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Midazolam as a Conscious Sedation in Dental Practice: A Systematic Review

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Abstract

Background: Conscious sedation is a guidance technique used to control the behavior of anxious or uncooperative patients. A variety of drugs are used in the sedation process, including inhalation agents such as orally or parenterally midazolam and other benzodiazepines. Midazolam is considered a member of the benzodiazepine family with the highest lipid-soluble properties. ***Objective:*** This article aims to review the use of Midazolam for conscious sedation in dental practice and illustrate each route of administration. ***Materials and Methods*:** This study involved a review of published articles related to the use of Midazolam for conscious sedation in dental practice. The PubMed search engine and Cochrane electronic databases were used to collect the most relevant and recent information on midazolam in dental practice. ***Results:*** By applying this method, 10 articles were gathered and used in the current review. ***Conclusion*:** Midazolam has shown its ability to be a safe and effective drug in conscious sedation in dental practice. However, some points must be considered before administering midazolam, including patient age and weight, the dose required, drug-drug interaction, special care patients, route of administration, and level of anxiety.

Keywords: Conscious sedation, Midazolam, Dental practice, intranasal route, oral route, intravenous route.

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1. INTRODUCTION

Anxiety has always been considered an undesirable sensation associated with dental experience in many patients [1]. Symptoms of anxiety are often observed in patients undergoing dental treatment, regardless of whether the treatment is simple or is in more aggressive forms such as surgery [2].These symptoms may manifest as arrhythmia, sweating, vasovagal response, and tremors [3]. As accepted, if the first impression in the dental experience was bad for the patient, further experiences are not expected to be any superior [1]. In the moderate time, new techniques have been introduced for sedation in the dental practice [1]. Conscious sedation is a guidance technique used to control the behavior of anxious or uncooperative patients, which, in turn, is caused by the lack of mental maturity, or psychological technique used to control the behavior of anxious or uncooperative patients, which is caused by the lack of mental maturity, or psychological and emotional problems, etc [4]. Moderate conscious sedation is recognized as the use of a drug or drugs that cause a formal depression of the central nervous system while also enhancing patient safety, psychological control, and the ability to control behavior and anxiety, which helps ongoing the treatment. However, verbal communication with the patient is preserved during the sedation [1, 3, 5]. Aims of conscious sedation are to control behavior during dental pediatric rehabilitation, lower apprehension, enhance patient's behavior, maximize amnesia potential, and decrease the undesirable psychological reaction towards treatment by reducing anxiety [6]. A variety of medications are used in the sedation process. These include inhalation agents such as orally or parenterally midazolam and other benzodiazepines, nitrous oxide, psych-sedative agents, and other sedative-hypnotics [1]. Commonly used drugs include intravenous, intranasal, oral midazolam, and nitrous oxide [1]. Midazolam is a member of the benzodiazepine family with amnesic, anxiolytic, and highest lipid-soluble properties associated with short-acting sedation and a few adverse effects [3, 7, 8]. Fast absorption and metabolism in the GI tract and the efficient entry in the brain tissue are

attributed to its lipophilic nature [8]. Midazolam is generally used as a premedication for dental fear, pediatric patient, and oral surgery [9]. The advantages of midazolam include an excellent safety profile, good haemo-dynamic stability, rapid onset, dose-dependent anxiolysis, fast action, and anterograde amnestic effect [10, 11]. The indications for using midazolam include premedication, sedation in anesthesia, conscious sedation, sedation in intensive care, and management of status epilepticus [12]. Presently, oral administration is the most common form of midazolam for sedation in young patients [7]. However rectal administration has shown a faster onset compared to oral administration due to its rapid absorption [8]. The efficiency of oral sedation in children depends on weight, age, time of day, temperament, and level of anxiety [8]. In this article, we will review the use of Midazolam for conscious sedation in dental practice and illustrate each route of administration.

2. MATERIALS AND METHODS

This study involved a review of published articles related to the use of Midazolam for conscious sedation in dental practice. Various databases like PubMed, Cochrane electronic databases, and web of science were used to collect the most applicable and recent information on midazolam in dental practice. A search set was applied to combine a range of keywords: (Midazolam) and (Conscious sedation) and (Dental practice). By using this method, Midazolam aimed at conscious sedation articles and studies were obtained. Additional studies were also gathered from Google Scholar. In inclusion criteria, we included all papers discussing the usage and routes of administrations of midazolam for conscious sedation in dentistry, including systematic reviews, meta-analysis of randomized controlled trials, case reports, series, and cohorts' articles. PubMed Central indexed publications were included if they described the following: 1) Midazolam administration routes, 2) Conscious sedation in dental practice, and 3) Mechanism of action of Midazolam. On the other hand, articles were excluded if they were related to 1) Midazolam uses in other specialties other than dentistry, 2) Midazolam uses non-related to conscious sedation. We excluded all Midazolam articles nonrelated to conscious sedation and papers non-related to dental practice. The initial search revealed 92 articles related to the usage of midazolam. After removing duplicates and records papers that did not match the above selection criteria, the most significant studies were chosen and used in this review. The review was conducted by studying 10 articles related to the use of midazolam for conscious sedation in dental practice (Fig-1).

