Pesquisa Brasileira em Odontopediatria e Clínica Integrada 2023; 23:e210213
https://doi.org/10.1590/pboci.2023.014
ISSN 1519-0501 / eISSN 1983-4632

SYSTEMATIC REVIEW

Efficacy and Safety of Oral Midazolam Sedation Compared with its Combination with Hydroxyzine Use in Pediatric Dentistry: A Systematic Review

Gustavo Henrique Porto Oliveira[1], Diogo Gomes Brandão[1], Fernando José Camello de Lima[2], Patricia Batista Lopes do Nascimento[1], Priscylla Gonçalves Correia Leite de Marcelos[1], Daniela Maria Carvalho Pugliesi[1], Leopoldo Cosme-Silva, Valdeci Elias dos Santos Júnior[1]

[1]Department of Pediatric Dentistry, School of Dentistry, Federal University of Alagoas, Maceió, AL, Brazil.
[2]Department of Biological Science, Federal University of Alagoas, Maceió, AL, Brazil.

Correspondence: Valdeci Elias dos Santos Júnior, Department of Pediatric Dentistry, School of Dentistry, Federal University of Alagoas, Rua Lourival Melo Mota, S/N, Tabuleiro do Martins, Maceió, AL, Brazil. **E-mail:** valdeciodonto@gmail.com

Academic Editor: Catarina Ribeiro Barros de Alencar

Received: 23 November 2021 / **Review:** 19 April 2022 / **Accepted:** 25 April 2022

How to cite: Oliveira GHP, Brandão DG, Lima FJC, Nascimento PBL, Marcelos PGCL, Pugliesi DMC, et al. Efficacy and safety of oral midazolam sedation compared with its combination with hydroxyzine use in pediatric dentistry: a systematic review. Pesqui Bras Odontopediatria Clín Integr. 2023; 23:e210213. https://doi.org/10.1590/pboci.2023.014

ABSTRACT

Objective: To assess the efficacy and safety of the use of midazolam as monotherapy, compared to the associated use of midazolam and hydroxyzine for minimum and moderate sedation of children in dental offices, using data obtained from clinical trials. **Material and Methods:** A systematic review protocol was developed and registered on PROSPERO (CR42020208633). An electronic search was carried out in Pubmed, Lilacs, Science Direct, Open Gray, Web of Science, and central Cochrane Library. No language restrictions were included. Clinical trials were carried out with children aged 0-12 years, using midazolam as monotherapy compared to the use of midazolam associated with hydroxyzine to verify the effectiveness and safety of oral sedation. The quality of the studies was individually assessed and grouped using the RoB 2 (Revised Cochrane risk-of-bias tool for randomized trials) and GRADE (Grading of Recommendations Assessment, Development and Evaluation) systems, respectively. **Results:** A total of 749 studies were found. After analyzing the inclusion and removal of duplicates, two studies were analyzed for the quality of evidence. Through this analysis, it was possible to verify the very low level of scientific evidence on the superiority of the efficacy and safety of the combined use of midazolam and hydroxyzine for oral sedation in children in dental offices. **Conclusion:** The conflicting results and limitations of the studies enabled to establish that there is insufficient evidence to support the use of these drugs combined. There is only evidence for the use of midazolam as monotherapy.

Keywords: Benzodiazepines; Conscious Sedation; Hydroxyzine; Midazolam; Pediatric Dentistry.

Introduction

Dental treatment is often associated with unpleasant feelings for various individuals, namely leading to moments of stress and pain, being strictly potentialized by feelings of anxiety and fear, impairing clinical practices for both patients and professionals [1]. Regarding pediatric patients, who are not often cooperative during dental care, treatment becomes even more challenging [2]. Despite the great technological breakthrough in dental care, the clinical success of pediatric dentistry still requires great levels of cooperation from children, who, at times, present an immature cognitive or special needs behavior, inherent from either physical or mental health issues [3]. Studies reveal that 11% of normoreactive children have an acute fear of going to the dentist, which increases significantly in children with special needs [4]. In this regard, preoperative oral sedation is considered a safe and effective alternative for a more protective and comfortable dental treatment [5].

