# Assessment of V*aleriana officinalis l.* (Valerian) for Conscious Sedation of Patients During the Extraction of Impacted Mandibular Third Molars: A Randomized, Split-Mouth, Double-Blind, Crossover Study

*Gustavo Jacobucci Farah, DDS, PhD,* * *Gustavo Zanna Ferreira, DDs, MS,* †
*Carolina Ferrairo Danieletto-Zanna, DDS, MS,* ‡
*Caroline Resquetti Luppi, DDS,* § *and Willian Pecin Jacomacci, DDS* ||

**Purpose:** The objective of the present study was to evaluate the effectiveness of an herbal drug (valerian) to control anxiety during mandibular third molar extraction compared with a reference benzodiazepine drug commonly used in dental procedures (midazolam).

**Materials and Methods:** Twenty anxious patients with an indication for bilateral extraction of mandibular third molars were selected. The patients received capsules containing valerian 100 mg or midazolam 15 mg orally 60 minutes before the procedures in a randomized, split-mouth, crossover design. Changes in the physiological parameters (eg, oxygen saturation, heart rate, blood pressure, respiratory rate) were assessed at specific times during surgery, and the patients completed a questionnaire postoperatively. The data were analyzed using the Wilcoxon and paired *t* tests, with a significance level of 5%.

**Results:** No statistically significant differences in oxygen saturation were observed, regardless of the drug used. However, the other physiological parameters were significantly lower when the patients had taken midazolam compared with valerian. Somnolence was the most common side effect reported with both drugs.

**Conclusions:** Although midazolam was more effective in reducing the physiological parameters studied, valerian seemed to provide the comfort and relaxation required, with no sedation and less somnolence than midazolam, during third molar extraction. Further studies are necessary before valerian can be clinically recommended.

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*Professor, Division of Oral and Maxillofacial Surgery, Department of Dentistry, State University of Maringá, Maringá, Brazil.

†Professor, Division of Oral and Maxillofacial Surgery, Department of Dentistry, UniCesumar, Maringá, Brazil; and PhD Student, Bauru School of Dentistry, University of São Paulo, São Paulo, Brazil.

‡Professor, Division of Oral and Maxillofacial Surgery, Department of Dentistry, UniCesumar, Maringá, Brazil; and PhD Student, Bauru School of Dentistry, University of São Paulo, São Paulo, Brazil.

§Specialist, Private Practitioner, Maringá, Paraná, Brazil.

||Specialist, Private Practitioner, Maringá, Paraná, Brazil.

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Address correspondence and reprint requests to Dr Ferreira: Department of Dentistry, UniCesumar, Avenida Bento Munhoz da Rocha Netto n° 1014, apto 63A, Maringá, PR 87030-010, Brazil; e-mail: gustavozanna@hotmail.com

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Despite the considerable advances in dentistry, anxiety regarding dental treatment is still a reality for many patients.[1,2] Dental anxiety can be identified by patients' attitudes toward dental treatment (eg, successive missed appointments, defensive posture), visible physical signs (eg, agitation, pallor, excessive sweating, hyperventilation), and increased systolic and diastolic blood pressure and heart rate. Although people with different levels of anxiety can tolerate minor dental treatments, they could be reluctant to undergo more invasive procedures.[2] The extraction of third molars, a common procedure in dentistry, can cause stress and fear in many patients, which can result in longer surgical times and poorer postoperative recovery. In situations such as these, measures to control anxiety could be required to improve surgeon satisfaction, increase patient comfort, and decrease peri- and postoperative pain.[3]

Anxious and fearful patients can be easily and safely treated with oral sedatives.[2] Benzodiazepines (eg, triazolam, lorazepam, diazepam, midazolam) have been the preferred class of drugs for anxiolysis and sedation before surgical procedures.[2,3] However, despite their proven clinical efficacy and enviable safety profile, benzodiazepines can result in some significant side effects such as drowsiness, confusion, dizziness, trembling, impaired coordination, vision problems, grogginess, feelings of depression, and headache. They can also potentialize the effects of alcohol and other depressants of the central nervous system, generate a paradoxical effect, and result in physical and/or psychological dependence when used chronically used.[4-7] Because of their residual effects, an adult escort is required, and patients should be recommended to not drive or operate heavy equipment while under the effects of the drug.[8] Benzodiazepines are also contraindicated for patients with severe respiratory failure, severe hepatic impairment, sleep apnea syndrome, myasthenia gravis, or known hypersensitivity to any component of the medication. Moreover, owing to the lack of familiarity and knowledge of the pharmacology of benzodiazepines, many dentists are insecure concerning its use.[9]

