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SYSTEMATIC REVIEW

Pharmacological Management of Anxiety on Pain Occurrence During Root Canal Treatment: A Systematic Review

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ABSTRACT

Objective: To answer the question: "Does the pharmacological management of dental anxiety influence pain occurrence during root canal treatment?"

Methods: Searches on MEDLINE/PubMed, Cochrane Library, Web of Science, Scopus, EMBASE and Open Grey were conducted until September 02, 2022. Only randomised clinical trials were included. The Cochrane risk of bias tool for randomized trials (RoB 2) was used. The overall quality of evidence was assessed through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Results: Initial screening resulted in 811 studies. Three hundred seventy-three were excluded for being duplicates. Of 438 eligible papers, ten studies met the inclusion criteria and were selected for full-text reading. Four studies were included in the final analysis. Three studies had a low risk of bias, and one was a high risk. GRADE demonstrated a low quality of evidence.

Conclusion: There is insufficient evidence to determine whether the pharmacological control of anxiety can influence intraoperative pain occurrence.

Keywords: Benzodiazepines, dental anxiety, endodontic, intraoperative pain, systematic review

HIGHLIGHTS

- The administration of benzodiazepines did not reduce intraoperative pain perception or improve the anaesthetic efficacy in endodontic treatments.
- Conscious sedation with nitrous oxide gas significantly reduces pain perception during endodontic treatment.
- Three out of four studies included were classified as low risk of bias.
- GRADE analysis showed a low quality of evidence mainly because of the serious risk of bias.

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INTRODUCTION

Pain perception is related to cognitive and emotional factors, such as previous experiences, the patient's understanding of the procedures to be performed, and the perception of sounds and movements during the procedures (1). Endodontic treatment is one of the procedures where the relationship between anxiety and pain is commonly found (2, 3). The patient often fears the need to perform these procedures because of their negative connotation in social awareness and the anticipation of a possible painful experience, increasing the patient's dental anxiety (3).

According to the American Association of Anesthesiologists, conscious sedation is a reduction of consciousness through pharmacological interventions in which the patient still demonstrates the ability to respond to verbal commands or mild tactile stimuli (4).

In dental practice, conscious sedation is an option to manage the patient's dental anxiety and

pain experience (5). For this, benzodiazepines can promote conscious sedation (5). Benzodiazepines are often administered orally, and their main limitation is related to the inability to manage the dose according to the patient's response. Its relatively unpredictable effects are some limitations of these drugs (6).

Conscious sedation in the dental office can also be achieved using nitrous oxide gas. Nitrous oxide gas provides a rapid onset of action, and its dosage is obtained with the gradual increase of the drug concentration (7). Its clinical use is considered relatively safe, and in addition to the sedative and hypnotic properties, it also promotes a mild analgesic effect (7). Its adverse effects generally include gastrointestinal, nervous, and psychiatric disorders (7). The professional qualification to operate the nitrous oxide gas device and conduct the procedure is a limitation of the technique. Additionally, specific equipment is necessary to induce conscious sedation.

Anxious patients are reported to be twice as likely to experience intraoperative pain (2). For this reason, it is essential to understand how to manage dental anxiety. Besides, the control of dental anxiety can improve the management of the patient, the conduction and acceptance of the procedures, and facilitate the completion of the treatment (5).

Once the control of dental anxiety can present benefits during endodontic procedures, it is necessary to verify the available information regarding the effectiveness of pharmacological interventions for dental anxiety through the induction of conscious sedation and intraoperative pain. So far, no systematic review has been performed to evaluate such information. Therefore, this systematic review aims to answer the question: "Does the pharmacological management of dental anxiety influence pain occurrence during root canal treatment?".

MATERIALS AND METHODS

This systematic review followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations (http://www.prisma-statement.org) and was registered on the PROSPERO database under the number CRD42021226740.

Search Strategy

The search was performed independently by two examiners (I.A.S. and C.J.D.A.) in the following electronic databases: MEDLINE/PubMed, Cochrane Library, Web of Science, Scopus, EMBASE, and Open Grey. The search was conducted for articles published until September 22, 2022, without language or year restriction. The electronic search strategy was developed using the most cited descriptors in previous publications on this theme combining Medical Subject Heading (MeSH) terms and text words. For each database, the following terms were combined: 'Root canal', 'Root canal therapy', 'Root canal treatment', 'Endodont*', 'Dental anxiety', 'Anxiety', 'Pain', 'Intraoperative pain', 'Pain control', 'Analgesia', 'Anesthetic', 'Anesthesia'. Then, the Boolean operators' AND' and 'OR' were applied to combine the terms and create a search strategy.