The choice of medication depends on individual risk analyses, as well as of the procedure and the singularities of every pediatric patient, which can either depend on local or systemic characteristics [6]. Midazolam is a benzodiazepine medication and is considered the first choice for the conscious sedation of children, although its use is recommended when anxiety levels and clinical times are moderate. In cases when the use of medication proves to be more challenging or when requiring longer intervention periods, midazolam can be used in combination with Other pharmacological agents, such as hydroxyzine, a first-generation antihistamine capable of potentializing sedation or providing greater relaxation and sleepiness [7].

The combined use of these medications is justified by their different mechanisms and acting sites on the central nervous system, which is corroborated by a synergistic effect, potentializing sedation [2,8]. However, there are still scientific gaps regarding the wide recommendation of the combined use of these medications, namely in terms of standard dosage, administration, side effects and their efficacy [9]. In this regard, the present systematic literature review is aimed at analyzing the efficacy and safety of the use of midazolam as monotherapy, compared to the associated use of midazolam and hydroxyzine for minimum and moderate sedation of children in dental offices.

Material and Methods

Literature Review

A systematic review protocol was developed and registered on PROSPERO (CR42020208633), which guided the search and analysis of data. In December 2020, the eligible studies were identified by an analysis of PubMed, Scopus, Lilacs, Open Grey, Science Direct, Web of Science and Central Cochrane databases. The search strategy was developed to answer the following PICO question: What is the effectiveness and safety of the associated use of midazolam and hydroxyzine for oral sedation in children when compared to midazolam as monotherapy?

Keywords (MeSH and/or words) and Boolean operators were used to ensure a wider search for the subsequent analysis of the inclusion criteria. The following words were appropriately combined and modified for each platform: "Child; Children; Pediatric Dentistry; Anxiety; Sedation; Morbidity; Complications; Adverse Effects; Behavior; Hydroxyzine; and Midazolam. The search was independently carried out by two calibrated researchers and any disagreements were resolved by consensus or through a third revisor. The detailed research strategy for each platform can be requested to the authors and/or consulted in Supplementary Table 1.

Inclusion Criteria

In order to be included in the study, papers should meet the following criteria: be in an article format; have a title and abstract similar to the objectives of the present work; have full text published; studies addressing the effectiveness in controlling anxiety in children aged between 0- 12 years old and/or the possible side effects of the use of midazolam as monotherapy and its association with hydroxyzine as oral sedation; studies involving children who underwent dental procedures; and work involving clinical trials. No language restrictions or specific time frames were imposed until December 2020.

All works which did not comply with these criteria were excluded, as illustrated in Figure 1, with the selected articles being read and assessed in full for final inclusion in the results section. Any disagreements regarding the inclusion of papers were resolved by consensus.

Data Extraction

With the full papers available, the following data were extracted: authors, year of publication, sample categorization, doses employed, results of the primary outcome (effectiveness), results of the secondary outcome (side effects), assessment scale and main conclusions.

Quality Assessment

The quality assessment of each individual manuscript was carried out through the Cochrane risk of bias tool (RoB 2), which assesses the risk of bias taking into account the following domains: domain 1- Risk of bias arising from the randomization process; domain 2 - Risk of bias due to deviations from the intended interventions (effect of assignment to intervention); domain 3 - Missing outcome data; domain 4 - Risk of bias when measuring the outcome; domain 5 - Risk of bias in the selection of the reported result. Following the analysis of these five domains, the overall risk of bias of each study was verified. The combined quality of the studies was evaluated through the GRADE criteria system to identify any limitations, inconsistencies, indirect evidence, inaccuracies and any other relevant considerations. Through this analysis, it is possible to classify the quality of evidence as high, moderate, low and very low.

Results

Research Data

A total of 749 potentially eligible articles were found in the databases selected (Figure 1). Following the analysis of titles and abstracts, 40 duplicated articles were identified, which were promptly excluded. Out of the 709 previously eligible articles, 592 did not meet the specific objective of the present systematic review, with the remaining 117 manuscripts being analyzed in full. Subsequently, 115 studies were discarded due to the following reasons: a) adult patient or patient with special needs: (n=11); and b) different sedative drug than that considered in the object of study: (n=104). Therefore, 2 studies were selected to be included in this systematic review. The references included in these 2 studies (n=39) were also analyzed, though no additional manuscript was integrated in the present study.