Currently, herbal medicines with anxiolytic and hypnotic properties have attracted increasing interest in different areas of medicine because of their low incidence of side effects.[10-13] *Valeriana officinalis L.* (valerian) is an herbaceous plant of the Valerianaceae family, which historically has been used as a sedative, antiseptic, anticonvulsant, and pain reliever.[14] Valerian active metabolites (ie, valepotriates, sesquiterpenes, lignans) have been shown to cause a marked anxiolytic effect.[14] Recent studies have demonstrated that valerian is clinically safe and effective in treating anxiety and stress-induced insomnia, with little to no side effects.[12] Valerian has also been shown to contain pharmacological reactivity in situations of psychological tension induced under laboratory conditions.[15] In low dosages (100 mg), valerian has thymoleptic and sedative effects. At higher dosages, anticonvulsive and spasmolytic effects have also been observed.[16] In clinical trials, valerian showed an important sedative-hypnotic effect at a dosage of 400 to 900 mg taken 30 to 60 minutes before bedtime.[17,18] Unlike benzodiazepines, valerian extracts do not interfere with the voluntary coordination of movement and speech and do not cause physical and/or psychological dependence.[17]

Considering the potential benefits of using alternative drugs to control anxiety, especially for patients for whom benzodiazepines are contraindicated, further research conducted in a controlled manner and with clear study designs are required to ascertain the effects of valerian in specific dental procedures. Therefore, the objective of the present study was to evaluate the effectiveness of valerian to control anxiety during the extraction of mandibular third molars compared with a reference benzodiazepine drug commonly used in dentistry (midazolam).

## Materials and Methods

This prospective, randomized, split-mouth, crossover, double-blind study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and was approved by the Ethics Committee for the Research Involving Human Beings of the State University of Maringá, Brazil (protocol No. 1 306 346) The included patients had all provided written informed consent after being thoroughly informed about the general objectives of the study and the procedures involved.

### SAMPLE SELECTION

The present study included 20 patients of both genders with an indication for bilateral extraction of mandibular third molars requiring osteotomy and odontosection. The participants were evaluated and selected according to the following inclusion criteria: *1)* American Society of Anesthesiologists I and II physical classification[19]; *2)* age 18 years or older; *3)* asymptomatic bilateral mandibular third molars at similar surgical positions[20]; and *4)* anxiety about undergoing the procedure.

The level of anxiety of the patients was determined using the Corah Anxiety Scale.[21] The scale consists of a questionnaire with 4 questions, and 5 responses per question to determine the score (score range, 1 to 5). The patients were classified according to the sum of the scores for each question. Only patients with a

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score of 11 (mildly anxious) or more were selected for the present study.

Patients presenting with the following characteristics were excluded from the present study: *1)* contraindication to the use of benzodiazepines such as a history of severe respiratory deficiency, obstructive sleep apnea, alcoholism, narrow angle glaucoma, myasthenia gravis, congestive heart failure, hepatic and/or renal impairment, and the use of other depressant medications; *2)* pregnancy and/or lactation; *3)* a history of pericoronitis; and *4)* hypersensitivity to any component of the medications, substances, or materials used in the study.

### DRUG PREPARATION

Valerian extract 100 mg was formulated and produced in uncoated capsules (Dermatológica Ltda., Maringá, Brazil) within 30 days before the procedures. The valerian formulation was submitted to a study of authenticity (macroscopic and microscopic organoleptic properties) to verify the presence and content of volatile oils and moisture and foreign elements. Commercially available midazolam tablets 15 mg (Dormonid; Roche, Rio de Janeiro, Brazil) were macerated and specially prepared in uncoated capsules of identical composition, shape, size, and color as those used for the valerian.