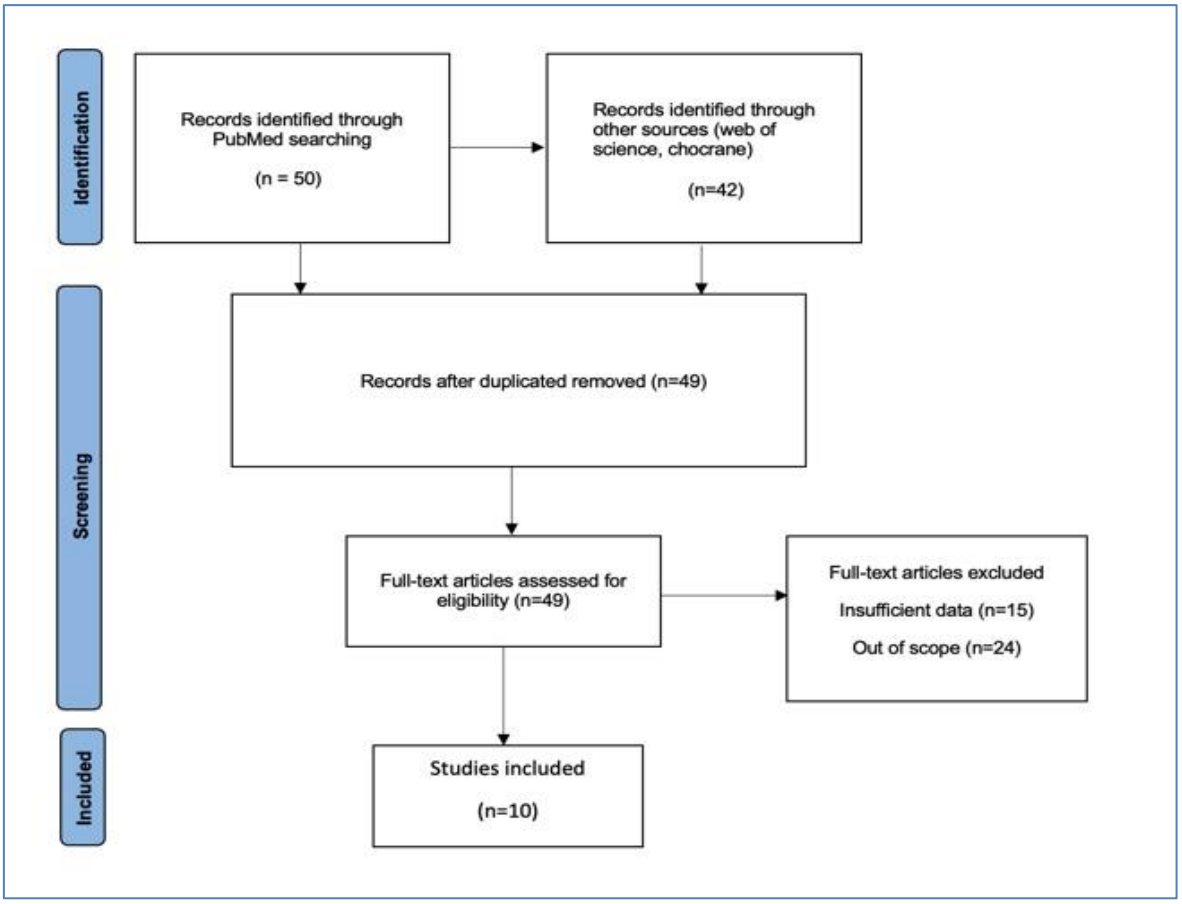

Fig-1: Study flow chart

3. Mechanism of action

Mediators responsible for stress such as catecholamines, glucocorticoids, corticotrophin-releasing hormone, and adrenocorticotropic hormone are produced by the body through the Hypothalamus-Pituitary-Adrenal (HPA). All these mediators are responsible for increasing cellular metabolism, mental activity, heart rate, and blood pressure. After stress exposure, it requires about 15 to 20 minutes for cortisol to reach the bloodstream and an additional two minutes to reach the saliva [10]. Benzodiazepines retain an electronegative halogen substituent that is essential for providing hypnotic and sedative effects. Midazolam is a member of the benzodiazepine family with short-acting properties affecting Gamma-Aminobutyric Acid (GABA-ergic) transmission, which, in turn, induces responses in the central nervous system [13, 14]. Enzymes involved in the metabolism and metabolites of midazolam are demonstrated in (fig.2) [13].