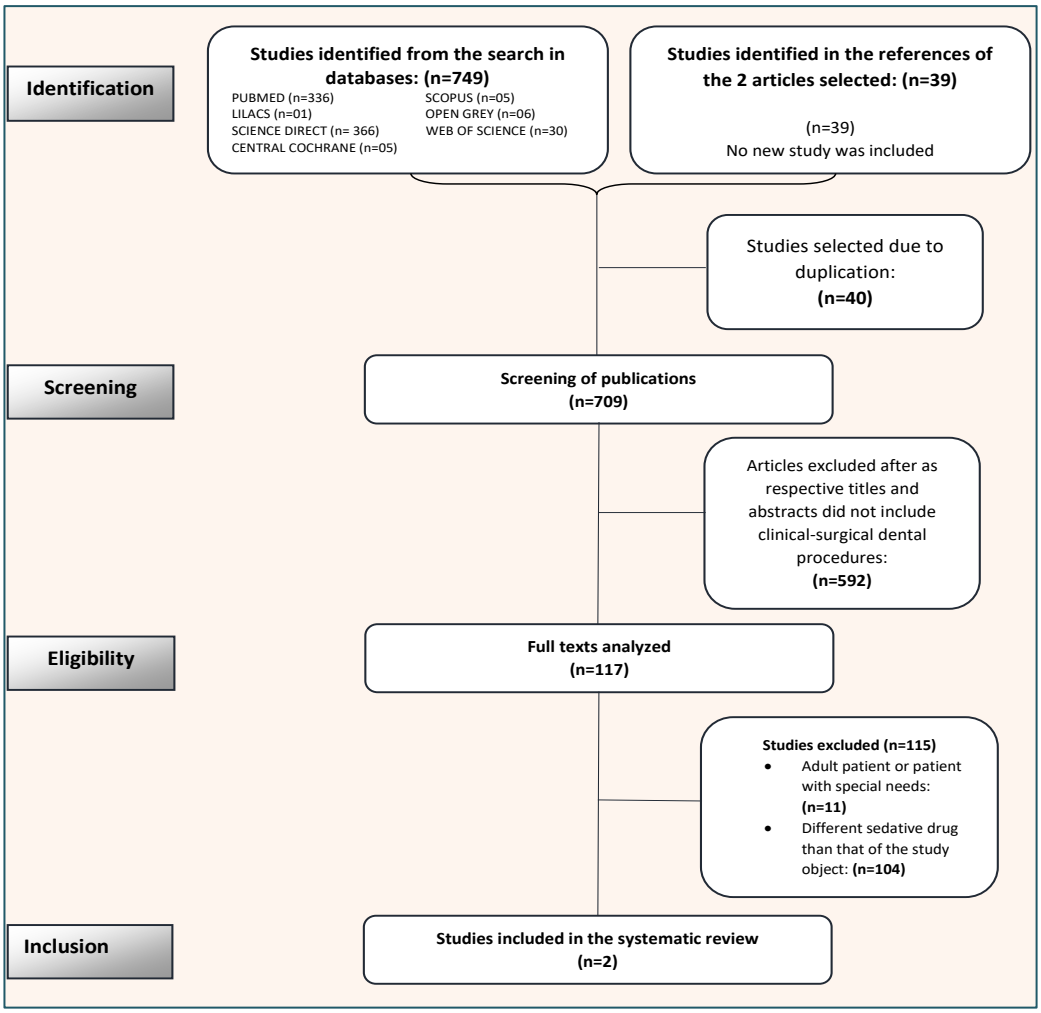

Figure 1. Flowchart showing the research steps and selection analysis adopted for the systematic review.

General Characteristics of the Clinical Trials Selected

Two articles were included in this systematic review, one of which was carried out in Brazil while the other was in Israel. Both studies were respectively published in 2003 and 2004. Combined, the studies analyzed 39 children aged between 21 and 56 months old. The doses of medication used also varied between the studies. The studies also used different scales to assess the effectiveness of sedation. The characteristics of both studies are described in Table 1.