### SURGICAL AND THERAPEUTIC INTERVENTIONS

All the surgical procedures were conducted at the Surgery and Buco-Maxillofacial Traumatology Department at the State University of Maringá, Brazil, from February to May 2015. The patients, surgeon, and investigator were not aware of the drug used during the procedures. The side to be treated first and the drug to be used were randomized using the Research Randomizer, version 4.0 (available at: https://www.randomizer.org). An assistant (G.Z.F.) at the surgery department was responsible for conducting the randomization, informing the surgical side, and delivering the drug to the patient at the time of surgery.

The patients were given a capsule containing either valerian or midazolam orally 60 minutes before the start of the surgical procedures. During this period, the patients had no access to any electronic media or contact with anyone. To prevent hyperalgesia and to control edema, the patients also received a single dose of dexamethasone 4 mg (Decadron; Aché, Guarulhos, Brazil) orally.

At the start of the surgical period, intraoral and extraoral antisepsis was performed with 0.12 and 2% chlorhexidine digluconate aqueous solutions (Dermatológica Ltd, Maringá, Brazil), respectively. Local anesthesia of the mandibular buccal and lingual alveolar nerve was obtained with a maximum volume of 5.4 mL (equivalent to 3 tubes) of anesthetic solution containing mepivacaine 2% with epinephrine 1:100,000 (Mepiadre; DFL, Rio de Janeiro, Brazil). All mandibular third molar procedures were conducted by a single surgeon with ample experience with this type of intervention and always following the same protocol.

Relaxing incisions in the mesiobuccal region of the second molar, followed by a conventional incision for mandibular third molar extraction, were performed with a no. 15 scalpel blade (Feather Safety Razor Co, Osaka, Japan). After the soft tissues had been lifted to expose the surgical cavity, osteotomy and odontosection were performed with 702 carbide drills mounted on a high-speed handpiece (350,000 rpm) under constant irrigation with sterile saline 0.9% (Eurofarma, São Paulo, Brazil). Extraction was performed with the aid of a straight Seldin elevator, followed by careful curettage, bone regularization, and cleaning of the surgical cavity with copious irrigation with saline. The incision was sutured with interrupted stitches using 4-0 silk thread (Ethicon; Johnson & Johnson, São Paulo, Brazil).

After surgery, the patients received written instructions on local hemostatic measures, eating, cleaning of the surgical area, physical activity restrictions, and other routine recommendations for this type of intervention. From the day after the tooth extraction, chlorhexidine digluconate aqueous solution 0.12% every 12 hours for 7 days was recommended as an antiseptic agent. The patients also received 12 tablets of dipyrone 500 mg (Novalgina; Sanofi-Aventis, São Paulo, Brazil) to be taken every 6 hours only in the case of pain. The sutures were removed on the seventh day postoperatively.

The minimum interval between the first and second intervention (observation period) was 21 days, as recommended previously.[22] At the second surgery, the patients were scheduled for the same day of the week and approximately the same time of the day to prevent variations in chronopharmacology.[23]

### OUTCOME MEASURES

The data collection times (Table 1) were defined in terms of their importance during the intervention period, such that the effect of the drugs could be assessed as homogeneously as possible. Physical parameters were assessed by the investigator (C.R.L.) at the defined times (T1 to T11), as follows:

1. The oxygen saturation was monitored noninvasively with a pulse oximeter (Onyx 9500; Nonin Medical Inc, Plymouth, MA) at every time point, except for T7, to verify the possibility, however remote, of respiratory depression (nail varnish

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was carefully removed whenever necessary before oximeter placement)[24]
2. The heart rate (HR) was monitored noninvasively with the same pulse oximeter at every time point, except for T7
3. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed using a sphygmomanometer (Aneroid blood pressure BD Monitor 2700; Becton, Dickinson and Co, Franklin Lakes, NJ) and a stethoscope (3M Littmann Classic II 71 cm; 3M Company, St. Paul, MN) with the patient sitting with their back straight in the chair at T1, T2, T7, and T11
4. The respiratory rate (RR) was measured by observing chest expansion and counting the number of breaths per minute at T1, T2, T7, and T11 with care taken such that the patient was unaware of the procedure
5. The sedation level of the patients was assessed throughout the surgical procedures using the Ramsay scale[25] (at the end of the surgery, the researcher classified the general status of the patient during the surgical period as anxious, cooperative, sleepy, sleeping and responding quickly to glabellar stimulus, sleeping and responding slowly to glabellar stimulus, or sleeping without response)

