Comparison between oral midazolam and inhaled nitrous oxide/oxygen mixture for sedation during ambulatory lower third molar surgery

Comparação entre midazolam via oral e a mistura de óxido nitroso/oxigênio via inalatória para sedação durante cirurgia ambulatorial de terceiro molar inferior

Received: 2023-09-10 | Accepted: 2023-10-20 | Published: 2023-10-27

ABSTRACT

In dental surgery, patient anxiety is a common concern, potentially impacting pain tolerance. This study compared oral midazolam and nitrous oxide/oxygen (N2O/O2) inhalation as anxiety control methods. We conducted a split-mouth study for lower third molar extractions, assessing anxiety and satisfaction using Corah’s scale, modified State-Trait Anxiety Inventory (STAI), and Visual Analogue Scale (VAS). We also monitored blood pressure, heart and respiratory rates, oxygen saturation, and electrocardiogram (ECG) changes non-invasively. Results showed no statistically significant differences in questionnaire-based parameters. However, fewer N2O/O2 group patients were “very anxious” on the modified STAI scale, favoring N2O for future surgeries. Regarding non-invasive blood pressure, midazolam group had higher levels, and N2O group exhibited elevated saturation, but these lacked clinical significance. In conclusion, both anxiolytic medications effectively induced adequate sedation. Questionnaire and multiparameter monitor data revealed minor variations between groups, indicating the suitability of either approach for dental surgery anxiety management.

Keywords: Oral surgery; Conscious sedation; Nitrous oxide; Midazolam; Third molar.
RESUMO

Em cirurgias odontológicas, a ansiedade do paciente é uma preocupação comum que pode impactar a tolerância à dor. Este estudo comparou o midazolam via oral e a inalação de óxido nitroso/oxigênio (N2O/O2) como métodos de controle da ansiedade. Realizamos um estudo dividido para extração de terceiros molares inferiores, avaliando a ansiedade e a satisfação dos pacientes usando a escala de Corah, o Inventário de Ansiedade Estado-Traço modificado (STAI) e a Escala Analógica Visual (VAS). Também monitoramos a pressão arterial não invasiva, as taxas cardíaca e respiratória, a saturação de oxigênio e alterações no eletrocardiograma (ECG). Os resultados não mostraram diferenças estatisticamente significativas nos parâmetros baseados nos questionários. No entanto, menos pacientes do grupo N2O/O2 foram categorizados como "muito ansiosos" na escala STAI modificada, preferindo a sedação com N2O para futuras cirurgias. Em relação às medidas não invasivas de pressão arterial, o grupo do midazolam apresentou níveis mais altos, enquanto o grupo N2O mostrou valores elevados de saturação, mas sem significado clínico.

Com o conclusão, ambos os medicamentos ansiolíticos induziram efetivamente uma sedação adequada. Os dados dos questionários e do monitor multiparâmetro revelaram variações menores entre os grupos, indicando a adequação de ambos os métodos no controle da ansiedade em cirurgias odontológicas.

Palavras-chave: Cirurgia bucal; Sedação consciente; Oxido Nitroso; Midazolam; Terceiro molar.

INTRODUCTION

Fear and anxiety associated with dental procedures can lead to reduced pain tolerance, resulting in prolonged or more intense discomfort during typically non-harmful dental treatments, posing a challenge. Patients with negative prior dental experiences, for instance, often exhibit heightened pain sensitivity during anesthesia, which may not align with the actual procedure (van Wijk & Makkes, 2008).

Various strategies exist to mitigate dental anxiety, including the inhalation of oral benzodiazepines (BZD) and nitrous oxide (N2O) combined with oxygen (O2). BZDs act as positive allosteric modulators on gamma-aminobutyric acid (GABA)-A receptors, reducing neuronal excitability and inducing a calming effect (Fox et al., 2011; Griffin et al., 2013). N2O's mechanisms, though not entirely understood, involve multiple targets within the central nervous system. It is thought to provide anesthesia via non-competitive inhibition of N-methyl-d-aspartate receptors (NMDARs) and analgesia through endogenous opioid release, akin to morphine, while exerting anxiolytic effects through GABA-A activation (Emmanouil & Quock, 2007; Griffin et al., 2013).

To address the comparative efficacy of these sedatives in lower third molar surgical extractions, we conducted a split-mouth study utilizing midazolam and N2O/O2.