Individual and Combined Quality Assessment of Evidence

Both studies were individually assessed, according to the 5 domains of the Revised Cochrane risk of bias tool for randomized trials (RoB 2). Table 2 presents a summary of these domains for each study, classified as high, with some concerns and low. The most critical biases found in both studies regard the selection bias related to randomization and random allocation. In the study by Lima et al. [10], randomization was carried out by the pediatrician, without considering any scientific randomization technique. The study carried out by Shapira et al. [11], only mentions the randomization employed, though the technique used cannot be determined. Both studies did not present any differences between any baseline groups as they were crossover clinical trials. Thus, following the analysis of the RoB 2 flowchart for domain 1, the first study was classified as of high risk of bias, while the second study was classified as being of low risk of bias.

Table 1. Individual characteristics of the studies selected for the risk of bias analysis.

Author	Year	Sample/Age	Type of Study	Groups	Results Primary Outcome	Results Secondary Outcome	Assessment Scale	Conclusion
Lima et al. [10]	2003	11 children	Controlled, crossover and double-blind clinical trial.	Group 1: Placebo (P)	The overall behavioral analysis showed that group M presented significantly better results than groups (P) and (MH). The success rates for each group only taking into account general scores for satisfactory behavioral management were 7.7% (P), 77.0% (M) and 30.8% (MH). Group M showed better and more statistically significant results when compared to group P (p=0.011) and MH (p=0.022).	No adverse reaction was observed and/or reported in the study during the sessions.	The behavioral assessment was based on the behavioral rating scale proposed by Houpt.	The MH group presented sleepiness at the beginning of the sessions. The overall behavior was better in (M) than in (P) and (MH). Group (M) was effective and safe, while the combination (MH) did not lead to significant advantages for pediatric dentistry sedation.
Shapira et al. [11]	2004	28 children (21 to 56 months old)	Controlled, crossover and double-blind clinical trial.	Group 1: Midazolam (M) [M = 0.5 mg/kg] Group 2: Midazolam (M) and Hydroxyzine (H) [M = 0.3 mg/kg, combined with H = 3.7 mg/kg].	Regarding the effectiveness of sedation in the overall behavioral analysis, both regimes presented a 75% success rate. Therefore, no statistically significant difference was observed amongst the groups (p=0.518)	No adverse reaction was observed and/or reported in the study during the sessions.	A modified version of the behavioral scale from Ohio State University was used, as well as the scale proposed by Houpt.	Both approaches are effective for sedation. However, the use of Midazolam as a sedative drug is recommended for short dental procedures, with its combined use with hydroxyzine being recommended for longer procedures.

Regarding the analysis of biases in domain 2 (performance bias), it was verified that, in both studies, no child was aware of the interventions applied. However, in the study carried out by Lima et al. [10], the parents were previously warned about the possibility of using placebos. Such studies were not assessed intention-to-treat, though there was no significant impact on the results for not doing so. Following the analysis of the RoB 2 flowchart for domain 2, the studies were classified as with some concerns.

Domain 3 addresses the lack or loss of data from the results. For both studies, such domain was classified as a low risk of bias, as all data from the results are available in the segments proposed. However, a high risk of bias was observed in domain 4 for the two studies due to the use of physical constraints when the dental treatment could not be carried out. In the study by Shapira et al. [11], in particular, nitrous oxide was also used in more difficult cases of behavioral management. The additional use of these forms of behavior control generated confusion biases in terms of the analysis of the results regarding the effectiveness and/or safety of the results.

Domain 5 analyzes the risk of bias related to the selectivity of the results reported. None of the studies specified whether the data was analyzed according to a pre-established protocol before the research. No registration of clinical trial is available in the manuscript nor in any registration platform often used in this type of study. Nonetheless, both studies assessed the results through assessment scales previously validated in the literature, with clear specifications of behavioral diagnosis. Thus, after the analysis of the RoB 2 flowchart, both studies presented a low risk of bias.

Table 2. Risk of bias assessment of the studies included in the present study taking into account the five domains of the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

Studies	Domains					
	1	2	3	4	5	Overall
Lima et al. [10]	-	?	+	-	+	-
Shapira et al. [11]	+	?	+	-	+	-

Key: (+)Low Risk of Bias; (?)Some Considerations; (-)High Risk of Bias.