### SELF-ASSESSMENT

After each surgical procedure, the participants received a self-assessment questionnaire. They were requested to report their anterograde experience and any adverse effects during the first 24 hours after the surgery. After the second surgery, patients were also requested to indicate their preference for the first or second procedure). The patients were instructed to return the form at their next visit for removal of the sutures.

**Table 1. TIME POINTS FOR COLLECTION OF PHYSICAL PARAMETER DATA**

| Time Point | Procedure |
|---|---|
| T1 | Immediately before administration of medication |
| T2 | 60 Minutes after medication (before starting procedure) |
| T3 | Extraoral antisepsis |
| T4 | Local anesthesia |
| T5 | Incision |
| T6 | Osteotomy |
| T7 | Between osteotomy and odontosection |
| T8 | Odontosection |
| T9 | Curettage of surgical cavity |
| T10 | Suturing |
| T11 | After surgery (immediately after patients had received the standardized postoperative care information) |

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### STATISTICAL ANALYSIS

The oxygen saturation, cardiovascular parameters (HR, SBP, and DBP), and RR data were analyzed using the Shapiro-Wilk normality test. When the data presented with normality, the paired *t* test was used, otherwise the Wilcoxon test was used. Statistical tests were performed using GraphPad INSTAT software and GraphPad Prism 5 (GraphPad Software, San Diego, CA), adopting the significance level of 5% ($P < .05$) for all variables.

## Results

A total of 20 patients, 11 women (55%) and 9 men (45%), mean age of 23.7 years, participated in the present study. Three patients (15%) were classified as extremely anxious and 17 (85%) were classified as mildly anxious using to the Corah Anxiety scale. No complications or episodes of anxiety were observed during the surgical procedures. The operative time ranged from 52 to 57 minutes. All the patients complied with the instructions contained in the study protocol and recovered from the procedures uneventfully.

### OUTCOME MEASURES

Oxygen saturation was within normality in all cases (97.85 to 98.45%), and no statistically significant differences between the 2 drugs ($P < .05$) were observed at any experimental time point. The HR demonstrated no statistically significant differences between the 2 drugs at drug administration (T1) or after surgery (T11). However, at all other time points (T2 to T10), the HR was significantly lower with midazolam than with valerian (Table 2).

Although no significant differences were observed at T1 and T11, the SBP was significantly lower with the use of midazolam at T2 ($P = .0478$) and T7 ($P = .0021$) compared with the SBP with valerian. For the DBP, no statistically significant differences between the 2 drugs were observed at T1, T2, or T11. However, at T7, the DBP was significantly lower when midazolam was used ($P = .0119$). The RR was also significantly lower at T7 ($P = .0007$) and at T11 ($P = .0139$) when midazolam had been administered. No statistical significant differences between the 2 drugs were observed at T1 and T2.

Concerning the level of sedation, as recorded by the researcher at the end of the surgery, 19 patients (95%) were rated as calm, and 1 (5%) was sleepy; however, no patient had fallen asleep during the surgery when valerian was used. In contrast, with midazolam, only

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**Table 2. HEART RATE OBTAINED USING PULSE OXIMETER AT EACH POINT***