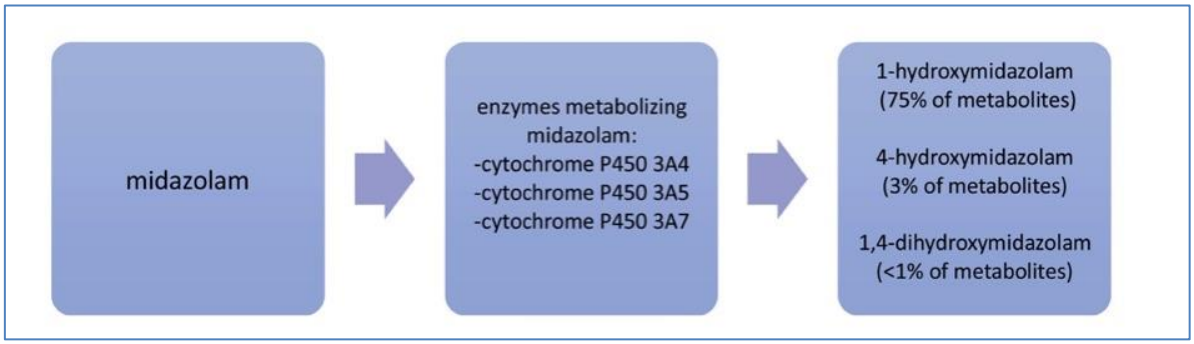

Fig-2: Enzymes involved in the metabolism and metabolites of midazolam [13]

4. Midazolam in pediatric patients

Treatment of young children is known to result in some difficulties, especially in dental practice. The children are suggested to be uncooperative and more anxious between 3 and 7 years however, this anxiety reduces as their age increases [10]. Dental explorer, extraction forceps, syringe carpules, and rubber dam punch has proven to be causes of increasing children's anxiety about dental care [10]. Children's anxiety about dental care could cause behavioral management problems for the dental practitioner [15]. A positive approach to the child and performing effective dental treatment are some of the responsibilities of a pediatric dentist. [10] Uncooperative children belong to the category that requires supplementary invasive procedures and common methods as conscious sedation [6, 10]. A study was directed to determine the safety and effectiveness of 3 different doses of midazolam for conscious sedation in 2 to 4-years-old pediatric children with multiple dental treatments and negative behavior. According to the findings, sedated children demonstrated more positive behavior at the beginning of the appointment and during the local anesthesia administration [16]. In addition, a study proved that Oral midazolam at a dose of (0.15-0.70 mg/kg) might be an acceptable and safe method of sedation for pediatric patients [17]. Another study in Israel was carried out to inspect the recovery time for children who had conscious sedation with oral or rectal midazolam. The study illustrated that the time to discharge the patient after midazolam sedation was related to the child's weight and age and the overall amount of administered midazolam. However, sedation was found to have a negative effect on behavior in 43.6% of the patients [8].

5. Midazolam in oral surgery

Midazolam has been well recognized as an appropriate sedative option in dental surgery [14]. Midazolam could be used as an addition to pain control when severe pain is anticipated, which could lead to improved acceptance of treatment by the patient, reduced pain, and less consumption of analgesics [14]. Studies have shown that when experiencing surgery or dental treatment, up to 60% of all children may present with negative behavior [18]. A dental extraction is considered an aggressive procedure in many patients, especially in children [19]. A study in China aimed to evaluate the effectiveness of midazolam to control anxiety in third molar extraction surgery. As per the findings, midazolam could be effective in controlling anxiety during third molar extraction surgery [3].

6. Midazolam in elderly and special care patients

Few articles have discussed the effect of midazolam in elderly and special care patients. These included a study in Sweden to evaluate the treatment after oral administration of midazolam for dental patients with major neurocognitive disorders. The results showed rare unfavorable side effects, such as hyperactive and drowsiness [9]. Another study was conducted to assess the effectiveness of Midazolam in the dental treatment of patients with neurological diseases. Midazolam was found to be effective in 89% of dental procedures in patients with behavioral and neurological disturbances. However, it ended up reducing effectiveness for patients' behavioral and neurological disturbances. However, Midazolam had reduced effectiveness for patients with autism [20].

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7. Oral route

The oral route is considered the easiest and most universally accepted technique of drug sedation [6]. Oral sedation is preferred for many reasons. For example, it is fairly inexpensive, can be administered easily, and does not require injection as for IV, or child cooperation as for inhalation sedation. However, it carries a risk of over sedation since determining the appropriate dose is difficult. In addition, it is associated with a longer recovery and duration of onset compared to other routes of sedation [6, 19]. Oral route is advocated for relatively short dental procedures associated with anxious patients [6]. This technique is considered safe alone and produces effective conscious sedation in the dental treatment of pediatric patients. Meanwhile, oral midazolam is commonly preferred because it is more easily accepted by children [21]. An article aimed to review the effect of oral administration of midazolam sedation in a group of uncooperative pediatric dental patients and analyze the effect of child age on the treatment results and safety. It was found that oral midazolam for conscious sedation at a dose of 0.50 - 0.75 mg/kg is safer and more effective in pediatric dental patients above three years of age [22, 23].

