

UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

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**Anxiety control with benzodiazepine in low third molar
surgery: systematic review**

**Controle da ansiedade com benzodiazepínicos em
cirurgias de terceiros molares inferior: revisão
sistemática**

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Orientador: Prof. Dr. Flávio Augusto Cardoso de Faria

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DEDICATÓRIA

Dedico este trabalho à, minha **família** e ao **Ministério do Ensino Superior, Ciência e Tecnologia (MESCYT)**, que tornou meu sonho realidade ao me permitir e me ajudar a vir ao Brasil e me apoiar financeira e emocionalmente. Sou grato com todos vocês.

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“Talvez não tenha conseguido fazer o melhor, mas lutei para que o melhor fosse feito. Não sou o que deveria ser, mas Graças a Deus, não sou o que era antes”.

Martin Luther King

RESUMO

A ansiedade causada pela remoção de terceiros molares impactados tem sido tratada com benzodiazepínicos, associados ou não a outros grupos de fármacos. Este trabalho tem como objetivo investigar na literatura se os benzodiazepínicos isoladamente são mais eficazes para o controle da ansiedade pré-operatória do que o uso de nenhum medicamento ou placebo. Pretende-se também avaliar o percentual e gravidade dos principais efeitos colaterais observados, causados por este grupo de medicamentos, quando da remoção de terceiros molares inferiores. Métodos: para isso, foi realizada uma busca eletrônica nas bases de dados PubMed, Scopus, BVS, WOS e Embase, no período de 2000 a 2020, usando os termos "third molar", "low third molar", "anxiolytic", "benzodiazepine" e "sedation", combinados entre si. Os estudos foram analisados por dois revisores independentes de modo a preencher os critérios de inclusão. Resultados: Na busca inicial, 1192 estudos foram encontrados, e após a leitura dos títulos e resumos foram selecionados 58 artigos (4,86% do total) que poderiam preencher os critérios de elegibilidade para a presente revisão. Finalmente 4 (0.3%) artigos preencheram todos os critérios propostos nessa revisão sistemática. Apenas um estudo avaliou possíveis efeitos colaterais dos benzodiazepínicos sobre a amnesia anterógrada. Dois estudos que avaliaram os pacientes subjetivamente por meio de escalas mostraram redução significativa da ansiedade no grupo tratado com benzodiazepínicos. Os efeitos dos benzodiazepínicos foram avaliados objetivamente por meio de parâmetros hemodinâmicos; dois estudos mostraram não haver nenhum benefício sobre a ansiedade, quando comparados aos grupos pré-medicados com placebo. Entretanto, um dos estudos mostrou redução do cortisol salivar após a medicação pré-operatória. Conclusão: A ansiedade parece ser efetivamente reduzida quando os benzodiazepínicos são utilizados na fase pré-operatória, quando comparados com pacientes que receberam medicação placebo, nas condições propostas nesta revisão, embora sejam necessárias medidas mais objetivas em futuros estudos que comprovem esta evidência.

Palavras-chave: Benzodiazepínico; Ansiolítico; Sedação; Terceiro molar.

ABSTRACT

Anxiety control with benzodiazepine in low third molar surgery: systematic review

Anxiety caused by the removal of impacted third molars is treated with benzodiazepines alone or in association with other drugs. Aim: Through this systematic review we hope to know if benzodiazepines are more effective for the control of preoperative anxiety when compared with no medication or the use of placebo. It is also intended to evaluate in the scientific literature the percentage and severity of the main side effects caused by this group of drugs. Methods: An electronic search was carried out in the PubMed, Scopus, BVS, WOS and Embase databases, from 2000 to 2020, using the terms "third molar", "low third molar", sedation, anxiolytic, and benzodiazepine. The studies were selected after two reviewers independently assessed the articles with respect to the inclusion and exclusion criteria. Results: In the initial search, 1192 studies were found, 58 studies were selected by title and abstracts (4.86% of the total), Finally, the exclusion criteria were applied and only 4 (0.3% of the total) studies were included in the investigation. Two studies that evaluated patients subjectively using scales showed a significant reduction in anxiety in the group treated with benzodiazepines. Using hemodynamic parameters, two studies showed no benefit on anxiety when compared to premedicated groups with placebo. However, one of them show a reduction in saliva cortisol level after the use of a benzodiazepine. Only one study evaluated possible side effects of benzodiazepines on anterograde amnesia. Conclusions: Anxiety seems to be effectively reduced when benzodiazepines are used in the preoperative phase, when compared with patients who received placebo medication, in double-blind randomized clinical trials. However, more objective methods are necessary to confirm this evidence in future studies.

