2</sub> O/O <sub>2</sub>
1B	10	1	Intravenous Midazolam
1C	10	1	Combined sedation technique
Group 2 (surgicals)			
2A	10	1	Inhalation of N <sub>2</sub> O/O <sub>2</sub>
2B	10	1	Intravenous Midazolam
2C	10	1	Combined sedation technique

oxide/oxygen and Midazolam. The patient was initially titrated with 10% nitrous oxide, increased by increments of 10% up to a maximum of 40% nitrous oxide and 60% oxygen. Midazolam was then titrated similarly as in subgroup (B) whilst still administering 40% nitrous oxide. Patient allocation is summarized in Table 1.

All patients recruited were referred to the Department of Oral and Maxillofacial Surgery at Newcastle Dental Hospital for dental extractions or minor oral surgery under local anaesthesia and sedation. Only patients between 16 and 65 years of age, and only ASA categories I and II were recruited. Following informed consent and agreeing to take part in the study, the patients were randomly allocated to differing sedation techniques by the throw of dice.

All patients underwent a standardized assessment procedure to ensure their suitability for sedation. A Corah anxiety questionnaire<sup>4</sup>, which assesses patients' response to 4 clinical scenario questions, was used to assess the anxiety score. Consent was obtained and pre and postoperative instructions were given. The patients were monitored during the whole procedure by the researcher (G. R. V.) and an experienced sedation nurse. A pulse oximeter and blood pressure monitor (Dinamap Procure 300 pulse oximeter and blood pressure monitor by GE Medical Systems) were always used and the data recorded. Readings were recorded every 10 min. Clinical signs such as colour, heart rate, breathing rhythm, response to verbal command and consciousness were observed and recorded.

On completion of operative treatment, patients were transferred to the recovery

room with the escort and supervised by a sedation nurse. The level of alertness during recovery was recorded every 10 min, by assessment of coherent speech, straight line walking, simple psychomotor testing and response to verbal instruction, until the patient was fit to be discharged.

### Oral surgery procedures

All procedures were carried out by one author (G. R. V.) acting as both operator and sedationist. All patients were administered 2% Lidocaine and 1:80,000 Epinephrine local analgesic in a standard technique. Buccal and palatal/lingual infiltrations were administered for removal of maxillary teeth and lower anterior teeth (canines and incisors). Inferior dental and long buccal blocks were administered for mandibular posterior teeth (molars and premolars).

Extractions were performed using forceps and/or elevators. A standard oral surgical technique was used when dento-alveolar surgery was performed: a full thickness muco-periosteal flap was raised, bone was removed with burs where appropriate, teeth were sectioned where required, fragments were elevated, debridement was performed and resorbable vicryl sutures used.

A numerical score was used to summarize patient co-operation during the operative procedure using a scale of 1–3 (Table 2). All measurements recorded during the study are summarized in Table 3.

### Statistical method

Subjects were randomly allocated to the 6 subgroups, with the restriction that once 10 subjects had been allocated to any

Table 3. Measurements

1	Assessment criteria
2	Anxiety score
3	Safety parameters
4	Type and amount of sedative agents administered
5	Type and amount of local anaesthetic administered
6	Type and length of procedure
7	Co-operation score
8	Recovery time

subgroup no more were added. This was a practical number that could be recruited in a reasonable time period. Initial statistical analysis after recruiting 3 patients to each subgroup confirmed that 10 per subgroup would be sufficient to detect significant difference with reasonable certainty.

Patients requiring extractions were randomly allocated to subgroups 1A–1C, whilst those requiring surgery were allocated to groups 2A–2C (Table 1). Control subgroups were 1B and 2B (where intravenous Midazolam alone was used). Unpaired *t*-tests were used to compare subgroup 1B against 1C, and subgroup 2B against 2C (Table 4).

### Results

Thirty patients requiring dental extraction and 27 patients undergoing surgical procedures were recruited. Subgroup 2A (inhalation sedation only for surgical procedures) was discontinued because the patients became anxious and unco-operative and the technique had to be aborted. It was clear that in this study this technique did not provide appropriate sedation.

Thirty-seven females and 20 males with an age range of 16–65 years were involved in the study. The mean age for group 1 was 35.3 years and for group 2, 36.4 years. All patients were either ASA I (75%) or ASA II (25%).

The mean Corah anxiety score was 15.48 and ranged from 5 to 20. There was no statistically significant difference in anxiety scores between the subgroups compared ( $P > 0.1$ ).