8. Intranasal route

Intranasal midazolam has gained a lot of popularity for patients who cannot cooperate with IV cannulation [19]. This technique is administered by a mucosal atomizer device (MAD) (fig. 3) and can be absorbed rapidly into the systematic circulation due to the high vascularity of the nasal mucosa [10, 19, 24]. The main advantage of this technique is that its duration onset is three times faster than oral sedation because of its rapid absorption [19]. Meanwhile, it also reduced the risk of children spitting out the medication outside the mouth [19]. A study was conducted to measure the safety and effectiveness of using intranasal midazolam in a concentrated form for pediatric patients. The results demonstrated that in selected cases, intranasal sedation offers an effective and safe substitute for general anesthesia in short invasive procedures that is restricted to one or two quadrants in pediatric patients [25]. Another article was aimed to compare and evaluate intranasal and oral midazolam for the effect on the time of onset, behavior, efficacy, safety for dental patients, and maximum working time. The results demonstrated that the mean onset time was about three times faster with the intranasal route compared to the oral route and that the mean working time was about 10 minutes longer with the oral route than it was with the intranasal route. Generally, the behavior under oral administration and intranasal administration was similar. However, toward the end of the dental appointment, less sleep and more movement were exhibited in subjects under the intranasal route than those under the oral route. Vital signs were all stable during the procedures and no significant differences were found between intranasal and oral administration [26].

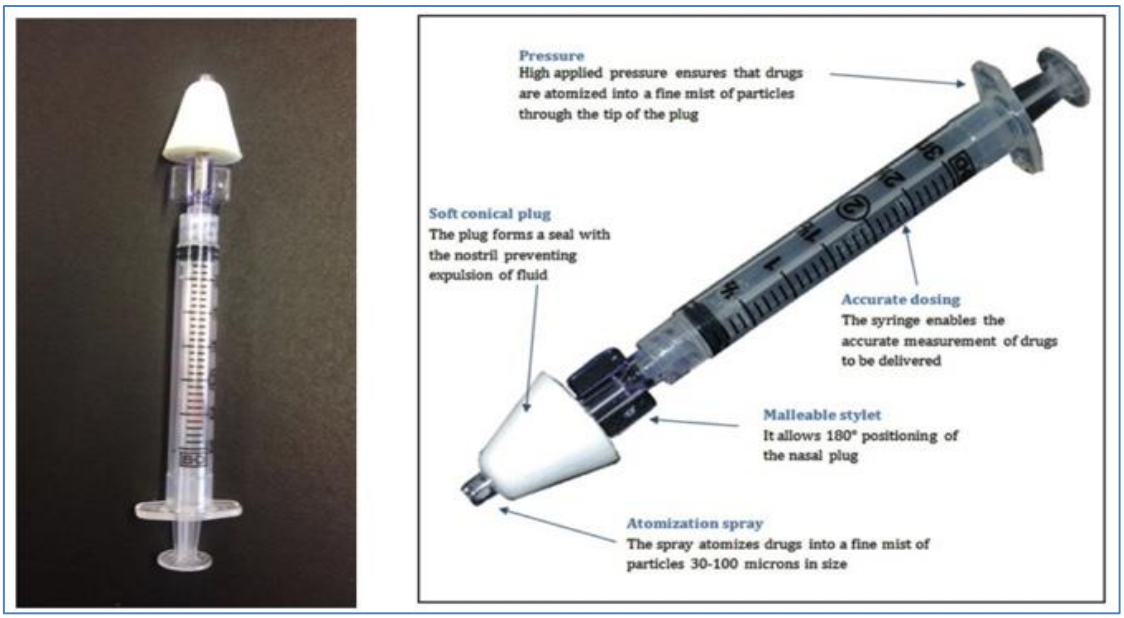

Fig-3: Demonstration of mucosal atomizer device (MAD) [27, 28]

9. Oral versus intranasal administration

Several studies have compared the use of oral and intranasal midazolam for conscious sedation. Among these studies, a study was carried out to compare the efficacy and safety between oral and intranasal administration of midazolam in healthy children by evaluating their behavioral and physiological reactions. According to the results, both procedures have similar behavioral results. The oral group demonstrated an improvement in crying and behavior early in the session; furthermore, the providers considered oral sedatives to be more effective compare to intranasal sedation [29].