The search strategies for each database and the following findings are summarised in Table 1.

Additional screening on the selected studies' references was performed, and the related articles were searched in the PubMed database. Finally, all articles selected were imported into the Mendeley© (Mendeley Ltd, London, United Kingdom) reference manager to catalogue the references and facilitate the exclusion of duplicates.

Eligibility Criteria

The eligibility criteria were based on the PICOS strategy (8).

- Population (P): adult patients undergoing root canal treatment;
- Intervention (I): pharmacological control of dental anxiety;
- Comparison (C): a control group and placebo;
- Outcome (O): Primary: intraoperative pain;

Secondary: anaesthetic efficacy and dental anxiety levels;

- Study design (S): Only randomised clinical trials (RCTs).

Selection of the Studies

The first stage consisted of excluding the duplicated studies, considering only once, and examining the selected studies' retrieved titles and abstracts by two independent authors (I.A.S. e C.J.D.A.). The second stage consisted of reading the potentially eligible studies' full texts based on the PICOS strategy's eligibility criteria. A consensus with a third author (T.W.) solved disagreements on study inclusion. Finally, when it was impossible to judge the studies by title and abstract, the full text was accessed and read for the final decision.

Data Extraction

Two authors (I.A.S. and C.J.D.A.) independently collected the data from the included studies. Disagreements were solved by a third author (T.W.). The following data were extracted from the included studies: name of the author (s), year of publication, number of participants per group, dental anxiety scale, preoperative dental anxiety scores, pain scale, preoperative pain scores, anaesthetic technique, endodontic diagnosis, endodontic intervention, pharmacological intervention, control group, drug administration protocol, moments of evaluation and main findings. In cases of missing data, the authors were contacted three times by e-mail.

Quality Assessment and Strength of Evidence

The methodological risk assessment of bias for each study was performed by two independent authors (I.A.S. and C.J.D.A.). In case of disagreement, it was resolved by a third author (T.W.).

The studies' qualitative analysis was performed from the risk of bias assessment using the Cochrane risk of bias tool for randomised clinical trials (RoB 2): 'Bias Risk Assessment of Randomized Controlled Studies' – Cochrane Handbook 6.0 (9).

Each included study was judged as having a 'high' risk of bias for negative domain response (red), a 'low' risk of bias for positive domain response (green), and a 'some concerns' risk of bias (yellow) when the response was not clear. When the study was judged as having 'some concerns', the authors

TABLE 1. Search strategy in each database

Database	Search strategy	Findings
MEDLINE/PubMed	#1: (((root canal) OR (root canal therapy)) OR (root canal treatment)) OR (endodont*)	62.778
	#2: (dental anxiety) OR (anxiety)	298.174
	#3: (((((pain) OR (intraoperative pain)) OR (pain control)) OR (analgesia)) OR (anesthetic)) OR (anesthesia)	1.643.707
	#1 AND #2 AND #3	176
Cochrane library	#1: root canal OR root canal therapy OR root canal treatment OR endodont*	5.348
	#2: dental anxiety OR anxiety	65.636
	#3: pain OR intraoperative pain OR pain control OR analgesia OR anesthetic OR anesthesia	280.426
	#1 AND #2 AND #3	129
Scopus	#1: (TITLE-ABS-KEY (root AND canal) OR TITLE-ABS-KEY (root AND canal AND therapy) OR TITLE-ABS-KEY (root AND canal AND treatment) OR TITLE-ABS-KEY (endodont*))	64.480
	#2: (TITLE-ABS-KEY (dental AND anxiety) OR TITLE-ABS-KEY (anxiety))	478.475
	#3: (TITLE-ABS-KEY (pain) OR TITLE-ABS-KEY (intraoperative AND pain) OR TITLE-ABS-KEY (pain AND control) OR TITLE-ABS-KEY (analgesia) OR TITLE-ABS-KEY (anesthetic) OR TITLE-ABS-KEY (anesthesia))	1.800.243
	#1 AND #2 AND #3	176
Web of Science	#1: TS=(root canal OR root canal therapy OR root canal treatment OR endodont*)	30.492
	#2: TS=(dental anxiety OR anxiety)	352.836
	#3: TS=(pain OR intraoperative pain OR pain control OR analgesia OR anesthetic OR anesthesia)	962.210
	#1 AND #2 AND #3	81
EMBASE	#1: root AND canal OR (root AND canal AND therapy) OR (root AND canal AND treatment) OR endodont*	75.289
	#2: dental AND anxiety OR anxiety	468.884
	#3: pain OR (intraoperative AND pain) OR (pain AND control) OR analgesia OR anesthetic OR anesthesia	2.079.567
	#1 AND #2 AND #3	249
Grey literature report	#1: (root canal OR root canal therapy OR root canal treatment OR endodont*)	0
	#2: (dental anxiety OR anxiety)	1
	#3: (pain OR intraoperative pain OR pain control OR analgesia OR anesthetic OR anesthesia)	0
	#1 AND #2 AND #3	0