The length of procedure in the dental

Table 2. Co-operation score

Score	Definition
3	Co-operative and not agitated during the whole procedure
2	Co-operative and not agitated during most of the procedure but agitated at time of local anaesthetic administration, dental extraction and/or elevation
1	Agitated during most of the procedure

Table 4. Subgroups used for comparing results

1B	against	1C
Midazolam Extraction Unpaired		Combined Extraction Unpaired
2B	against	2C
Midazolam Surgical Unpaired		Combined Surgical Unpaired

Table 5. Types of procedure

	Subgroups		
	1A	1B	1C
Number of cases of incisor and canine extraction	2	1	1
Number of cases of premolar and molar extraction	8	9	9
	Subgroups		
	2B	2C	
Number of cases of non-3rd molar surgically removed	4	5	
Number of cases of 3rd molar surgically removal	6	5	

extraction group ranged from 15 to 30 min, and in the surgical group from 15 to 40 min. The mean length of procedure in the extraction group was 18 min and in the surgical group 21.6 min. There was no statistically significant difference in length of time of procedure between the groups being compared ( $P > 0.1$ ).

The types of dental and surgical procedure carried out in the compared subgroups were similar (Table 5).

Lidocaine 2% with Epinephrine 1:80,000 was used as the local anaesthetic agent in all cases. The amount of local anaesthetic used in the dental extraction group and in the surgical group ranged from 2.2 to 6.6 ml. The mean amount of local anaesthetic used in the extraction group was 3.85 ml and in the surgical group 4.29 ml. There was no statistically significant difference in the amount of local anaesthetic used between subgroups compared ( $P > 0.1$ ).

There were no adverse effects noted, postoperative nausea and vomiting which is an uncommon side effect when using nitrous oxide/oxygen sedation was not observed in any of the patients and loss of consciousness was not observed in any patient. Similarly, there was no loss of response to verbal commands by any of the patients.

The lowest oxygen saturation recorded when administering intravenous Midazolam alone was 93% but when administering the combined technique the lowest saturation recorded rose to 96%. The mean lowest oxygen saturation with intravenous Midazolam alone was 95.5%, but using the combined technique this rose to 98.4%.

Table 6 summarizes the lowest individual and mean lowest oxygen saturation recorded in each subgroup. The results show that there was a statistically significant improvement in oxygen saturation ( $P < 0.001$ ), when a combination of nitrous oxide/oxygen and intravenous Midazolam was used, compared to intravenous Midazolam alone. The concentration of nitrous oxide used with the combined technique of nitrous oxide/oxygen and intravenous Midazolam was 40%.

The mean amount of Midazolam used, recovery time and co-operation score for relevant subgroups are summarized in Table 7. The results show a highly statistically significant reduction in Midazolam required to achieve effective sedation ( $P < 0.001$ ), when a combined technique of N<sub>2</sub>O/O<sub>2</sub> and Midazolam is used, compared to intravenous Midazolam alone.

Similarly, there is a significant reduction in recovery time ( $P < 0.001$ ), when a combined technique of N<sub>2</sub>O/O<sub>2</sub> and Mid-

azolam is used, compared to intravenous Midazolam alone. There is also a significant improvement in patient co-operation ( $P < 0.01$ ), when a combined technique of N<sub>2</sub>O/O<sub>2</sub> and Midazolam is used, compared to intravenous Midazolam alone.

## Discussion

The choice of techniques and drugs used for sedation in surgical practice should be governed by the principle of minimum intervention, and the amount of any drug administered should be the minimum necessary to achieve the desired effect<sup>8</sup>. This combined technique adheres to that principle. We observed a statistically significant reduction in the amount of Midazolam required to achieve effective sedation when 40% nitrous oxide and 60% oxygen was simultaneously administered. This resulted in a significant reduction in recovery time, and an improvement in patient co-operation.

The combined technique proved to be safe, with no adverse effects, no loss of response to verbal command and no loss of consciousness. There was also a demonstrable improvement in oxygen saturation during treatment. The lowest oxygen saturation recorded with i.v. Midazolam alone was 93%, but with the combined technique this rose to 96%. The mean lowest oxygen saturation recorded with the i.v. Midazolam alone technique was 95.5%, but with the combined technique 98.4%. These oxygen saturation readings were all, of course, within the recognized safe limits and indeed well above the minimum accepted level of 90%.

Whilst the various clinical assessments of patients during surgery and their co-operation score were recorded by the clinician administering the sedation techniques (who was not therefore blinded to the technique used), we feel that this is not inappropriate, as it does reflect the reality of clinical practice in this field. All recovery assessments were recorded by a second sedation-trained nurse who was blinded to the sedation technique used.

The flexibility of being able to decrease the level of sedation at any point during treatment by altering the concentration of nitrous oxide together with higher arterial oxygen saturation makes the combined technique safer than that of intravenous Midazolam alone.

The benzodiazepine antagonist Flumazenil is used to reverse intravenous sedation with Midazolam but is not recommended for routine use<sup>15,16</sup>. Reversal of sedation should be considered when patients have been over sedated or if they

Table 6. Lowest and mean lowest arterial oxygen saturation

Oxygen saturation	Lowest percent	Mean lowest percent
1B Midazolam	94	95.6
1C Combined	96	98.2*
2B Midazolam	93	95.3
2C Combined	96	98.6*

\* Significant differences  $P < 0.001$ .