Keywords: Benzodiazepine; Anxiolytic; Sedation; Third molar.

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LISTA DE ABREVIATURA E SIGLAS

Braz J Oral Sci	Brazilian Journal of Oral Sciences
PubMed	Publisher Medline
WOS	Web of Science
BVS	Biblioteca Virtual em Saude
RGP	Resposta Galvânica da Pele
GABA	Gamma Amino Butyric Acid
BP	Blood Pressure
HR	Heart Rate
RR	Respiratory Rate
PO2	Partial Pressure of Oxigen
HAD	Hospital Anxiety and Drepression
VAS	Visual Analogue Scale
TMT	Trail Marking Test
DSST	Digit Symbol
PROSPERO	International prospective register of systematic reviews

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1 INTRODUÇÃO

ANSIEDADE E ODONTOLOGIA

Dentre os pacientes odontológicos, muito frequentes são os sinais de ansiedade demonstrados antes e durante os diferentes procedimentos, especialmente quando é necessário utilizar instrumentos e materiais cirúrgicos. Armfield e colaboradores (ARMFIELD et al., 2007) relataram que o medo e a ansiedade, relacionados ao tratamento odontológico, podem criar um comportamento aversivo às visitas ao cirurgião-dentista, evitando exames regulares dos dentes e tecidos bucais, o que, certamente, conduziria à deterioração da saúde oral.

Em estudo conduzido na França em 2007 por Nicolas e colaboradores, cerca de 20% dos participantes reportaram evitar o tratamento odontológico (NICOLAS et al., 2007). Outro estudo conduzido por Armfield em 2013 na população australiana, mostrou que aproximadamente 17% dos participantes relataram evitar o tratamento odontológico por sentirem medo ou total aversão ao mesmo (ARMFIELD, 2013a).

A ansiedade pode ser compreendida como uma antecipação de determinado evento, quando ainda não ocorreu nenhum estímulo externo ameaçador. Com isso, ocorre a ativação do sistema nervoso simpático, de maneira autonômica, independente de nossa vontade, produzindo mecanismos de defesa reflexos, preparando o organismo para a luta ou fuga (CANNON, 1929). Dentre estes mecanismos reflexos está a secreção de corticosteróides pelo córtex da glândula suprarrenal, bem como uma imensa descarga de adrenalina e noradrenalina na corrente sanguínea, causada pelas células medulares desta mesma glândula.

O estado de ansiedade pode ser tratado com abordagens psicológicas e por meio de certos grupos de fármacos. Os ansiolíticos e hipnóticos são medicamentos tradicionalmente empregados no tratamento de pacientes que relatam medo, pânico, conflito, ansiedade e depressão, embora outros grupos farmacológicos possam também ser utilizados, tais como os antidepressivos e

antipsicóticos, associados ou não aos benzodiazepínicos (OGLE & HERTZ, 2012).