| | Midazolam | | Valerian | | |
|---|---|---|---|---|---|
| Time Point | Mean ± SD | Median | Mean ± SD | Median | *P* Value |
| T1 | 80.95 ± 13.62 | 78.00 | 82.90 ± 11.97 | 80.00 | .4072 |
| T2 | 72.00 ± 11.05 | 69.00 | 76.20 ± 8.256 | 74.00 | .0327 |
| T3 | 73.85 ± 11.30 | 72.50 | 78.95 ± 8.224 | 79.50 | .0274 |
| T4 | 84.50 ± 12.26 | 80.50 | 93.05 ± 9.378 | 94.50 | .0060 |
| T5 | 80.65 ± 10.96 | 77.00 | 87.85 ± 8.911 | 88.00 | .0092 |
| T6 | 81.60 ± 10.01 | 80.00 | 89.15 ± 9.571 | 88.00 | .0012 |
| T7 | 79.40 ± 10.41 | 76.00 | 86.25 ± 8.699 | 84.50 | .0084 |
| T8 | 75.35 ± 9.427 | 72.50 | 82.80 ± 9.929 | 82.00 | .0078 |
| T9 | 74.90 ± 8.019 | 73.00 | 80.30 ± 8.374 | 78.50 | .0021 |
| T10 | 77.20 ± 10.36 | 75.50 | 79.90 ± 9.497 | 80 | .1121 |

Abbreviation: SD, standard deviation.
* Wilcoxon test.

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5 patients (25%) were rated as calm and relaxed, 7 (35%) were somnolent, and 8 (40%) had actually fallen asleep during the surgery, with 2 patients (10%) responding quickly and 6 (30%) responding slowly to glabellar stimulus.

### SELF-ASSESSMENT

From the answers obtained from the returned questionnaires, a statistically significant difference ($P < .001$) was observed between the 2 drugs regarding the occurrence of anterograde amnesia (ie, forgetting facts occurring during the peak drug concentration). When valerian was used, all 20 patients (100%) reported remembering all stages of the surgical procedure. When midazolam was used, however, only 5 patients (25%) reported remembering all the steps, 7 (35%) remembered most steps, 5 (25%) remembered something unspecific, and 3 (15%) remembered practically nothing.

Concerning the adverse effects reported by the patients within the 24 hours after surgery, no statistically significant differences were found between the 2 drugs ($P = .163$). The most commonly reported side effect of the drugs was somnolence, with no adverse effects at all reported by 6 patients (30%) when valerian was used and by 2 patients (10%) when midazolam was used (Table 3).

Statistically significant differences between the 2 drugs were found on how the patients felt during the surgical procedure ($P = .0092$). When midazolam was given, 8 patients (40%) reported feeling peaceful, 10 (50%) slightly anxious, and 2 (10%) moderately anxious; no patient reported being extremely anxious. However, when valerian was administered, 4 patients (20%) reported feeling calm, 10 (50%) slightly anxious, 5 (25%) moderately anxious, and 1 (5%) extremely anxious.

Regarding the procedure of choice, again, no statistically significant difference was found between the 2 drugs ($P = .8312$). Although 9 patients (45%) preferred the surgery with midazolam, 11 patients (55%) preferred the surgery with valerian. The main complaint concerning the use of midazolam was the anterograde amnesia, which was generally described as unsettling.

## Discussion

The present study was designed to evaluate the effectiveness of valerian 100 mg compared with midazolam 15 mg as an alternative drug to control the anxiety of patients undergoing mandibular third molar extraction. These results have demonstrated that valerian seems to have the potential to provide patients with the comfort and relaxation required without sedation and less somnolence than midazolam.

**Table 3. ABSOLUTE AND RELATIVE NUMBERS OF ADVERSE EFFECTS OF DRUGS WITHIN 24 HOURS AFTER SURGERY REPORTED BY PATIENTS***

| Adverse Effect | Midazolam | Valerian |
|---|---|---|
| None | 2 (10) | 6 (30) |
| Somnolence | 13 (65) | 10 (50) |
| Dizziness | 0 (0) | 1 (5) |
| Sluggishness | 4 (20) | 1 (5) |
| Stomach alterations | 3 (15) | 1 (5) |
| Cardiovascular alterations | 1 (5) | 0 (0) |

*Note:* Data presented as n (%).
* $P = .164$ (Wilcoxon test).