The quality of evidence was also jointly analyzed using the GRADE system. Therefore, the existence of strong limitations and inconsistencies was verified, as presented in Table 3. Among the issues verified, the small sample size, issues regarding the choice of clinical design trial, inadequate randomization methods and biases regarding the outcome assessment throughout the trial stood out. Through this assessment, it was possible to identify that the quality of evidence available regarding the outcome analyzed is considered very low.

Table 3. Flowchart showing the research steps and selection analysis adopted for the systematic review.

Question: For oral sedation in children, is the combined use of midazolam and hydroxyzine more effective than midazolam as monotherapy? Quality analysis by GRADE. Context: Oral sedation effectiveness in children in dental setting.							
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Outcome: Oral Sedation Effectiveness							
2 (39 children)	Crossover Clinical Trial	Serious limitations[1]	Serious inconsistencies[2]	No serious indirectness	Serious imprecision[3]	None	Very Low

1. All clinical trials did not have adequate randomization and absence of analysis by intention to treat; 2. There are variabilities in the diagnostic criteria for the analysis of the outcome; the children's age was different; The doses were different in the studies analyzed; There are deviations from the intended interventions (effect of assignment to intervention - addition of a physical restraint method to assess drug sedation); 3. Both studies do not report the sample calculation and have a very small sample.

Results of Studies (Sedation)

The studies report distinct conclusions regarding the combined use of midazolam and hydroxyzine. For Lima et al. [10], this association was not considered more effective than midazolam as monotherapy. On the other hand, Shapira et al. [11] ratify that for a longer and deeper sedation, these 2 drugs should be used together. However, both papers agree that midazolam as monotherapy is effective for the sedation of children in dental offices. Regarding the secondary outcome (safety analysis), none of the studies reported any side effect for any of the regimes or drugs analyzed.

Discussion

The limitation regarding the heterogeneity and quality of evidence of clinical trials included in this systematic review highlights the need of a more cautious interpretation of individual data of each study [12]. Through the analysis of the evidence available, contradicting positions could be observed regarding the combined use of midazolam and hydroxyzine in children [13]. Despite being based on the reasoning that two drugs acting in different sites of the central nervous system would lead to a synergistic effect and a potential reduction in side effects [1], the quality of evidence does not enable to consider this effect as pragmatic. For Lima et al. [10], the additional use of hydroxyzine for sedation with midazolam does not lead to any improvements to the primary outcome (sedation) or the secondary outcome (side effects).

Conversely, Shapira et al. [11] recommend the combined use of these 2 drugs, especially When requiring deeper sedation. The heterogeneity of these results is a consequence of the methodology employed in the two studies. The choice of a crossover clinical leads to natural problems, arising from the possibility of generating memory bias. Although in different periods, patients allocated to both groups are biased from the previous experience, which may limit the analysis of the effectiveness of both drugs [14]. Thus, parallel-arm design and randomized studies need to be carried out more often, as they are more suitable for the assessment of the outcomes considered in the present study [15].

The heterogeneity observed in the results presented could also be explained by the characterization of the patient's age and by the different doses employed. However, none of the studies selected exhibited data on the eligibility of patients for sedation to be used prior to dental treatment. This would require a complete and complex analysis of the neuro-cardio-respiratory systems, as well as of the medical background and pre-existing illnesses. The thorough assessment of these parameters determines good practices of sedation and cannot be neglected [16,17].

The small sample size reduces the trustworthiness of the results and, thus, the quality and recommendation of evidence presented [15]. In total, only 39 children took part in the studies, with 11 being part of the study by Lima et al. [10], and 28 children in the study carried out by Shapira et al. [11]. In addition, only children in their early childhood were included in both studies, with a cognitive system not yet entirely developed, which led to confusion regarding the effectiveness of the drugs for behavioral management. Managing children in this age group in dental offices is often difficult, thus, extrapolating the data of both studies to other age groups has to be prudently considered [18]. In this regard, the literature still lacks studies that compare the effectiveness of midazolam combined or not with hydroxyzine in different childhood age groups and dental offices.