were contacted by e-mail at least three times for more information and allowed to be classified as 'low' (green) or 'high' (red) risk of bias. Once this information was not acquired, the articles presented 'some concerns' bias risks. The overall risk of bias was determined by combining the bias levels in each domain. Overall quality was based on the scores in individual domains. When it was verified that there was a low risk of bias for all domains, the overall quality was of low risk of bias. When at least one domain was of some risk, the overall quality was of some risk of bias. The high risk of bias was also scored when at least one domain was assessed as high or three or more domains were classified as some concerns. Each domain was recorded as low, moderate, serious, critical, or no information available for risk of bias.

The strength of the evidence of the included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.) (10). The GRADE tool has five domains that can be downgraded and reduce the evidence quality (11).

RESULTS

Study Selection

Figure 1 presents the flow diagram of the search strategy. Initial screening of databases resulted in 811 studies. Of these articles, 373 were excluded as they were duplicates. From analysing the titles and abstracts of the 438 eligible papers, ten studies (2, 3, 6, 12–18) met the inclusion criteria and were selected for full-text reading.

One study (2) was excluded for being a prevalence study, one study (6) was excluded for not having assessed intraoperative pain levels, and five studies were excluded for not having evaluated pharmacological interventions (3, 12, 14, 15, 18). An additional search on the reference list of the retrieved studies was performed, and one additional study was obtained (19). Therefore, four studies met the inclusion criteria and were selected for analysis (13, 16, 17, 19).

Data Extraction

Table 2 presents the characteristics and main findings of the included studies. Authors of studies presenting missing information were contacted three times by e-mail. However, no additional information was obtained.

Regarding the assessment of dental anxiety level, three studies used Corah Dental Anxiety Scale (CDAS) (16, 17, 19), and one study used the Modified Dental Anxiety Scale (MDAS) (13).

Concerning preoperative dental anxiety levels, two studies found CDAS scores of 11±4 (mean±SD) in both groups (16, 17), one study found CDAS values of 11.1±4.6 in the intervention group and 9.4±4.4 in the placebo group (19). One study