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10. Sublingual route

Sublingual mucosa has a high permeability that contributes to a high systematic absorption compared to the parental routes (fig.4). [10]. A study that was conducted to compare the behavior and dental anxiety during sublingual and intranasal midazolam revealed that sublingual and intranasal routes of midazolam were equally effective in reducing dental anxiety [10]. However, another article concluded that premedication with sublingual midazolam is more effective than the oral route in children [30].

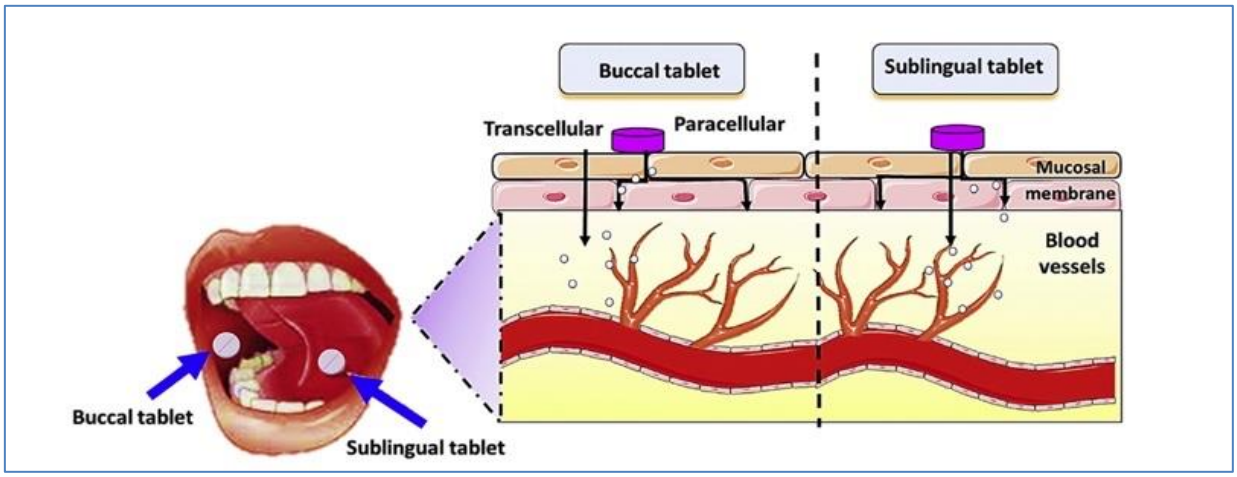

Fig-4: Demonstration of transmucosal drug delivery [31]

11. Intravenous route

Intravenous midazolam is preferred due to the continuous venous access that improves the overall safety by permitting rapid injection of any medication such as flumazenil (antagonist), if necessary. Additionally, intravenous routes permit a gradual adjustment of midazolam, which limits the risk of over or under sedation by allowing the clinician to control the level of sedation for each individual patient [32]. A study was conducted to determine the frequency, nature, and sequelae of complications occurring in patients under dental treatment with intravenous midazolam sedation. The results showed that intravenous midazolam is a safe sedation procedure and suitable for adult patients undergoing dental treatment in primary care when administered by skilled personnel on wisely chosen patients and in compliance with nationally approved guidelines and protocols [11]. Another study was done to evaluate the probability that intravenous midazolam could replace general anesthesia in dental procedures. The results showed that in cases of several dental management issues, the conscious sedation method was not found to be a suitable replacement for general anesthesia [33].

12. Safety and Side effects

Conscious sedation should be applied in consonance with nationally agreed guidelines and protocols to reduce the risk of subsequent harm and overdose [11]. The side effects of midazolam in the British National Formulary for Children are listed as follows: increased appetite, cardiac arrest, muscle weakness, heart rate changes, urinary retention or incontinence, hypotension, involuntary movements, convulsions, vertigo, anaphylaxis, dizziness, thrombosis, ataxia, laryngospasm, jaundice, bronchospasm, dysarthria, respiratory depression and arrest, gastrointestinal disturbances, blood disorders, dry mouth, skin reactions, hiccups, salivation changes, drowsiness, euphoria, confusion, paradoxical excitement and aggression, amnesia, headache, hallucinations, injection site reactions with intravenous administration, visual disturbances including diplopia, and with intranasal administration, lacrimation, irritation of nasal mucosa, and burning sensation [12]. Overall, the side effects of midazolam are reported to be uncommon. However, hypoxemia and hypoventilation have been associated with high doses [34]. Arterial hypoxemia results due to respiratory depression following overdose which is commonly caused by bolus injection or improper titration [11]. Regarding drug-drug interaction, midazolam has shown its ability to reduce systematic vascular resistance. In addition, there has been some evidence that it may potentiate the antihypertensive effect of B-adrenoceptor blocking drugs [35]. A lot of study's illustrated the safety of using midazolam in the dental practice, including a study in china that aimed to evaluate the safety and effectiveness of oral midazolam combined with nitrous oxide for reducing dental fear in children. The results showed that oral midazolam is harmless and effective for reducing dental fear in young patients, whereas the combination of oral midazolam with 30%-40% nitrous oxide has demonstrated its ability to enhance the behaviors of children throughout the dental treatment. In addition, another study recommended the use of a combination of midazolam and nitrous oxide rather than the use of each drug as an individual due to the benefit of reduction in the dose of midazolam used, which contributes to a better safety profile [1, 36].