MATERIALS AND METHODS

Study Design and Patient Sample
This prospective, split-mouth, double-blind, randomized clinical trial was approved by the Research Ethics Committee of the State University of Campinas according to registration number 55529016.3.0000.5418. The study included patients who attended the Department of Oral and Maxillofacial Surgery of the Piracicaba Dental School between April 2019 and July 2021 for lower third molar extractions. All patients aged between 18 and 35 years old signed an informed consent form before participating in the study on a voluntary basis. They were in good general health according to the American Society of Anaesthesiologists I (ASA-I) physical status, that is, the patients had to be healthy and present no physiological, biochemical or psychiatric disorders, with indication for extraction of bilaterally impacted third molars in a similar position based on the radiographic classification by George Winter and Pell and Gregori.

The patients received two different treatments at different assessment time points as follows:

- Oral midazolam group, with patients receiving one tablet of 15-mg midazolam 45 minutes before the surgical procedure.
- Inhaled nitrous oxide/oxygen group, with patients receiving N₂O and O₂ at individualized concentrations administered in a gas mixture with 10-70% of N₂O.

Anti-inflammatory medication was given to both groups of patients, which consisted of one tablet of nimesulide every 12 hours for 3 days after the surgical procedure. The analgesic chosen was paracetamol 750 mg every 6 hours for 2 days.

Inhaled sedation was performed by a professional qualified for administering minimal sedation with N₂O and O₂.

Before and during the surgery, a blind examiner identified variables related to the surgical procedure, such as age and gender of the patient, third molar classification, time of surgical procedures, specific forms and data from the multiparameter monitor.

**Surgical Procedure**

The surgical procedure was performed bilaterally by the same surgeon in all cases, with a minimum interval of 21 days between the two sides according to the following sequence: intraoral antisepsis with chlorhexidine digluconate 0.12% mouthwash for 1 minute; extraoral antisepsis with an aqueous solution of chlorhexidine digluconate 2%; topical anaesthesia with benzocaine 20%; anaesthesia of the lower alveolar, buccal and lingual nerves with lidocaine 2% and epinephrine 1:100,000 by using a cartridge-type syringe with a 27G gingival needle; straight mucoperiosteal incision in the distal region
of the lower second molar by using a #15 scalpel blade with or without a relaxing buccal incision in the mesial region of the second molar (standardized side-to-side incision in the same patient); syndesmotomy and mucoperiosteal detachment by using a Molt periosteal elevator; ostectomy and odontosection, when necessary, by using #702 dental burs; extraction by using Seldin elevators (#2, 1R or 1L); curettage, careful inspection, removal of bone spicules by using a bone file, and abundant irrigation of the surgical site with sterile saline solution (NaCl 0.9%); and coaptation of the wound edges, followed by silk suture.

Data Collection

Data on the anxiety and satisfaction of the patients were collected by using specific questionnaires and indicators of clinical status were collected by using a multiparameter monitor (Dixtal – Model DX 2021), which are described below.

Assessment of Preoperative Anxiety

Corah’s scale (Corah NL, 1969) validated Portuguese version (Hu LW et al., 2007) was used to assess the preoperative anxiety of the patients, thus making it possible to compare two assessment time points. This scale has been used to assess manifestations of dental anxiety since the 1970s. For interpreting the degree of anxiety, patients whose sum of responses was less than 5 points were considered very little anxious; from 6 to 10 points, slightly anxious; from 11 to 15 points, moderately anxious; and greater than 15 points, extremely anxious (Freeman RE, 1985).

Assessment of Comfort during Surgery

At the end of the procedures, the visual analogue scale (VAS) was used to assess the patient’s satisfaction, with scores ranging from 0 to 10 in which 0 indicates dissatisfaction with sedation and 10 indicates full satisfaction with sedation. In addition, after completing the second (last) procedure, the patients were asked which anxiolytic therapy they liked the most and which one they would choose if they needed a new oral surgery.

Assessment of Postoperative Anxiety

Immediately after the procedure, the patients were asked to answer the short version of the Spielberger’s STAI questionnaire as proposed and validated by Kaipper et al10 for allowing the assessment of the level of anxiety soon after the surgical procedure.

Doses of N₂O during Procedures
Because of physiological differences, the sufficient amount of N₂O in the mixture with O₂ should be different for each patient for an adequate sedation without signs of oversedation. Therefore, sedation was administered by increments of 10% of N₂O in order to adjust the amount considered ideal for each patient. When signs of oversedation were observed, the dose was modified to increments of 5%. Moreover, it was possible to determine the average percentages used.