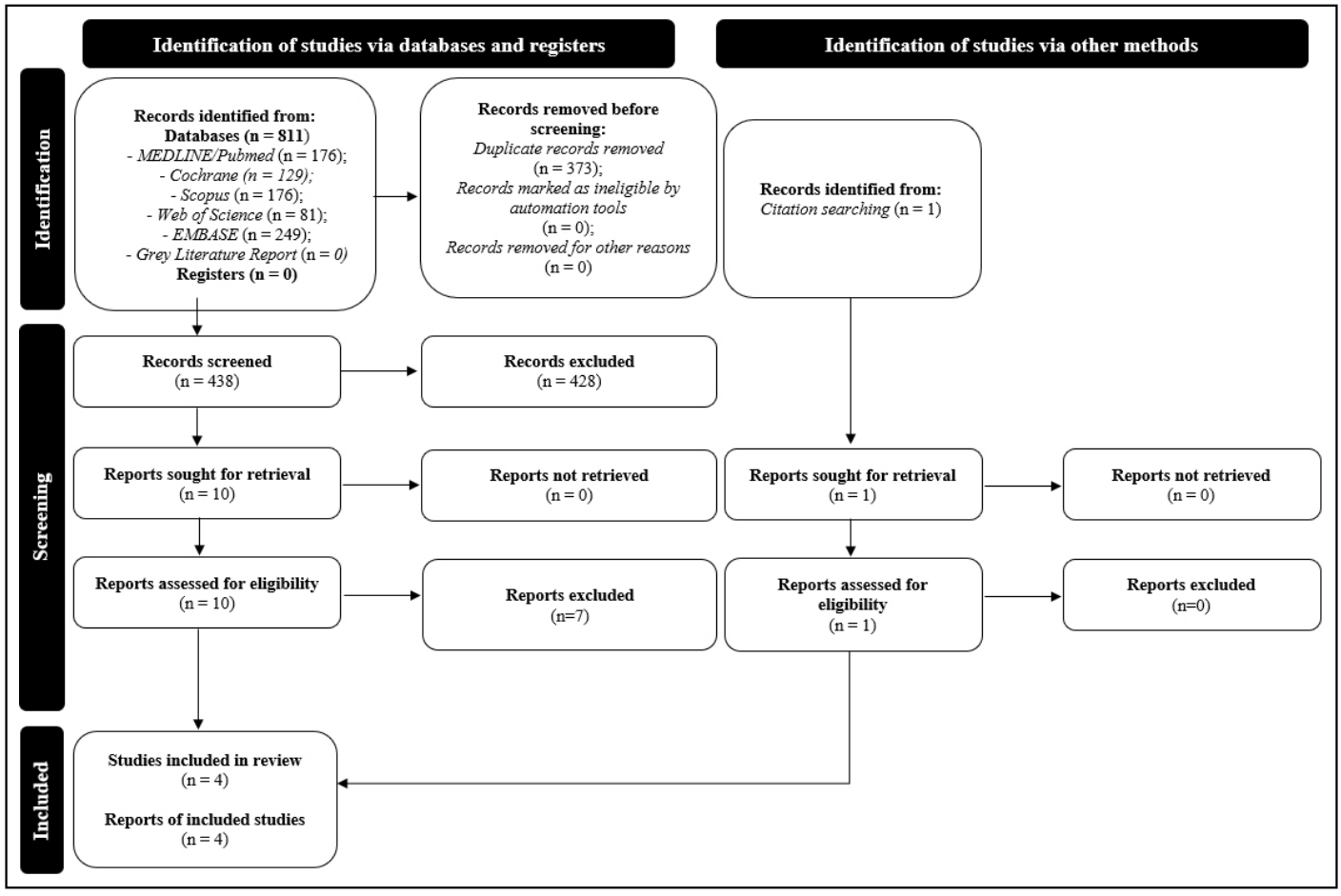

Figure 1. PRISMA flow diagram representing the systematic review process

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

found MDAS scores of 20.27 in the control group and 20.67 in the intervention group (13). Regarding the assessment of pain levels, all studies used Heft-Parker Visual Analogue Scale (HF-VAS) (13, 16, 17, 19).

As for the preoperative pain scores, one study found HF-VAS scores of 125±21.1 (mean±SD) in the intervention group and 124±23.3 in the placebo group (19), one study found HF-VAS values of 109 ± 50 in the intervention group and 106±4 to the placebo group (16), and one study found HF-VAS values of 128±25 to the intervention group and 130±23 to the placebo group (17). One study did not report the preoperative pain values (13).

Regarding the pharmacological control strategies used, one study managed 0.5 mg alprazolam or a placebo 45 min before the normal inferior alveolar nerve block (IANB) using a 27-gauge, 1.5-inch needle attached to a standard aspirating syringe with 1.8 mL of 2% lidocaine with 1:100,000 epinephrine (Lignospan; Septodont, Saint Maur des Fosses, France) (19). In another study, 0.25 mg triazolam or a placebo 30 min before local anaesthesia with a standard IANB using a 27-gauge, 11⁄4 inch needle (Monoject; Sherwood Services, Mansfield, MA) attached to a standard aspirating syringe, with 3.6 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; Astra Zeneca LP, Dentsply, York, PA) (16). In one study that used nitrous oxide, 5 min before the administration of local anaesthesia with a standard IANB using a standard aspirating syringe and a 27G needle, with 3.6 mL of 2% lidocaine with 1:100,000 epinephrine (xylocaine; Astra Zeneca LP, York, PA, USA), the intervention group received 6 L/min of 100% oxygen for 5 min; and 5 min of nitrous oxide (30–50%)/oxygen until sedation; the control group received only local anaesthesia (13). Another study that used nitrous oxide, 10 min before the administration of local anaesthesia with a standard IANB by using a standard aspirating syringe and a 27-gauge 11⁄4-inch needle and with 3.6 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; Astra Zeneca LP, York, PA), the intervention group received, during 5 min, 6 L/min of 100% oxygen and 5 min of nitrous oxide (30–50%)/oxygen until sedation, and the placebo group received 6 L/min of 100% room air/oxygen. Both groups maintained their protocols during the entire treatment (17).

About the moments of evaluation of dental anxiety and pain, three studies evaluated dental anxiety and pain levels in baseline and if the patient felt pain during the endodontic procedure (16, 17, 19). One study evaluated preoperative and postoperative dental anxiety levels and pain during local anaesthesia administration and access opening (13).