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13. DISCUSSION

Midazolam has shown its ability to be a safe and effective drug in conscious sedation in dental practice. However, some points must be considered before the administration of midazolam, including patient age and weight, the dose required, drug-drug interaction, special care patients, level of anxiety, and route of administration. The oral route is advocated for relatively short dental procedures associated with anxious patients [6]. However, it carries a risk of over sedation since determining the appropriate dose is difficult. In addition, the medication has a longer recovery and duration of onset compared to other routes of sedation [6, 19]. The main advantage of the intranasal route is that its duration onset is three times faster than oral sedation because of its rapid absorption. In addition, it reduces the risk of children spitting out the medication outside the mouth [19]. The sublingual route is preferred due to the high permeability of sublingual mucosa, which then contributes to high systematic absorption in comparison to the parental routes [10]. The intravenous route has the advantage of continuous venous access which improves overall safety. Additionally, intravenous routes permit a gradual adjustment of midazolam, which limits the risk of over or under sedation by allowing the clinician to control the level of sedation for each patient [32]. Our study didn't incorporate Scopus database in the search methodology. However various electronic databases were used to collect the most applicable and recent information on midazolam in dental practice.

Table-1: Summary of relevant articles discussing the routes of administration of Midazolam

Author	Year of publication	Number of patients	Route of administration	Conclusion
Gomes HS	2017	84 children	Intranasally ketamine plus midazolam administration	In children, it could be suitable to combine ketamine with midazolam to provide a better outcome.
Dantas LP	2017	40 volunteers	Oral administration	Passiflora incarnata showed a similar result to midazolam in terms of anxiolytic effect.
Ma L, Zhang J	2017	77 children	Oral administration	Oral midazolam is effective for reducing dental fear in young patients.
Rignell L	2017	61 patients	Oral administration	Oral administration of midazolam is safe and effective in the treatment of uncooperative patients with major neurocognitive disorders.
Collado V	2013	142 patients	Intravenous administration	Intravenous midazolam is effective and safe in patients with intellectual disabilities.
Shanmugaavel AK	2016	20 children	Intranasal and sublingual administration	Sublingual and intranasal routes of midazolam are equally effective in reducing dental anxiety.
Wood M.	2011	114 children	Intranasal administration	Intranasal sedation offers an effective and safe substitute for general anesthesia in short invasive procedures.
Wilson KE	2011	401 patients	Intravenous administration	A safe sedation procedure, intravenous midazolam is a safe sedation procedure is suitable for adult patients undergoing dental treatment in primary care.
Tyagi P	2013	40 patients	Oral Midazolam, Intravenous Midazolam and Oral Diazepam	Sedation with oral diazepam and oral midazolam were comparable, while intravenous midazolam produced more sedation effects.
Lee-Kim SJ	2004	40 patients	Intranasal and oral administration	Mean onset time was about 3 times faster with the intranasal route compared to the oral route.

Author's contribution

BF and AA conducted and designed the study and started the initial review of articles and studies. They also wrote the initial manuscript. OAF provided research scope and collecting of data. BF and AA did the data analysis. BF, AA, and OAF wrote the final drafts of the article. OAF provided logistic support. All authors have critically reviewed and approved the final draft.