A ansiedade prévia ao atendimento odontológico tem sido bem estudada desde o final dos anos 1960 (LITTLE, 2003; SMITH; HEATON, 2003; MILGROM et al., 2010; ARMFIELD, 2013b). Diversas e distintas abordagens têm sido utilizadas com a finalidade de diminuir a dor e o medo, possibilitando assim ao paciente o enfrentamento desta situação estressante. Dentre estas abordagens destaca-se o uso de medicamentos do grupo dos benzodiazepínicos. Outras drogas também empregadas para reduzir a dor e o medo, são os analgésicos opióides, anti-inflamatórios não esteroidais, antidepressivos tricíclicos e antidepressivos inibidores específicos da recaptação de serotonina. Abordagens não farmacológicas incluem terapias holísticas e comportamentais, como massagens, técnicas respiratórias, terapias com músicas e outras distintas técnicas de relaxamento (ROBB; MEECHAN, 1997; SHAH et al., 2003; GEORGELIN-GURGEL et al., 2009; KAVIANI et al., 2011; OGLE; HERTZ, 2012).

O uso pré-operatório dos benzodiazepínicos, especialmente alprazolam e midazolam, tem sido estudado há um certo tempo em Odontologia. O midazolam em muitos estudos é empregado por via intravenosa, nas cirurgias de terceiros molares inferiores impactados (BELL; KELLY, 2000; JERJES et al., 2009; GUPTA; SHARMA; DHIMAN, 2012; PEREIRA-SANTOS et al., 2013; CHEN et al., 2015; JOSHI et al., 2016). Outros autores relatam conseguir a sedação utilizando apenas métodos alternativos, como a auriculoterapia, diminuindo assim a ansiedade do paciente (BRIGNARDELLO-PETERSEN, 2019; DELLOVO et al., 2019; YAMASHITA et al., 2019). Os medicamentos pertencentes ao grupo dos benzodiazepínicos, frequentemente utilizados em muitas áreas da Medicina para controle da ansiedade e tratamento de insônia, são agonistas dos receptores GABA_A, localizados nos canais de cloro. Quando ligados a seus receptores, os benzodiazepínicos facilitam a ligação do GABA, um conhecido neurotransmissor inibitório presente em todo o Sistema Nervoso Central, a seus sítios de ligação, neste mesmo canal de cloro. Isso aumenta a probabilidade de abertura dos canais, com conseqüente influxo deste íon para o citoplasma dos neurônios, causando sua hiperpolarização (TAN; RUDOLPH; LÜSCHER, 2011). Neurônios bulbares responsáveis pelo controle ventilatório podem ser deprimidos pelo uso dos benzodiazepínicos, da mesma forma que

um grande grupo de células localizadas na base do cérebro, relacionadas com o controle de nossas emoções e da memória. Graças a esta depressão da atividade neuronal, se atingem os efeitos clínicos desejados, bem como algumas reações adversas indesejadas, como a amnésia anterógrada e a depressão respiratória (O'DONNELL; BIES; SHELTON, 2017).

A cirurgia de terceiro molar tem sido bastante utilizada como procedimento de referência para avaliar a ansiedade pré-operatória dos pacientes já há algumas décadas (BELL et al. 2000, LEITCH et al. 2004; JERJES et al. 2005). Em artigo publicado em 2014, Aznar-Arasa e colaboradores concluíram que as extrações de terceiros molares inferiores impactados são significativamente mais difíceis em pacientes ansiosos; afirmaram também que outros fatores tais como idade, grau de impactação, angulação do terceiro molar, proximidade do canal mandibular, bem como a necessidade de realizar osteotomia e/ou odontosseção também estão relacionados significativamente com a dificuldade cirúrgica (AZNAR-ARASA et al., 2014).

A ansiedade em Odontologia pode ser mensurada por métodos objetivos e subjetivos. Um dos métodos objetivos utilizado é a medida da condutância da pele. Existe correlação estatisticamente significativa entre a condutância da pele e a ansiedade odontológica (CAPRARA et al., 2003). Najafpour e colaboradores (2017) sugeriram que a resposta galvânica da pele poderia ser um método válido e confiável na avaliação da ansiedade odontológica infantil. Tal resposta poderia ajudar na identificação de crianças clinicamente ansiosas antes do tratamento odontológico, de maneira a planejar melhor as intervenções apropriadas (NAJAFPOUR et al., 2017). Em estudo randomizado e controlado com placebo em cirurgias orais, comparando duas doses distintas de alprazolam (respectivamente 0,25 mg e 1 mg administradas por via oral), Wolf e colaboradores (2003) mostraram que, 90 minutos após a administração do fármaco, houve redução estatisticamente significativa ($p < 0,05$) na ansiedade, mensurada tanto por métodos subjetivos como pelo nível de condutância da pele, nos indivíduos tratados com alprazolam, quando comparados com aqueles tratados com placebo, com ambas as doses (WOLF et al., 2003).