*Multiparameter Data Collection*

We used a multiparameter monitor (Dixtal – Model DX 2021), previously calibrated and verified by a company certified by the manufacturer, to assess indicators of clinical status at four different assessment time points, namely: at the beginning of the procedure, with the patient under the effect of sedation; right after the end of anaesthesia (60 seconds later); 15 minutes after the end of anaesthesia; and at the end of the surgery. Data on mean non-invasive blood pressure, heart rate, respiratory rate and oxygen saturation were collected and analysed by using statistical models. Electrocardiogram (ECG) recordings during the surgical procedure were also collected and analysed by three cardiologists to describe possible patterns of differences between the groups.

*Statistical Analysis*

The demographic characteristics of the sedation groups were determined by descriptive analysis. Shapiro-Wilk’s test was used to assess data normality and either parametric or non-parametric tests were used depending on the result obtained. Due to the split-mouth study design, paired tests were used for comparison between groups and between assessment time points. Because of the non-normality of the data, blood pressure and oxygen saturation were compared between the groups by using Wilcoxon’s test, whereas the times points were compared by using Friedman’s test, followed by post-hoc analysis. Data on respiratory and heart rates were assessed by using two-way ANOVA test for repeated measures and Tukey’s test. The comparison between groups for the patient’s satisfaction, which was measured by the VAS scale, was performed by using Wilcoxon’s test. McNemar’s test was used to compare the frequency of preoperative anxiety identified by the Corah’s scale and patient satisfaction questionnaire. All tests were performed at a significance level of 5% and the figures were created by using the JMP Pro software (version 14.0).

**RESULTS**

Initially, 21 patients underwent lower third molar surgery during the study, but five ones were excluded. Of these, three patients chose not to have the contralateral lower third molar
removed; one patient had nausea and vomiting during sedation with N₂O/O₂; one patient showed behaviour suggestive of hallucinations of sexual nature, albeit mildly to moderately (Figure 1). We observed no other adverse reactions related to the sedative medications. The final sample composition had 16 patients, being nine males and seven females. The mean age of the patients included was 23.8 years (Table I).

Figure 1: Flowchart diagram of the study protocol.
Table 1: Characteristics of the patients and surgical variables.

<table>
<thead>
<tr>
<th>Patient sample (n=16)</th>
<th>Number of Third molar (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Midazolam</td>
</tr>
<tr>
<td>Mean Age</td>
<td>23.8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Tooth extracted</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>48</td>
</tr>
<tr>
<td>Dental Classification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2 (Bilaterally)=3 (18,75%)</td>
</tr>
<tr>
<td></td>
<td>B1 (Bilaterally)=7 (43,75%)</td>
</tr>
<tr>
<td></td>
<td>B2 (bilaterally)=4 (25%)</td>
</tr>
<tr>
<td></td>
<td>B3 (Bilaterally)=2 (12,5)</td>
</tr>
<tr>
<td>Surgical Time</td>
<td>38,5 min (mean)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 presents the Corah’s scale (preoperative), VAS (postoperative) and reduced STAI (postoperative) questionnaires, as well as the comparative analysis between the groups.

According to the Corah’s scale, which was completed before the surgery, 12 patients were classified as slightly anxious (6 to 10 points) and four as moderately anxious (11 to 15 points) in...
both groups. There were no statistical differences between the group using midazolam and that using N₂O/O₂. No patient was classified in the extremes of the scale, that is, very little anxious (up to 5 points) and extremely anxious (16 to 20 points).

VAS was applied at the end of the surgical procedure and no statistical difference between the sedation groups was observed. The levels of anxiety after surgery was assessed by using the modified STAI scale, and there was also no statistical difference between the groups ($P = 0.31$), although a lower frequency of very anxious patients was observed in the group using N₂O/O₂. When the patients were asked which sedation they would choose if they needed a new oral surgical procedure, 11 chose sedation with N₂O/O₂ and five sedation with midazolam.

The doses of N₂O in the mixture with O₂ were individualized for each patient, ranging from 40% to 65%, with a mean percentage of 52.18%.

Figure 3 describes the data collected from the multiparameter monitor, namely, mean blood pressure, heart rate, respiratory rate and O₂ saturation.

![Figure 3: Data on blood pressure, heart/respiratory rate and oxygen saturation (mean ± standard deviation), collected by the multiparameter monitor, for each of the groups at different assessment time points. *Upper case letters represent differences between groups for each of the time points and lower case letters represent differences in the different assessment time points for each of the treatments.](image)

Assessment of the mean non-invasive blood pressure showed statistical difference between patients sedated with midazolam or N₂O/O₂ in the first three assessment time points. Blood pressure levels were higher in the group using midazolam, which were observed immediately and 15 minutes after anaesthesia, returning to baseline levels at the end of the surgical procedure. In the group using N₂O/O₂, on the other hand, no variation was observed during the surgery.
As for heart rate, there was no statistical difference between the group using midazolam and that using N₂O/O₂, but statistically significant differences were observed between the assessment time points. As for both types of sedation, a peak heart rate was observed shortly after anaesthesia and a reduction was observed during surgery. Greater variations over time were observed in the group using midazolam.