REFERENCES

1. Sivaramakrishnan, G., & Sridharan, K. (2017). Nitrous Oxide and Midazolam Sedation: A Systematic Review and Meta-Analysis. *Anesthesia progress*, *64*(2), 59–65. https://doi.org/10.2344/anpr-63-03-06
2. Dantas, L. P., de Oliveira-Ribeiro, A., de Almeida-Souza, L. M., & Groppo, F. C. (2017). Effects of passiflora incarnata and midazolam for control of anxiety in patients undergoing dental extraction. *Medicina oral, patologia oral y cirugia bucal*, *22*(1), e95–e101. https://doi.org/10.4317/medoral.21140
3. Chen, Q., Wang, L., Ge, L., Gao, Y., & Wang, H. (2015). The anxiolytic effect of midazolam in third molar extraction: a systematic review. *PloS one*, *10*(4), e0121410. https://doi.org/10.1371/journal.pone.0121410
4. Gomes, H. S., Miranda, A. R., Viana, K. A., Batista, A. C., Costa, P. S., Daher, A., Machado, G. C., Sado-Filho, J., Vieira, L. A., Corrêa-Faria, P., Hosey, M. T., & Costa, L. R. (2017). Intranasal sedation using ketamine and midazolam for pediatric dental treatment (NASO): study protocol for a randomized controlled trial. *Trials*, *18*(1), 172. https://doi.org/10.1186/s13063-017-1919-2
5. Lobb, D., Clarke, A., & Lai, H. (2018). Administration order of midazolam/fentanyl for moderate dental sedation. *Journal of dental anesthesia and pain medicine*, *18*(1), 47–56. https://doi.org/10.17245/jdapm.2018.18.1.47
6. Shabbir, A., Bhat, S. S., Sundeep Hegde, K., & Salman, M. (2011). Comparison of oral midazolam and triclofos in conscious sedation of uncooperative children. *The Journal of clinical pediatric dentistry*, *36*(2), 189–196. https://doi.org/10.17796/jcpd.36.2.0346178414pvw865
7. Vasakova, J., Duskova, J., Lunackova, J., Drapalova, K., Zuzankova, L., Starka, L., Duskova, M., & Broukal, Z. (2020). Midazolam and its effect on vital signs and behavior in children under conscious sedation in dentistry. *Physiological research*, *69*(Suppl 2), S305–S314. https://doi.org/10.33549/physiolres.934511
8. Blumer, S., Peretz, B., Zisman, G., & Ratson, T. (2017). Effect of Sedation with Midazolam and Time to Discharge among Pediatric Dental Patients. *The Journal of clinical pediatric dentistry*, *41*(5), 384–387. https://doi.org/10.17796/1053-4628-41.5.384
9. Rignell, L., Mikati, M., Wertsén, M., & Hägglin, C. (2017). Sedation with orally administered midazolam in elderly dental patients with major neurocognitive disorder. *Gerodontology*, *34*(3), 299–305. https://doi.org/10.1111/ger.12262
10. Shanmugaavel, A. K., Asokan, S., Baby, J. J., Priya, G., & Gnana Devi, J. (2016). Comparison of Behavior and Dental Anxiety During Intranasal and Sublingual Midazolam Sedation - A Randomized Controlled Trial. *The Journal of clinical pediatric dentistry*, *40*(1), 81–87. https://doi.org/10.17796/1053-4628-40.1.81
11. Wilson, K. E., Thorpe, R. J., McCabe, J. F., & Girdler, N. M. (2011). Complications associated with intravenous midazolam sedation in anxious dental patients. *Primary dental care: journal of the Faculty of General Dental Practitioners (UK)*, *18*(4), 161–166. https://doi.org/10.1308/135576111797512801
12. Papineni McIntosh, A., Ashley, P. F., & Lourenço-Matharu, L. (2015). Reported side effects of intravenous midazolam sedation when used in paediatric dentistry: a review. *International journal of paediatric dentistry*, *25*(3), 153–164. https://doi.org/10.1111/ipd.12127
13. Zaporowska-Stachowiak, I., Szymański, K., Oduah, M. T., Stachowiak-Szymczak, K., Łuczak, J., & Sopata, M. (2019). Midazolam: Safety of use in palliative care: A systematic critical review. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *114*, 108838. https://doi.org/10.1016/j.biopha.2019.108838
14. Ong, C. K., Seymour, R. A., & Tan, J. M. (2004). Sedation with midazolam leads to reduced pain after dental surgery. *Anesthesia and analgesia*, *98*(5). https://doi.org/10.1213/01.ane.0000111107.18755.cc
15. Ashley, P. F., Chaudhary, M., & Lourenço-Matharu, L. (2018). Sedation of children undergoing dental treatment. *The Cochrane database of systematic reviews*, *12*(12), CD003877. https://doi.org/10.1002/14651858.CD003877.pub5
16. Azevedo, I. D., Ferreira, M. A., da Costa, A. P., Bosco, V. L., & Moritz, R. D. (2013). Efficacy and safety of midazolam for sedation in pediatric dentistry: a controlled clinical trial. *Journal of dentistry for children (Chicago, Ill.)*, *80*(3), 133–138.
17. Xia, B., Liu, K. Y., Wang, C. L., Sun, L. J., & Ge, L. H. (2010). *Beijing da xue xue bao. Yi xue ban = Journal of Peking University. Health sciences*, *42*(1), 78–81.
18. Tyagi, P., Tyagi, S., & Jain, A. (2013). Sedative effects of oral midazolam, intravenous midazolam and oral diazepam in the dental treatment of children. *The Journal of clinical pediatric dentistry*, *37*(3), 301–305. https://doi.org/10.17796/jcpd.37.3.6u482603r0388558
19. Peerbhay, F., & Elsheikhomer, A. M. (2016). Intranasal Midazolam Sedation in a Pediatric Emergency Dental Clinic. *Anesthesia progress*, *63*(3), 122–130. https://doi.org/10.2344/15-00016.1
20. Capp, P. L., de Faria, M. E., Siqueira, S. R., Cillo, M. T., Prado, E. G., & de Siqueira, J. T. (2010). Special care dentistry: Midazolam conscious sedation for patients with neurological