O nível de cortisol livre tem sido avaliado tanto em amostras de plasma e de saliva como medida objetiva indireta do nível de ansiedade. Sua análise na saliva tem a vantagem de proporcionar uma coleta não invasiva, sem

necessidade da remoção de sangue, fato que poderia influenciar na quantificação do hormônio, em função do estresse causado pela simples visualização da agulha. Opaleye e colaboradores (2020), avaliando o efeito sedativo de diazepam (5mg) quando da remoção de terceiro molar inferior, mostraram que o cortisol salivar é um bom marcador biológico do estresse fisiológico durante este procedimento cirúrgico (OPALAYE et al., 2020).

A simples injeção dos anestésicos locais em procedimentos cirúrgicos de terceiros molares aumenta o estresse, o medo e pode influir nos parâmetros hemodinâmicos (DE MORAIS et al., 2015). Assim, as alterações hemodinâmicas que eventualmente ocorrem durante uma cirurgia podem ser indicativas dos estados de estresse e ansiedade. Estudos recentes parecem indicar que o medo da injeção é o aspecto que mais produz ansiedade no tratamento odontológico moderno (DE MORAIS et al., 2015; GADVE et al., 2018; TARAZONA-ALVAREZ et al., 2019). Além disso, a ansiedade provocada pelo tratamento dentário pode afetar a pressão arterial e aumentar a frequência cardíaca (DE MORAIS et al., 2015).

Desde o século passado, vários pesquisadores têm utilizado "escalas" subjetivas para mensurar o nível de ansiedade que o paciente pode apresentar antes do tratamento odontológico (CORAH, 1969; GATCHEL, 1989; VASSEND, 1993; STOUTHARD; HOOGSTRATEN; MELLENBERGH, 1995; EHRICH et al., 1997; DOERR et al., 1998; NEWTON; BUCK, 2000; SLOVIN; FALAGARIO-WASSERMAN, 2009; BHOLA; MALHOTRA, 2014; DE MOARES et al., 2019). Por meio desta avaliação subjetiva, Mellor e colaboradores, em 1992, utilizando a Escala de Ansiedade Odontológica de Corah (CORAH, 1969) para avaliar o nível de ansiedade de 300 trabalhadores em três locais no noroeste da Inglaterra, mostraram que as situações dentárias que mais geraram ansiedade foram as causadas pela possibilidade de perfuração ou injeção de anestésico local (MELLOR, 1992).

Tomando por base a grande incidência de medo e ansiedade, demonstradas pelos pacientes previamente aos procedimentos odontológicos, bem como a possibilidade legal da utilização de benzodiazepínicos pelos cirurgiões-dentistas no Brasil, torna-se necessário ampliar as bases científicas que justifiquem ou não a utilização deste grupo de fármacos na Odontologia, levando em consideração seus potenciais benefícios e riscos.

2 ARTIGO

The article presented in this Dissertation was written according to the **Brazilian Journal of Oral Sciences** instructions and guidelines for article submission.