Table 7. Mean Midazolam, recovery time and co-operation

	Midazolam (mg)	Recovery (min)	Co-operation score
1A N <sub>2</sub> O/O <sub>2</sub>	0	10	2.5
1B Midazolam	9.3	54	1.8
1C Combined	2.1*	15*	3.0 <sup>#</sup>
2B Midazolam	7.1	53	2.0
2C Combined	3.6*	23*	2.8

\* Significant differences  $P < 0.001$ .

<sup>#</sup> Significant differences  $P < 0.01$ .

Table 8. Benefits and adverse effects of advanced techniques and the combined technique

	Combined technique (2003)	WILSON et al. <sup>25</sup> Oral Midazolam (2002)	AVERLEY & LAHOUD <sup>3</sup> Inhalation N2O/Sevoflurane (2002)	CRAIG et al. <sup>5</sup> Intravenous Midazolam + Propofol (2000)	LEITH et al. <sup>12</sup> Patient maintained i.v. infusion of Propofol (2003)
Basic training	Yes	Yes	Yes	Yes	Yes
Advanced training and additional theory	No	No	Yes	Yes	Yes
Additional equipment	No	No	Yes	Yes	Yes
Life support training	Basic	Basic	Basic	Advanced	Advanced
Single operator/sedationist	Yes	Yes	No	No	No
Advanced training and additional theory for second appropriate person	No	No	N/A	N/A	N/A
Flexibility of ↑ or ↓ sedation level	Yes	No	Yes	Yes	Yes
Titration possible	Yes	No	Yes	Yes	Yes
Rapid reversal	Yes	No	Yes	Yes	Yes
Additional cost	No	No	Yes	Yes	Yes
Supplemental O <sub>2</sub>	Yes	No	Yes	No	No
Analgesia	Yes	No	Yes	No	No
Suitable for needle phobics	Yes	Yes	Yes	No	No
Risk of over sedation	Negligible	Possible	Possible	Possible	Possible

become hyperactive and unmanageable. This is a very important safety feature of any sedation technique. The combined technique can be reversed rapidly by turning off the nitrous oxide and administering 100% oxygen and Flumazenil can still be used if required.

When the sedation endpoint is reached during intravenous Midazolam sedation and treatment is still under progress, further increments of Midazolam to lengthen the period of effective sedation can lead to respiratory depression and is not recommended<sup>15</sup>. The combined technique, however, allows lengthening of the period of both effective sedation and pain control by safely increasing the concentration of nitrous oxide at a time when Midazolam and local anaesthetic effects may be lessening.

The improvement in patient co-operation observed when administering the combined technique is attributed to the enhanced analgesia provided by nitrous oxide. This finding is consistent with LUHMANN et al.<sup>14</sup> who highlighted the analgesic properties of nitrous oxide when combined with oral Midazolam. The combined technique, therefore, allows effective sedation and pain control for more difficult and protracted oral surgical procedures which might otherwise have required deeper sedation or even general anaesthesia.

Needle phobics benefit from the combined technique. Nitrous oxide/oxygen, with its anxiolytic and analgesic properties, is always given prior to intravenous cannulation and local anaesthetic administration.

The elderly and medically compromised may be suitable for combination of nitrous oxide/oxygen and Midazolam,

because high dosages of Midazolam are undesirable, but these patients did not form part of this study group and further trials will be necessary before recommending the technique.

Intravenous sedation with Midazolam and inhalation Nitrous oxide/oxygen are considered basic techniques and are now taught to most undergraduate dental students<sup>9</sup>. Advanced techniques include multiple intravenous drugs, continuous intravenous infusion, oral sedation, inhalation sedation with volatile agents and mixed oral/intravenous route techniques<sup>6</sup>. Whilst recent publications have highlighted benefits of these techniques, there are well-recognized adverse effects, which are thus only justified when basic techniques are inappropriate<sup>3,5,12,21,25</sup>. There are increased costs, additional equipment is required for such techniques and they do not provide analgesia. The sedationist administering advanced techniques must have specialized training and many of these techniques are not suitable for a single operator/sedationist<sup>6</sup>.

The combined technique described in this paper, however, is very suitable for a single operator/sedationist assisted by a second appropriately trained person and the two agents used (nitrous oxide and Midazolam), administered via different routes, and acting at different receptor sites, provides improved and safer sedation.

Table 8 compares the benefits and adverse effects of advanced techniques with this combined technique. The combined technique of inhalation nitrous oxide/oxygen and intravenous Midazolam during oral surgery procedures was found in this study to be a

- safe and reliable technique requiring;
- reduced doses of Midazolam with;
- improvement in patient recovery and;
- improved patient co-operation.

Due to relatively small number of cases, further assessment and a large study is necessary to confirm our findings.

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