diseases. *European journal of paediatric dentistry*, *11*(4), 162–164.
21. Wan, K., Jing, Q., & Zhao, J. Z. (2006). Evaluation of oral midazolam as conscious sedation for pediatric patients in oral restoration. *Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih*, *21*(3), 163–166.
22. Jing, Q., Wan, K., Ma, L., Chen, X., & Tong, Y. L. (2010). *Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology*, *45*(12), 770–772.
23. Ma, L., Jing, Q., & Wan, K. (2012). *Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi = West China journal of stomatology*, *30*(3), 271–274.
24. Greaves A. (2016). The use of Midazolam as an Intranasal Sedative in Dentistry. *SAAD digest*, *32*, 46–49.
25. Wood M. (2011). The safety and efficacy of using a concentrated intranasal midazolam formulation for paediatric dental sedation. *SAAD digest*, *27*, 16–23.
26. Lee-Kim, S. J., Fadavi, S., Punwani, I., & Koerber, A. (2004). Nasal versus oral midazolam sedation for pediatric dental patients. *Journal of dentistry for children (Chicago, Ill.)*, *71*(2), 126–130.
27. Charalambous, M., Bhatti, S., Van Ham, L., Platt, S., Jeffery, N. D., Tipold, A., Siedenburg, J., Volk, H. A., Hasegawa, D., Gallucci, A., Gandini, G., Musteata, M., Ives, E., & Vanhaesebrouck, A. E. (2017). Intranasal Midazolam versus Rectal Diazepam for the Management of Canine Status Epilepticus: A Multicenter Randomized Parallel-Group Clinical Trial. *Journal of veterinary internal medicine*, *31*(4), 1149–1158. https://doi.org/10.1111/jvim.14734
28. Fantacci, C., Fabrizio, G. C., Ferrara, P., Franceschi, F., & Chiaretti, A. (2018). Intranasal drug administration for procedural sedation in children admitted to pediatric Emergency Room. *European review for medical and pharmacological sciences*, *22*(1), 217–222. https://doi.org/10.26355/eurrev_201801_14120
29. Johnson, E., Briskie, D., Majewski, R., Edwards, S., & Reynolds, P. (2010). The physiologic and behavioral effects of oral and intranasal midazolam in pediatric dental patients. *Pediatric dentistry*, *32*(3), 229–238.
30. Gupta, S., Gadani, H., & Kedia, S. (2011). Is premedication with midazolam more effective by the sublingual than the oral route?. *Anesthesia, essays and researches*, *5*(1), 43–47. https://doi.org/10.4103/0259-1162.84186
31. Ashika Advankar, Rahul Maheshwari, Vishakha Tambe, Pooja Todke, Nidhi Raval, Devesh Kapoor, Rakesh K. Tekade. (2019). Chapter 13 - Specialized tablets: ancient history to modern developments, Editor(s): Rakesh K. Tekade, In Advances in Pharmaceutical Product Development and Research, Drug Delivery Systems, Academic Press, Pages 615-664, ISBN 9780128144879, https://doi.org/10.1016/B978-0-12-814487-9.00013-2.
32. Collado, V., Faulks, D., Nicolas, E., & Hennequin, M. (2013). Conscious sedation procedures using intravenous midazolam for dental care in patients with different cognitive profiles: a prospective study of effectiveness and safety. *PloS one*, *8*(8), e71240. https://doi.org/10.1371/journal.pone.0071240
33. Silay, E., Candirli, C., Taskesen, F., Coskuner, I., Ceyhanli, K. T., & Yildiz, H. (2013). Could conscious sedation with midazolam for dental procedures be an alternative to general anesthesia?. *Nigerian journal of clinical practice*, *16*(2), 211–215. https://doi.org/10.4103/1119-3077.110160
34. Shehabi, Z., Flood, C., & Matthew, L. (2018). Midazolam use for dental conscious sedation: how safe are we?. *British dental journal*, *224*(2), 98–104. https://doi.org/10.1038/sj.bdj.2017.1042
35. Dundee, J. W., Halliday, N. J., Harper, K. W., & Brogden, R. N. (1984). Midazolam. A review of its pharmacological properties and therapeutic use. *Drugs*, *28*(6), 519–543. https://doi.org/10.2165/00003495-198428060-00002
36. Ma, L., Zhang, J., Hou, X. Y., Jing, Q., & Wan, K. (2019). *Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae*, *41*(1), 106–110. https://doi.org/10.3881/j.issn.1000-503X.10391