Regarding the dosage of drugs, Lima et al. [10] applied 1.0 mg/kg of midazolam in sample group (M) and 0.75 mg/kg of midazolam combined with 2.0 mg/kg of hydroxyzine in group (MH). On the other hand, Shapira et al. [11] used 0.5 mg/kg of midazolam in group (M) and 0.3 mg/kg of midazolam combined with 3.7 mg/kg of hydroxyzine in group (MH). The lack of a standard dose amongst both studies selected and not adopting a single scale to assess the outcomes have contributed to the heterogenous effectiveness observed [19]. The difficulty in finding a homogeneous group of studies in terms of the outcomes of sedation, combined with the low quality of evidence of both studies selected (study limitations, inaccuracy and risk of bias), prevented carrying out a metanalysis for the direct comparison of the effectiveness of midazolam as monotherapy and of midazolam combined with hydroxyzine. Moreover, in both studies selected, the use of physical intervention in more difficult cases of behavioral management led to distinct treatments and results. It was also worth noting

that the behavior rating scales used are not presented by the authors to assess a successful behavioral management in the conditions of restricted movement as a result of physical intervention [20].

Although such procedure is effective and commonly used in pediatric dental practice [4,13,14], its application in these studies led to important limitations regarding the recommendation of the evidence presented. Although midazolam is safely and effectively used, the literature often associates this drug with possible cardio-respiratory complications, anterograde amnesia and a paradoxical effect [21-23]. Midazolam has already been widely compared to other sedative drugs such as ketamine, diazepam and dexmedetomidine [19,24,25], with most studies regarding midazolam as the first-choice drug due to its high effectiveness and safety as an oral sedative in children [26-28]. In an attempt to settle any possible unwanted side effects, some polypharmacy protocols have been tested, aimed at a global reduction of the individual dose of drugs used [29,30]. However, the different doses applied for this combination of drugs are only based on the individual decision-making and experience of health professionals (off-label use). Therefore, despite being a common clinical practice, it is not based on medical evidence.

No side effect was reported in the studies included in the present revision. Despite being consistent with the low incidence of cases, when using the recommended dose, the limitations and imprecisions of these studies may have impacted the analysis of the secondary outcomes. The incidence of adverse events, such as paradoxical reactions and respiratory events, besides the risk of hypersedation, increases with the use of higher doses. A systematic review points out that the safe dose of midazolam ranges between 0.25 and 1.5 mg/kg [31]. In turn, the safe dose of hydroxyzine varies from 0.6 to 1.5 mg/kg [32]. However, the safe dose for the combined use of midazolam and hydroxyzine has not yet been established due to the lack of more homogeneous studies. Therefore, randomized and properly designed clinical trials still need to be carried out in order to better understand the safety of this combined use of sedative drugs, as well as their effectiveness [33].

Conclusion

The present study shows the conflicting results, limitations and inconsistencies of the studies selected, resulting in limited evidence to support the combined use of midazolam and hydroxyzine as oral sedation in children who underwent dental treatment. There is still the need to carry out further studies to establish the appropriate dosage and possible side effects resulting from this combination. In this regard, there is only evidence for the use of midazolam as monotherapy.

Authors' Contributions

GHPO	https://orcid.org/0000-0002-7796-5359	Investigation, Writing - Original Draft.
DGB	https://orcid.org/0000-0001-6167-0399	Investigation, Writing - Original Draft.
FJCL	https://orcid.org/0000-0003-1593-7747	Conceptualization, Methodology, Writing - Original Draft, Writing - Review and Editing, Project Administration.
PBLN	https://orcid.org/0000-0002-2355-4810	Investigation, Writing - Original Draft.
PGLM	https://orcid.org/0000-0002-5623-6835	Investigation, Writing - Original Draft.
DMCP	https://orcid.org/0000-0002-7854-0416	Investigation, Writing - Original Draft.
LCS	https://orcid.org/0000-0002-5755-1933	Methodology, Writing - Original Draft.
VESJ	https://orcid.org/0000-0001-9748-5830	Conceptualization, Methodology, Writing - Original Draft, Writing - Review and Editing.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

Financial Support

The authors wish to thank the Department of Foundation to Support Research in the State of Alagoas (FAPEAL).

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

References

[1] Van Tuijl SG, Van Cauteren YJ, Pikhard T, Engel M, Schieveld JN. Management of pediatric delirium in critical illness: a practical update. Minerva Anestesiol 2015; 81(3):333-41.