As for the main findings, from those that evaluated the effects of nitrous oxide, one study reported a reduction in the

TABLE 2. Data extracted from the included studies

Author(s) (year of publication)	Number of participants (per group)	Dental anxiety scale and preoperative scores	Pain scale and preoperative scores	Endodontic diagnosis and intervention	Pharmacological intervention	Control group	Drug administration protocol	Moments of evaluation	Main findings
Lindemann M. et al (2008) (16)	n=58 (Triazolam group: 30; Placebo group: 28)	Scale: CDAS; Scores: Triazolam group: 11±4; Placebo group (PG): 11±4	Scale: HF-VAS; Scores: Triazolam group: 109±50 mm; PG: 106±4 mm	Diagnosis: Mandibular posterior tooth (molar or premolar) with irreversible pulpitis; Intervention: RCT	0.25 mg triazolam and local anaesthesia	Placebo and local anaesthesia	0.25 mg triazolam or placebo, 30 min before IANB	Anxiety: Baseline (previous to drug administration) Pain: Baseline and if the patient felt pain during the endodontic procedure	0.25 mg triazolam did not increase the success rate of IANB; Conscious sedation did not eliminate pain sensation during endodontic treatment
Khademi AA. et al (2012) (19)	n=60 (Alprazolam group: 30; Placebo group: 30)	Scale: CDAS; Scores: Alprazolam group: 11.1±4.6; PG: 9.4±4.4	Scale: HF-VAS; Scores: Alprazolam group: 125±21.1 mm; PG: 124±23.3 mm	Diagnosis: Mandibular molar with irreversible pulpitis; Intervention: RCT	0.5 mg alprazolam and local anaesthesia	Placebo and local anaesthesia	0.5 mg alprazolam capsule or a placebo 45 min before IANB	Anxiety: Baseline Pain: Baseline and if the patient felt pain during the endodontic procedure	0.5 mg alprazolam did not improve the success rate of IANB; Conscious sedation was not effective in eliminating the occurrence of intraoperative pain
Stanley W. et al. (2012) (17)	n=100 (Nitrous oxide/ oxygen-intervention group: 50; Room air/ oxygen-placebo-group: 50) Diagnosis:	Scale: CDAS; Scores: NO: 11±4; PG: 11±4	Scale: HF-VAS; Scores: Intervention group: 128±25 mm; PG: 130±23 mm	Mandibular molar with irreversible pulpitis; Intervention: RCT	Local anaesthesia and nitrous oxide/oxygen	Local anaesthesia and room air/oxygen (placebo)	Nitrous oxide group: 10 min before local anaesthesia; 6 L/min-5 min of oxygen and 5 min of nitrous oxide/ oxygen until the sedation Placebo group: 10 min before local anaesthesia; 6 L/min-room air/ oxygen;	Anxiety: Baseline Pain: Baseline and if the patient felt pain during the endodontic procedure	Administration of 30%/50% nitrous oxide/ oxygen increased the success rate of the IANB, reducing the occurrence of intraoperative pain
Gupta P. et al. (2019) (13)	n=60 (Control group: 30; Nitrous oxide group: 30)	Scale: MDAS; Scores: NO: 20.27; Intervention group: 20.67	Scale: HF-VAS; Scores: NR	Diagnosis: Mandibular molar with irreversible pulpitis; Intervention: RCT	Local anaesthesia and nitrous oxide/oxygen	Local anaesthesia only	Nitrous oxide group: 5 min before local anaesthesia; 6 L/min-5 min of oxygen and 5 min of nitrous oxide/oxygen until the sedation	Anxiety: Preoperative and postoperative; Pain: During the administration of local anaesthesia and access opening	Nitrous oxide effectively reduces pain perception during treatment and anxiety

CDAS: Corah Dental Anxiety Scale, HF-VAS: Heft-Parker Visual Analogue Scale, PG: Placebo group, RCT: Root Canal Treatment, IANB: Inferior Alveolar Nerve Block, NO: Nitrous oxide group, MDAS: Modified Dental Anxiety Scale