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Trials involving herbal medicines, such as our study, can be difficult to justify, especially when a drug with proven clinical efficacy is available. In the present case, however, it is important to remember that a group of anxious dental patients exist who might not benefit from the use of benzodiazepines owing to their well-known side effects. Benzodiazepine drugs for conscious sedation are contraindicated for patients with obstructive sleep apnea, chronic obstructive pulmonary disease, and other respiratory diseases.[26]

In these patients, benzodiazepines cause the hypopharynx musculature that supports the tongue to relax and drop onto the posterior pharyngeal wall, which can result in hypoxia. Thus, these patients might need to go to a hospital and have their teeth removed under general anesthesia, resulting in a procedure of greater complexity. Apart from the inconvenience to patients and clinicians, factors such as the risk of contamination and the high cost involved should be considered. Perhaps, even more clinically relevant at present, is the increasing number of people taking different types of depressant drugs. The synergic effect of using a benzodiazepine drug in such patients could lead to situations that could not be managed by clinicians in dental offices. Within this scenario, it would seem reasonable that new drugs should be tested to provide patients who currently cannot be treated with benzodiazepines with adequate alternatives.

It has been suggested that dental anxiety in its most acute and/or representative stage afflicts from 2.5 to 20% of the adult population worldwide.[20,27,28] The sample formed by mildly (85%) to extremely (15%) anxious patients participating in the present study can be considered representative of the clinical reality in dental offices. Arguably, the assessment of anxiety was somewhat subjective, because the patients themselves reported their status. Nonetheless, no objective method to assess anxiety is available, and the method applied to select the participants was the same as that used in several previous studies.[27,29,30]

To reduce the risk of bias and ensure standardization as much as possible, extreme care was exercised at every step of the methodologic design applied to the present study. The drugs were prepared in such a manner that the delivery vehicle (uncoated capsules) was exactly the same and were administered in the same fashion and always by the same person. Apart from ensuring blindness, the same route of administration, rate of dissolution, and where dissolution of the drugs occurred were also standardized. Moreover, just after drug administration, the patients were left on their own for 60 minutes before the surgery with no contact with other people or any type of electronic media to avoid any stress peaks. The second surgery was scheduled for the same day of the week and the same time of the day as the first surgery, also in an attempt to avoid possible variations in the chronopharmacology of the drugs. The pharmacodynamics and pharmacokinetics of many drugs are circadian, and the drug efficacy and safety profiles can vary with the time of day.[23] All surgical and data collection procedures were conducted by the same investigators and strictly followed the same protocol. The assessment time points (T1 to T11) were defined by their importance during mandibular third molar extraction procedures, and allowed for the assessment of anxiety at different stages.

Data collection was performed always very discretely and did not follow pre-established times (ie, they were conducted according to the surgical stage, regardless of the elapsed time). A short interval of ~40 to 50 seconds was created between odontosection and osteotomy (T7) to allow the patients to be positioned with their backs straight to permit SBP, DBP, and RR data collection always at the same surgical stage. Considering that no intercurrents were observed during surgeries, it may be inferred that data collection procedures along the surgery did not negatively affect the level of anxiety of the patients.

In situations of anxiety and pain, the autonomic nervous system increases the release of endogenous catecholamines, especially adrenaline. This increase can result in arterial constriction and increased arterial blood pressure, more noticeably, the SBP. Anxiety can also act on cardiac adrenergic receptors and cause alterations in the HR.[31] Therefore, monitoring these physiological parameters is essential to examine the anxiolytic effects of different drugs. The oxygen saturation remained stable (97.85 to 98.45%) throughout all the surgeries, regardless of the drug used. It is important to remember, however, that benzodiazepines can induce sleep and, in some cases, could decrease the oxygen saturation to dangerous levels, resulting in episodes of hypoxia. Nevertheless, in the present study, no respiratory complications were observed, confirming the safety of midazolam when used in patients without respiratory disorders who also do not use other depressant drugs, such as in the present sample.