[2] Dahlander A, Soares F, Grindefjord M, Dahllöf G. Factors associated with dental fear and anxiety in children aged 7 to 9 years. Dent J 2019; 7(3):68. https://doi.org/10.3390/dj7030068

[3] Monte IC, Dalcico R, Dias AA, Meneses NE de, Almeida IJ de, Tinôco MGDRR, et al. Use of methods to control dental fear and anxiety by dental surgeons in the city of Fortaleza. Braz J Develop 2020; 6(8):56894-916. https://doi.org/10.34117/bjdv6n8-194 [In Portuguese].

[4] Tsoi AK, Wilson S, Thikkurissy S. A study of the relationship of parenting styles, child temperament, and operatory behavior in healthy children. J Clin Pediatr Dent 2018; 42(4):273-8. https://doi.org/10.17796/1053-4628-42.4.6

[5] Carter AE, Carter G, Boschen M, AlShwaimi E, George R. Pathways of fear and anxiety in dentistry: a review. World J Clin Cases 2014; 2(11):642-53. https://doi.org/10.12998/wjcc.v2.i11.642

[6] Johnson C, Weber-Gasparoni K, Slayton RL, Qian F. Conscious sedation attitudes and perceptions: a survey of american academy of pediatric dentistry members. Pediatr Dent 2012; 34(2):132-7.

[7] Barends CR, Absalom A, van Minnen B, Vissink A, Visser A. Dexmedetomidine versus midazolam in procedural sedation. a systematic review of efficacy and safety. PLoS One 2017; 12(1):e0169525. https://doi.org/10.1371/journal.pone.0169525

[8] Frazão VT, Filippi ACZ. Midazolam: pharmacological aspects and their use at different sedation levels. Rev Saúde 2020; 11(1):36-41. http://doi.org/10.21727/rs.v11i1.2065

[9] Attri JP, Sharan R, Makkar V, Gupta KK, Khetarpal R, Kataria AP. Conscious sedation: emerging trends in pediatric dentistry. Anesth Essays Res 2017; 11(2):277-81. https://doi.org/10.4103/0259-1162.171458

[10] Lima AR, da Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. Pesqui Odontol Bras 2003; 17(3):206-11. https://doi.org/10.1590/s1517-74912003000300002

[11] Shapira J, Kupietzky A, Kadari A, Fuks AB, Holan G. Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. Pediatr Dent 2004; 26(6):492-6.

[12] Barbosa FT, Lira AB, Neto OB de O, Santos LL, Santos IO, Barbosa LT, et al. Tutorial for performing systematic review and meta-analysis with interventional anesthesia studies. Braz J Anesthesiol 2019; 69(3):299-306. https://doi.org/10.1016/j.bjan.2018.11.007

[13] Conway A, Chang K, Mafeld S, Sutherland J. Midazolam for sedation before procedures in adults and children: a systematic review update. Syst Rev 2021; 10(1):69. https://doi.org/10.1186/s13643-021-01617-5

[14] Gomes HS, Daher A, Costa PS, Batista AC, Costa LR. Crossover studies of pediatric dental sedation are inappropriate. Braz Dent J 2019; 30(4):404-9. https://doi.org/10.1590/0103-6440201902852

[15] Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012; 308(24):2594-2604. https://doi.org/10.1001/jama.2012.87802

[16] Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures: Update. Pediatrics 2016; 138(1):e20161212. https://doi.org/10.1542/peds.2016-1212

[17] Galeotti A, Garret Bernardin A, D'Antò V, Ferrazzano GF, Gentile T, Viarani V, et al. Inhalation conscious sedation with nitrous oxide and oxygen as alternative to general anesthesia in precooperative, fearful, and disabled pediatric dental patients: a large survey on 688 working sessions. Biomed Res Int 2016; 2016:7289310. https://doi.org/10.1155/2016/7289310

[18] Jain SA, Rathi N, Thosar N, Baliga S. Retraction: Midazolam use in pediatric dentistry: a review. J Dent Anesth Pain Med 2020; 20(2):105. https://doi.org/10.17245/jdapm.2020.20.2.105

[19] Oh S, Kingsley K. Efficacy of ketamine in pediatric sedation dentistry: a systematic review. Compend Contin Educ Dent 2018; 39(5):e1-e4.