In the assessment of respiratory rate, no statistically significant difference was found between the groups, but there were differences between the assessment time points in the group using midazolam. Higher respiratory rates were observed immediately and 15 minutes after anaesthesia, then returning to baseline levels at the end of the surgery.

When O₂ saturation was assessed, we found a statistical difference between the groups for all assessment time points, with higher values in the group using N₂O/O₂. However, no differences were observed between assessment time points in both groups.

ECG recordings were evaluated by cardiologists, with no changes between the groups, and it was also possible to determine sinus rhythm in most patients. In two patients, sinus bradycardia was observed during the use of N₂O/O₂, and in one of these patients, a first-degree (benign) atrioventricular block was also observed. In the group using midazolam, two patients with tachycardia had mild changes in repolarization.

DISCUSSION

During our study, we observed a limited number of complications associated with the various sedation methods employed. This finding aligns with existing literature, which emphasizes the safety of these drugs (van Wijk & Makkes, 2008; Fox et al., 2011; Griffin et al., 2013). There was only one instance of nausea and vomiting during sedation with N2O/O2, an occurrence previously documented in the literature (Fernández-Guisasola et al., 2010). Additionally, a patient who received midazolam exhibited behavior suggestive of sexual hallucinations. This complication has been reported in two other studies involving benzodiazepines and N2O/O2 (Balasubramaniam & Park, 2003; Orchard & Heidari, 2021), underscoring the importance of having a third person present in the room during sedation procedures.

The choice of a 15-mg dose of midazolam over the 7.5-mg dose was based on the potential ineffectiveness of the lower dose in certain patients, as discussed and recommended by another comparative study by Pereira-Santos et al. (2013). Regarding the dose of N2O in combination with O2, existing literature has highlighted the need to individualize doses to avoid
ineffectiveness and the risk of oversedation (Becker & Rosenberg, 2008; Mohan et al., 2015). Consequently, we administered N2O sedation in increments of 10%, with the option to reduce it to 5% if any signs of oversedation became apparent. The average percentage of N2O in the mixture administered to our patients was 52.18%, ranging from 40 to 65%.

We conducted a comparative analysis of the two sedation groups using specific scales and data collected from a multiparameter monitor. In terms of subjective data, the literature offers several scales for assessing patient anxiety levels (Corah, 1969; Hu et al., 2007; Kaipper et al., 2010). In our study, we selected Corah's scale for evaluating preoperative anxiety and the Visual Analog Scale (VAS) to gauge patient satisfaction with sedation. Additionally, we employed a modified State-Trait Anxiety Inventory (STAI) scale to assess potential differences between the groups.

The application of Corah's scale (Figure 2) allowed us to ascertain that most patients experienced mild to moderate anxiety levels, with no significant differences between the two sedation groups. Importantly, the random assignment of sedatives did not impact the pre-procedural anxiety levels measured using Corah’s scale, reinforcing the validity of our data collected post-sedation.

Postoperative data collected through VAS assessments (Figure 2) revealed no statistically significant differences between the two sedatives. Similarly, an analysis of data obtained using the abbreviated STAI scale (Figure 2) showed no statistical disparities between the groups, despite a slightly lower frequency of highly anxious patients in the N2O/O2 group. Among the 16 patients, 11 expressed a preference for N2O for any future surgeries, indicating a growing preference for this sedative.

Pereira-Santos et al. (2013) conducted a comparison between 7.5 mg of midazolam and 50% N2O/O2, concluding that both were suitable sedatives. They also reported lower cortisol levels in the midazolam group and suggested further investigation using a 15 mg dose of midazolam. Another study by Wilson et al. (2006) compared children sedated with 0.3 mg/kg of midazolam to those receiving incremental N2O/O2, finding no statistically significant differences in patient satisfaction or their preference for future sedation.