Use of benzodiazepines as preoperative medication in lower third molar surgeries: Systematic Review

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Abstract

Anxiety generated by the removal of lower third molars has been treated with benzodiazepines, associated or not with other medications. Our objective: to investigate in the literature whether they are more effective for the control of anxiety than the use of no medication or placebo, and to evaluate the percentage and severity of side effects caused by these drugs when removing lower third

molars. Methods: an electronic search in PubMed, Scopus, BVS, WOS, and Embase databases, from 2000 to 2020, using the terms "third molar", "low third molar", "anxiolytic", "benzodiazepine" and "sedation", combined, was performed. The studies were analyzed by two independent reviewers to fulfill the inclusion criteria. Results: 1192 studies were found. After reading the titles and abstracts, 58 were selected (4.86% of the total). Finally, 4 (0.3%) articles met all the criteria proposed for this systematic review. Only one study evaluated the side effect on anterograde amnesia. Two studies, with subjective assessment (scales), showed a significant reduction in anxiety in the group treated with benzodiazepines. The objective assessment of anxiety was performed using hemodynamic parameters. Two studies showed no benefit when compared to placebo-treated groups. However, one of the studies showed a reduction in salivary cortisol after midazolam. Conclusion: Anxiety seems to be reduced when benzodiazepines are used in the preoperative phase, compared to patients who received placebo medication, under the conditions proposed in this review.

Keywords: Benzodiazepine. Anxiolytic. Sedation. Lower third molar

Introduction

Anxiety and Dentistry

In dental patients, signs of anxiety, demonstrated before and during different procedures, are very frequent, especially when it is necessary to use surgical instruments and materials. Anxiety can be understood as an anticipation of a certain event when no threatening external stimulus has yet occurred. With this, the activation of the sympathetic nervous system occurs, in an autonomic way, independently of our will, producing reflex defense mechanisms, preparing the organism for fight or flight (CANNON, 1929).

The preoperative use of benzodiazepines, especially alprazolam and midazolam, has been studied for some time in dentistry. In many studies, midazolam is used intravenously in impacted lower third molar surgeries (BELL; KELLY, 2000; JERJES et al., 2009; GUPTA; SHARMA; DHIMAN, 2012; PEREIRA-SANTOS et al., 2013; CHEN et al., 2013; CHEN et al., 2015; JOSHI et al., 2016). Other authors report achieving sedation using only alternative

methods, such as auriculotherapy, thus reducing patient anxiety (BRIGNARDELLO-PETERSEN, 2019; DELLOVO et al., 2019; YAMASHITA et al., 2019).

Medications belonging to the group of benzodiazepines, frequently used in many areas of medicine to control anxiety and treat insomnia, are GABA_A receptor agonists, located in chloride channels. When bound to their receptors, benzodiazepines facilitate the binding of Gamma Amino Butyric Acid (GABA), a known inhibitory neurotransmitter present throughout the Central Nervous System, to its binding sites on this same chloride channel. This increases the probability of channels opening, with a consequent influx of this ion into the cytoplasm of the neurons, causing their hyperpolarization (TAN; RUDOLPH; LÜSCHER, 2011). Bulbar neurons responsible for ventilatory control can be depressed by the use of benzodiazepines, in the same way as a large group of cells located at the base of the brain, related to the control of our emotions and memory. Due to this depression of neuronal activity, the desired clinical effects are achieved, as well as some unwanted adverse reactions, such as anterograde amnesia and respiratory depression (O'DONNELL; BIES; SHELTON, 2017).

Third molar surgery has been widely used as a reference procedure to assess patients' preoperative anxiety for some decades (BELL et al. 2000, LEITCH et al. 2004; JERJES et al. 2005). In an article published in 2014, Aznar-Arasa and colleagues concluded that extractions of impacted lower third molars are significantly more difficult in anxious patients. In addition, they also stated that other factors such as age, degree of impaction, angulation of the third molar, proximity to the mandibular canal, as well as the need to perform osteotomy and/or odontosection are also significantly related to surgical difficulty (AZNAR-ARASA et al., 2014).

Anxiety in Dentistry can be measured by objective and subjective methods. One of the objective methods used is the measurement of skin conductance. There is a statistically significant correlation between skin conductance and dental anxiety (CAPRARA et al., 2003). In a randomized placebo-controlled study in oral surgery, comparing two different doses of alprazolam (respectively 0.25 mg and 1 mg administered orally), Wolf et al. (2003) showed that 90 minutes after drug administration there was a statistically significant ($p < 0.05$) reduction in anxiety, as measured by both subjective methods

and the level of skin conductance, in individuals treated with alprazolam compared to those treated with placebo of both doses (WOLF et al., 2003).