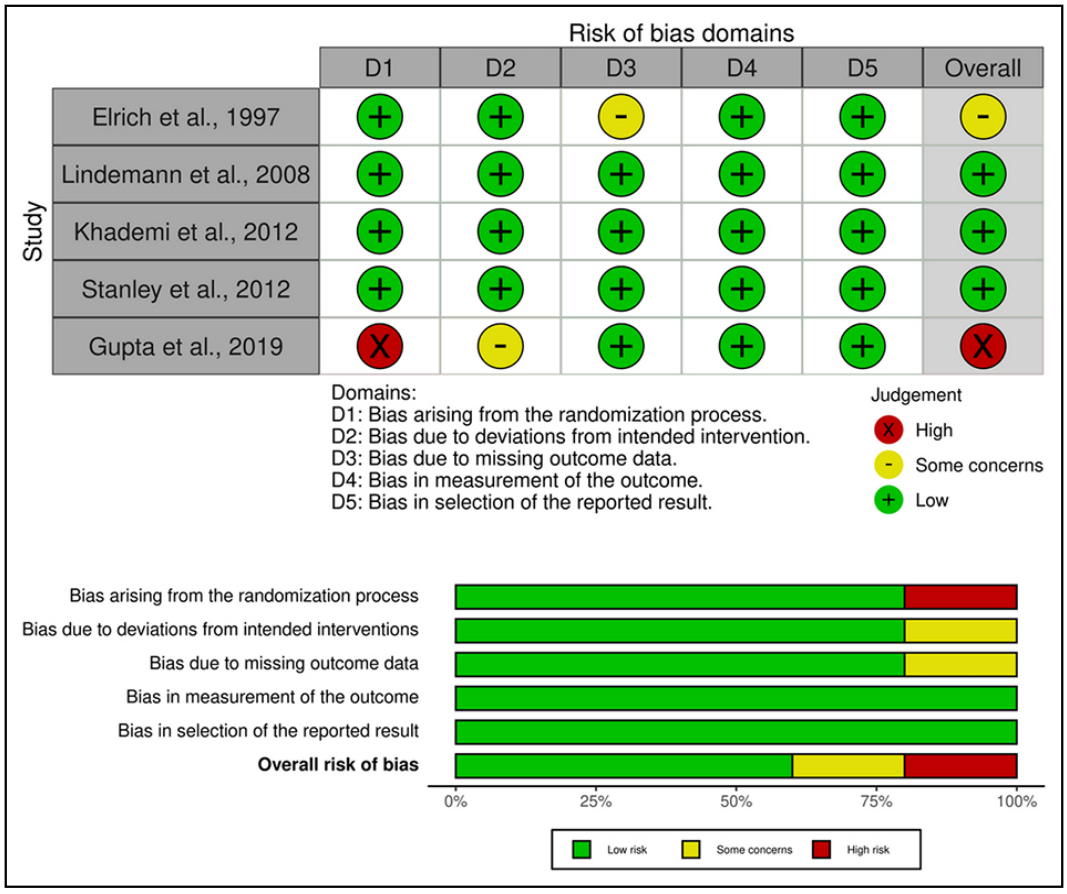

Figure 2. Quality assessment of the randomized clinical trials according to Cochrane Collaboration common scheme for bias and RoB 2 tool

pain perception of patients during anaesthesia and access opening (13), and the other study reported an increase in the success rate of the IANB and the occurrence of intraoperative pain (17). One study that evaluated the administration of 0.5 mg alprazolam reported that this medication did not improve the success rate of IANB and intraoperative pain occurrence (19). Furthermore, another study that evaluated the administration of 0.25 mg triazolam sublingual previously to local anaesthesia also reported that this medication did not improve the success rate of the IANB and intraoperative pain occurrence (16).

Quality Assessment

Figure 2 summarises the risk of bias in randomised clinical trials (20). From the four studies included in the analyses, three studies were classified as low risk of bias (16, 17, 19). Conversely, one study was classified as having a high risk of bias, with one domain (randomisation) presenting a high risk of bias and another domain (deviations from intended interventions) presenting some concerns (13).

Strength of Evidence

GRADE results are presented in Table 3. The GRADE tool demonstrated a low quality of evidence for the included studies (13, 16, 17, 19). These studies received the "serious" classification for risk of bias and imprecision and the "not serious" classification for inconsistency, indirectness, and no other considerations.

DISCUSSION

Since it has been reported that the control of dental anxiety can bring some benefits during endodontic treatment (3), this systematic review aimed to verify if the pharmacological management of dental anxiety influences intraoperative pain. In this systematic review, only randomised clinical trials that controlled dental anxiety through benzodiazepines and nitrous oxide gas were included since no other pharmacological method has been found. These sedation methods were selected because both promote a minimum sedation level, maintaining the patient's consciousness without impairing respiratory and cardiovascular functions (21).

This systematic review is the first that associates the effects of pharmacological control of dental anxiety through conscious sedation in reducing intraoperative pain experience in endodontic treatments. When evaluating the main findings, studies that performed conscious sedation through benzodiazepines did not report better pain perception or anaesthetic efficacy results than the control or placebo groups (16, 19). However, the studies that performed conscious sedation through nitrous oxide gas reported a significant reduction in pain perception during endodontic treatment (17), anaesthetic injection and efficacy (13, 17) and access cavity opening (13). These results can be explained due to the differences in both pharmacological interventions' mechanisms of action.