Evaluation of data collected through the multiparameter monitor revealed that non-invasive blood pressure was statistically higher in the midazolam group (Figure 3) (Eisele et al., 1976; DiSesa et al., 1987). Previous studies corroborate the potential for hypotension associated with N2O/O2 use (Eisele et al., 1976; DiSesa et al., 1987), while oral midazolam was found to induce minimal changes in blood pressure (Rodrigo & Rosenquist, 1988).
Heart rate did not exhibit significant differences between the two groups. However, both groups experienced peak heart rates shortly after anesthesia (Figure 3) (Lipp et al., 1993; Takahashi et al., 2005). Factors such as potential epinephrine absorption (when used as a vasoconstrictor alongside the anesthetic drug) due to inadvertent intravascular injection and the influence of pain and exogenous epinephrine action on specific receptors during anesthesia may contribute to the observed tachycardia. This effect results from increased release of endogenous epinephrine (Lipp et al., 1993; Takahashi et al., 2005).

Although no statistically significant differences were observed in respiratory rate between the groups, the midazolam group exhibited higher rates immediately and 15 minutes post-anesthesia (Figure 3) (Gonzalez Castro et al., 2017). Midazolam, particularly when administered intravenously, has the potential to induce respiratory depression (Gonzalez Castro et al., 2017). Conversely, the respiratory influence of oral midazolam is minimal (Rodrigo & Rosenquist, 1988). N2O, when used alone (without other depressant agents), does not depress ventilation or alter respiratory rate during light to moderate sedation. However, when combined with other sedatives or opioids that depress ventilation, N2O sedation may lead to more pronounced and clinically significant respiratory depression. Such effects were not observed in our study (Gonzalez Castro et al., 2017).

Levels of oxygen saturation were lower in surgical procedures performed with midazolam compared to those performed with N2O. However, no significant differences were observed between assessment time points within each group (Rodrigo & Rosenquist, 1988). While intravenous (IV) midazolam sedation may potentially lead to desaturation in rare cases, oral midazolam does not adversely affect oxygen saturation levels in healthy patients (Rodrigo & Rosenquist, 1988). The higher saturation values observed in the N2O/O2 group can be attributed to the greater concentration of oxygen available in the gas mixture administered to patients undergoing inhaled sedation. It is worth noting that none of the patients experienced a significant drop in saturation during the surgical procedures. Nevertheless, the use of a pulse oximeter or multiparameter monitor is recommended for all surgical procedures involving sedation.

With regard to electrocardiogram (ECG) recordings, the majority of patients exhibited normal sinus rhythm, with no discernible differences between the sedation methods. In the N2O/O2 group, two patients displayed sinus bradycardia, with one also exhibiting first-degree atrioventricular block—both conditions lacked clinical significance in healthy patients. These alterations have been previously documented in the literature (Dottori et al., 1970; Eisele, 1970). Among the patients in the midazolam group, two individuals with tachycardia showed slight repolarization changes, which also lacked clinical significance in asymptomatic patients. Cardiovascular changes associated with midazolam use appear to be dose-dependent and are more
commonly observed with intravenous administration. Episodes of both bradycardia and tachycardia have been reported in the literature (Reves et al., 1979; Jensen et al., 1982). Patients experiencing ECG changes were referred for evaluation by a cardiologist.

Regarding the possibility of combining these two sedatives, Al-Zahrani et al. (2009) compared the use of oral midazolam alone to its combination with inhaled N2O and O2. They reported superior outcomes and higher patient satisfaction with the combination (Al-Zahrani et al., 2009). A systematic review published in 2017 supported the combination of midazolam with N2O/O2, citing fewer adverse effects due to the reduced midazolam dosage required and improved patient acceptance, as indicated by the studies reviewed (Sivaramakrishnan & Sridharan, 2017).

Despite the advantages associated with combining these sedatives, there are certain disadvantages to this approach. While the rapid onset of action of N2O/O2 is advantageous, it renders patients unable to drive after sedation. Additionally, combining the two sedatives negates the cost-effectiveness and equipment-free advantages of midazolam.

Importantly, some studies have addressed the occupational hazards associated with N2O exposure. Chronic exposure to N2O has been linked to various health issues, including an elevated rate of spontaneous abortion, infertility, congenital anomalies, increased incidence of certain cancers, liver disease, bone marrow and immune system impairments, neurological disorders, and psychomotor impairment (Cohen et al., 1980; Gutmann & Johnsen, 1981; Vieira et al., 1983; Zaffina et al., 2019). Therefore, when selecting a sedative, the absence of these risks associated with midazolam should also be considered.

CONCLUSION

The results of the present study, according to the methodology applied, indicate that both oral midazolam and inhaled N2O/O2 are capable of providing good sedation for lower third molar extractions. No differences were observed between the data collected from the questionnaires. Multiparameter monitor data showed small differences between the groups, but without significant clinical repercussions. Due to the absence of occupational risk, lower cost, ease of use and similar results for comparison with N2O/O2, midazolam proved to be an excellent sedative medication for lower third molar surgery.
REFERENCES