[20] Mohamed Kawia H, Shariff Mbawalla H, Kokulengya Kahabuka F. Application of behavior management techniques for paediatric dental patients by Tanzanian dental practitioners. Open Dent J 2016; 9(1):455-61. https://doi.org/10.2174/1874210601509010455

[21] Jeon S, Lee HJ, Do W, Kim HK, Kwon JY, Hwang BY, et al. Randomized controlled trial assessing the effectiveness of midazolam premedication as an anxiolytic, analgesic, sedative, and hemodynamic stabilizer. Medicine 2018; 97(35):e12187. https://doi.org/10.1097/MD.0000000000012187

[22] Sriramka B, Mallik D, Singh J, Khetan M. Effect of hand-holding and conversation alone or with midazolam premedication on preoperative anxiety in adult patients – a randomised controlled trial. Indian J Anaesth 2021; 65(2):128-32. https://doi.org/10.4103/ija.IJA_705_20

[23] van Groen BD, Krekels EHJ, Mooij MG, van Duijn E, Vaes WHJ, Windhorst AD, et al. The oral bioavailability and metabolism of midazolam in stable critically ill children: a pharmacokinetic microtracing study. Clin Pharmacol Ther 2021; 109(1):140-9. https://doi.org/10.1002/cpt.1890

[24] Du Z, Zhang XY, Qu SQ, Song ZB, Wei SW, Xiang Z, et al. The comparison of dexmedetomidine and midazolam premedication on postoperative anxiety in children for hernia repair surgery: a randomized controlled trial. Paediatr Anaesth 2019; 29(8):843-9. https://doi.org/10.1111/pan.13667

[25] de Moares MB, Barbier WS, Raldi FV, Nascimento RD, dos Santos LM, Loureiro Sato FR. Comparison of three anxiety management protocols for extraction of third molars with the use of midazolam, diazepam, and nitrous oxide: a randomized clinical trial. J Oral Maxillofac Surg 2019; 77(11):2258.e1-2258.e8. https://doi.org/10.1016/j.joms.2019.06.001

[26] Rai K, Hegde AM, Goel K. Sedation in uncooperative children undergoing dental procedures: a comparative evaluation of midazolam, propofol and ketamine. J Clin Pediatr Dent 2007; 32(1):1-4. https://doi.org/10.17796/jcpd.32.1.v74872j8n74qu81k

[27] Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. J Indian Soc Pedod Prev Dent 2008; 26(3):97-101.

[28] Fan TWV, Ti LK, Islam I. Comparison of dexmedetomidine and midazolam for conscious sedation in dental surgery monitored by bispectral index. Br J Oral MaxillofacSurg 2013; 51(5):428-33. https://doi.org/10.1016/j.bjoms.2012.08.013

[29] Tsze DS, Ieni M, Fenster DB, Babineau J, Kriger J, Levin B, et al. Optimal volume of administration of intranasal midazolam in children: a randomized clinical trial. Ann Emerg Med 2017; 69(5):600-9. https://doi.org/10.1016/j.annemergmed.2016.08.450

[30] Cho EA, Cha YB, Shim JG, Ahn JH, Lee SH, Ryu KH. Comparison of single minimum dose administration of dexmedetomidine and midazolam for prevention of emergence delirium in children: a randomized controlled trial. J Anesth 2020; 34(1):59-65. https://doi.org/10.1007/s00540-019-02705-6

[31] Manso MA, Guittet C, Vandenhende F, Granier LA. Efficacy of oral midazolam for minimal and moderate sedation in pediatric patients: A systematic review. Paediatr Anaesth 2019; 29(11):1094-1106. https://doi.org/10.1111/pan.13747

[32] Wilson S, Alcaino EA. Survey on sedation in paediatric dentistry: A global perspective. Int J Paediatr Dent 2011; 21(5):321-32. https://doi.org/10.1111/j.1365-263X.2011.01127.x

[33] Torres-Pérez J, Tapia-García I, Rosales-Berber MÁ, Hernández-Sierra JF, Pozos-Guillén ADJ. Comparison of three conscious sedation regimens for pediatric dental patients. J Clin Pediatr Dent 2007; 31(3):183-6. https://doi.org/10.17796/jcpd.31.3.e82526q0432375n0