TABLE 3. Quality of evidence assessed using GRADE

Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence
4	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕◯◯ LOW

[a]: 1 study did not perform allocation concealment and did not perform blinding for patients and caregivers, [b]: Pool sample size lower than 400. GRADE: Grading of Recommendations Assessment, Development, and Evaluation

Nitrous oxide gas presents different mechanisms of action for its sedative and analgesic properties. Although the theory around the mechanism of action of its sedative effects is not well established, the most accepted is that the nitrous oxide gas is a non-competitive inhibitor of the subtype N-Methyl-D-Aspartate (NMDA) glutamate receptor, the primary excitatory neurotransmitter of the central nervous system (22). Another potential theory is that the nitrous oxide gas promotes a hyperpolarization of neurons by increasing the potassium conductance on the potassium canal, such as TREK-1 (23). Regarding the analgesic properties of the nitrous oxide gas, it appears that nitrous oxide induces the release of an opioid peptide in the periaqueductal grey matter (PAG) of the midbrain, leading to the activation of the descending inhibitory pathways, resulting in modulation of the pain at the nociceptive processing in the spinal cord (24). However, despite presenting sedative and analgesic effects, a proper local anaesthesia application is still mandatory to achieve pain control (17).

Meanwhile, benzodiazepines have their mechanism of action related to inhibiting the polysynaptic pathway through direct interaction with gamma-Aminobutyric acid (GABA) (25). GABA is an inhibitory neurotransmitter in the central nervous system and is divided into three subtypes: GABA-A, GABA-B, and GABA-C (25). The subtype responsible for the effects of the benzodiazepines is the GABA-A receptor, an anion-selective ligand-gated ion canal composed of five subunits: two alpha (α), two beta (β) and one gamma (γ) (26). These subunits form a canal that crosses the neuron's plasma membrane, where chloride ions pass (27). When benzodiazepines bind to the GABA-A receptor, there is a conformational change in the canal, which results in a more significant influx of chloride ions, leading to a hyperpolarization of the neural plasma membrane and, consequently, an inhibition of the central nervous system (28). Therefore, while nitrous oxide gas acts as a central nervous system depressor and an opioid-like drug, promoting sedative and analgesic effects, benzodiazepines only promote a sedative effect, which was found not to increase the anaesthetic efficacy (16, 19). It is important to note that not increasing the anaesthetic efficacy is not the same as not decreasing the anxiety levels during endodontic treatment. Furthermore, it may increase patient satisfaction during procedures.

In addition to their different mechanisms of action, these two methods of conscious sedation have different routes of administration that directly impact their clinical effects. Benzodiazepines are drugs that are commonly administered orally. Therefore, it is impossible to determine the exact dose necessary to induce conscious sedation in each case (6). In contrast, nitrous oxide is administered via inhalation, which allows the administered dose to be individually calculated for each patient (7). In addition, at the end of the procedure, the patient will no longer be under the effect of the gas being able to carry out his last activities usually (13).

Regarding adverse reactions to benzodiazepines, it has been reported that minimal changes in the patient's respiration rate when therapeutic doses of benzodiazepines were administered (29). In addition, some authors have found a relationship between the administration of these drugs with cognitive decline, interfering in recent memories' formation and inducing permanent memory loss if used during long periods (30). A previous study (31) showed that former users of benzodiazepines have persistent cognitive deficits in the months following withdrawal. Benzodiazepines can also cause paradoxical reactions, such as increased talkativeness, emotional release, excitement, excessive movement, and even hostility and rage (32). These effects are related to several predisposing risk factors like age, genetic predisposition, alcoholism, and psychiatric or personality disorders (33).

The adverse reactions to the nitrous oxide gas can include gastrointestinal disorders, such as vomiting and nausea, and nervous system and psychiatric disorders, mainly agitation and euphoria (34). Also, it has been reported that more serious adverse reactions can occur, including consciousness disorder, bradycardia, oxygen desaturation, laryngospasm, apnoea, convulsions, cardiac arrest, and narcolepsy (34). Therefore, it is crucial to emphasize that the use of nitrous oxide gas in the dental office should be preceded by an extensive training period, to correctly administrate this drug and reduce the risk of severe adverse reactions (34). The training period and the requirements to use nitrous oxide gas can change depending on the device and the laws of the country that will be used.