When patients received midazolam, significantly lower mean HR values were found between T2 and T9 compared with the HR with valerian. The HR decrease after midazolam use has been explained by the decrease in the baroreflex function and decreased sympathetic tone caused by the drug.[32,33] Valerian, however, did not seem to have a significant effect on the HR, confirming the findings of a previous study with a similar design, in which no changes in HR were observed when patients had valerian compared with a placebo drug.[30]

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Both SBP and DBP were also significantly lower when midazolam was used than when valerian was used at T2 (SBP) and T7 (SBP and DBP). These findings can be explained by the half-life of midazolam, whose peak effect (70 to 120 ng/mL) coincided with T2 (60 minutes after drug administration), leading to decreased arterial blood pressure during surgery owing to its vasodilating action.[31] In a study by Cropley et al[15] in 2002, reduced SBP, but not DBP, was observed with the use of significantly higher doses of valerian. Pinheiro et al[30] in 2014 observed decreased SBP and DBP after the administration of valerian 100 mg during third molar surgery compared with a placebo drug. The RR measurements were also significantly lower at T7 and T11 with the use of midazolam compared with valerian, indicating its more effective depressant action.

The consistency of the physiological results seems to suggest that midazolam possesses a greater capacity to control anxiety compared with valerian. These results seem to be confirmed by the self-reported level of anxiety during the surgery. Although 18 patients (90%) reported feeling calm or just slightly anxious during surgery after taking midazolam, 5 patients (25%) reported feeling moderately anxious, and 1 (5%) extremely anxious when valerian was administered. However, these results do not necessarily indicate that valerian was not effective in providing anxious patients with the necessary comfort during third molar surgery. More likely, the differences found only indicate that the working mechanisms of the drugs are different. It is important to remember that midazolam is a sedative drug and, hence, more effective in depressing the physiological parameters tested. In contrast, valerian is an anxiolytic drug, which causes relaxation in the patient without, however, inducing sleep.

The drowsiness caused by midazolam is the result of the drug interacting with the most abundant inhibitory neurotransmitter of the central nervous system, known as gamma-aminobutyric acid (GABA), which is able to act in the locus coeruleus—one of the key centers of sleep. After being synthesized and released in the synapses, the drug interacts with the GABA receptor/chloride ionophore complex, increasing the negative charge into the cells and decreasing the likelihood of a neuron reaching its threshold potential (neuronal inhibition). GABA exerts a similar action in the hypothalamus and the anterior portion of the brain, regions involved in the genesis of sleep.[34] For valerian, the recommended dose for hypnosis is 4 to 9 times greater than that used in present study.[17,18] Because of its various constituents, the working mechanism of valerian remains debated and little understood. An in vitro study by Riedel et al[35] in 1982 showed that valerenic acid decreases the rate of GABA degradation.

More recent studies have shown an increase in the concentration of GABA in synaptic clefts after valerian extract, rather than when isolated valerenic acid, was used,[36] which might explain the drowsiness observed in the present study. In contrast, relaxation results because valepotriates have spasmolytic activity, influencing the influx of calcium ions into the cells or modifying their link in the muscles.[37] This effect can be beneficial, because, according to Smyth,[38] agitation and muscle tension are the physical symptoms of anxiety. In our study, 6 patients (30%) did not report feeling any adverse effects when using valerian compared with 2 patients (10%) after midazolam use, reinforcing the apparent good tolerability of valerian.

Moreover, all individuals reported remembering all the surgical steps when valerian 100 mg was taken, corroborating the findings of Pinheiro et al,[30] who also observed no anterograde amnesia after valerian use. With midazolam, however, most patients reported having some difficulty remembering what had occurred during the surgery, a well-described feature of this type of medication.[25,39,40] Although some clinicians might consider amnesia a desirable effect during surgery, others could see it as an adverse effect, which could potentially harm the assimilation of postoperative recommendations. Also, some patients reported feeling uneasy experiencing this type of adverse effect.

From the results of the present study, midazolam was more effective in controlling the anxiety of adult patients undergoing mandibular third molar extraction than was valerian. However, despite the differences found in the physiological variables assessed, valerian demonstrated an anxiolytic effect in the patients. Based on the observations by the researcher and the feedback from patients themselves, valerian seemed to cause fewer adverse effects than did midazolam. Although valerian emerged as a possible alternative to control anxiety in selected cases, the lack of a more complete understanding of its working mechanism demands further studies to better ascertain the safety and the efficacy of the drug before it can be recommended clinically. The next logical step will be to study the effect of valerian 100 mg on specific target groups of patients for whom midazolam would be contraindicated, such as children, patients with respiratory disorders, alcoholics, and those using other antidepressant drugs.

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