Three studies included in this systematic review assessed patients' anxiety using CDAS (16, 17, 19). This scale consists of a 4-item questionnaire related to how the patient feels at different times of dental care. From the answers, the sum of the points is performed to measure the degree of anxiety that the patient presents. CDAS is considered reliable and valid, free of response bias (35). Additionally, one study used MDAS, an adaptation of the CDAS. It consists of 5 questions with five categories, ranging from "not anxious" to extremely anxious". The MDAS has an additional item regarding patient anxiety regarding local anaesthetic injection (36), which is essential to consider when evaluating the outcome of the present study. Scales to assess anxiety are commonly used and easy to administer (37).

Regarding the studies' risk of bias assessment, significant concerns were observed in three domains (randomisation process, deviations from intended interventions, and missing outcome data). One study (13) did not inform for randomisation method and neither for allocation concealment. The same study (13) did not perform blinding for the caregivers and participants, allowing them to know their assigned intervention.

Due to these limitations presented by the included studies, the overall quality of evidence presented by the GRADE tool was classified as low quality. In the 'risk of bias' domain (38), the studies received the "serious" classification because one study did not perform allocation concealment and did not perform blinding for participants and caregivers (13). The domain' inconsistency' (39) was considered 'not serious' since all included studies did not present unexplained heterogeneity of results. The domain' indirectness' (40) was also considered 'not serious' since all included studies had no significant differences in population, interventions, outcome measures, and indirect comparisons. Since a meta-analysis was not possible to be performed and, for this reason, it could not be assessed the single pooled estimate of the effect, the domain 'imprecision' was assessed following Murad et al. (41). It is recommended, in these situations, to consider the total number of participants of the included studies and the confidence intervals (CIs) of the most extensive studies. A threshold of fewer than 400 concerns imprecision, and results may be imprecise when the CIs of the most extensive studies include no effect and meaningful benefits or harms (41). Due to these reasons, the domain 'imprecision' was considered "serious" since the 95% CI of the studies with the widest samples did not include meaningful benefit or harm, and the pooled sample size was less than 400. The domain' other consideration' included the assessment of publication bias, significant effect, plausible confounding, and dose-response gradient (42). None of them was likely to interfere with the results or downgrade the certainty of the evidence of the included studies.

A meta-analysis could not be performed mainly due to the high methodological heterogeneity among the retrieved studies. Different benzodiazepines, dental anxiety and pain scales, and scores were observed, making it difficult to compare the results of the studies, one of the significant limitations of the present systematic review. Also, this systematic review was limited in only verifying if pharmacological interventions could decrease intraoperative pain experiences in endodontic treatments but did not evaluate non-pharmacological therapies, such as music therapy during endodontic treatment, which could present some influence on anxiety control (43). Furthermore, with this systematic review, it was not possible to determine whether the baseline anxiety or pain scores can present some influence on the intraoperative pain occurrence. In other words, patients presenting greater anxiety scores at baseline can present more intraoperative pain events compared to patients presenting lower anxiety scores at baseline.

This systematic review indicates the need for high-quality research on the topic, especially with a standardization of the adopted methodologies, so that an adequate comparison could be possible. Also, well-designed studies should compare the effect of benzodiazepines and nitrous oxide gas on the management of anxiety on pain occurrence during root canal treatment. As presented, several dental anxiety and pain scales were used in the studies. Therefore, a study evaluating the precision and accuracy of these scales could be recommended to determine the most reliable method to evaluate these parameters.

As for the future directions for clinical practice, based on the results of this systematic review, there seems to be no sufficient evidence to determine whether the pharmacological control of anxiety can present some influence on intraoperative pain occurrence. Therefore, it is only possible to suggest that nitrous oxide can present some benefits in reducing intraoperative pain during non-surgical endodontic treatment due to what is known regarding its mechanism of action. At the same time, the use of benzodiazepines seems not to be as effective. Nevertheless, it is essential to emphasize that local anaesthesia, even when conscious sedation or general anaesthesia is performed, is essential in preventing or controlling postoperative and non-odontogenic pain by locally blocking the conduction of nerve impulses that could generate painful sensations (44), thus, it must not be precluded. Meanwhile, in the absence of better-quality information that can confirm the above suggestions, using any of the referred techniques to control dental anxiety and promote a reduction in the intraoperative pain experience should be taken with caution.

CONCLUSION

Based on the findings of the present systematic review, it is possible to suggest that the pharmacological control of anxiety with benzodiazepines does not influence intraoperative pain occurrence. In addition, the use of nitrous oxide gas seems to reduce pain perception. However, such conclusions are based on low certainty of evidence from studies with high methodological heterogeneity.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

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