The level of free cortisol has been evaluated in both plasma and saliva samples as an indirect objective measure of anxiety level. Its analysis in saliva has the advantage of providing a non-invasive collection, without the need to remove blood, a fact that could influence the quantification of the hormone, due to the stress caused by the simple visualization of the needle. Opaleye et al (2020), evaluating the sedative effect of diazepam (5mg) when removing a lower third molar, showed that salivary cortisol is a good biological marker of physiological stress during this surgical procedure (OPALAYE et al., 2020).

The simple injection of local anesthetics in surgical procedures of third molars increases stress, and fear and can influence hemodynamic parameters (DE MORAIS et al., 2015). Thus, the hemodynamic changes that eventually occur during surgery may be an indication of states of stress and anxiety. Recent studies seem to indicate that fear of injection is the most anxiety-producing aspect of modern dental treatment (DE MORAIS et al., 2015; GADVE et al., 2018; TARAZONA-ALVAREZ et al., 2019). In addition, anxiety caused by dental treatment can affect blood pressure and increase heart rate (DE MORAIS et al., 2015).

Since the last century, several researchers have used subjective "scales" to measure the level of anxiety that the patient may present before dental treatment (CORAH, 1969; GATCHEL, 1989; VASSEND, 1993; STOUTHARD; HOOGSTRATEN; MELLENBERGH, 1995; EHRICH, 1995; EHRICH et al., 1997; DOERR et al., 1998; NEWTON; BUCK, 2000; SLOVIN; FALAGARIO-WASSERMAN, 2009; BHOLA; MALHOTRA, 2014; DE MOARES et al., 2019). Through this subjective assessment, Mellor and colleagues in 1992, using the Corah's Dental Anxiety Scale (CORAH, 1969) to assess the level of anxiety of 300 workers in three locations in northwest England, showed that the dental situations that most generated anxiety were those caused by the possibility of perforation or injection of local anesthetic (MELLOR, 1992).

Based on the high incidence of fear and anxiety, demonstrated by patients prior to dental procedures, as well as the legal possibility of using benzodiazepines by dentists in Brazil, it is necessary to expand the scientific

bases that justify or not the use of this drug group of drugs in Dentistry, taking into account their potential benefits and risks.

For this reason, through this systematic review, it is expected to know whether benzodiazepines are more effective in controlling the level of preoperative anxiety in patients (who underwent surgery to remove impacted third molars) when compared to groups of patients who did not receive any preoperative medication or received a placebo. We also intend to evaluate in the scientific literature the percentage and severity of the main side effects observed when using these drugs to control anxiety.

Material and Method

Search strategy

This systematic review was registered on the PROSPERO platform on 03/11/2021 and accepted under the number CRD42021241903 aiming to answer the following question: "There is no difference in the level of anxiety with the use of preoperative benzodiazepines, when compared to the use of placebo or no preoperative medication, during impacted third molar surgery?" For this, an electronic search in PubMed, Scopus, VHL, WOS, and Embase databases, from 2000 to 2020, with the following keywords (in English) combined: "third molar" and anxiolytic; "low third molar" and anxiolytic; "third molar" and benzodiazepine; "low third molar" and benzodiazepine; "third molar" and sedation; "low third molar" and sedation, was carried out.

Selection criteria

The studies were selected after a careful reading of the title and abstract to verify whether they corresponded to the guiding question. After the initial selection, the abstracts were read in full by two different examiners, and articles that met all the following inclusion criteria were chosen: studies with preoperative use of benzodiazepines and removal of third molars; comparison between benzodiazepines and placebo/no preoperative medication as a control; research carried out in human beings, regardless of the sample number; controlled and randomized clinical trials. Exclusion criteria were: animal research; studies with

medication other than benzodiazepine; studies outside the established date; studies that did not assess the anxiolytic effect of benzodiazepines; and other systematic reviews.

Data collection

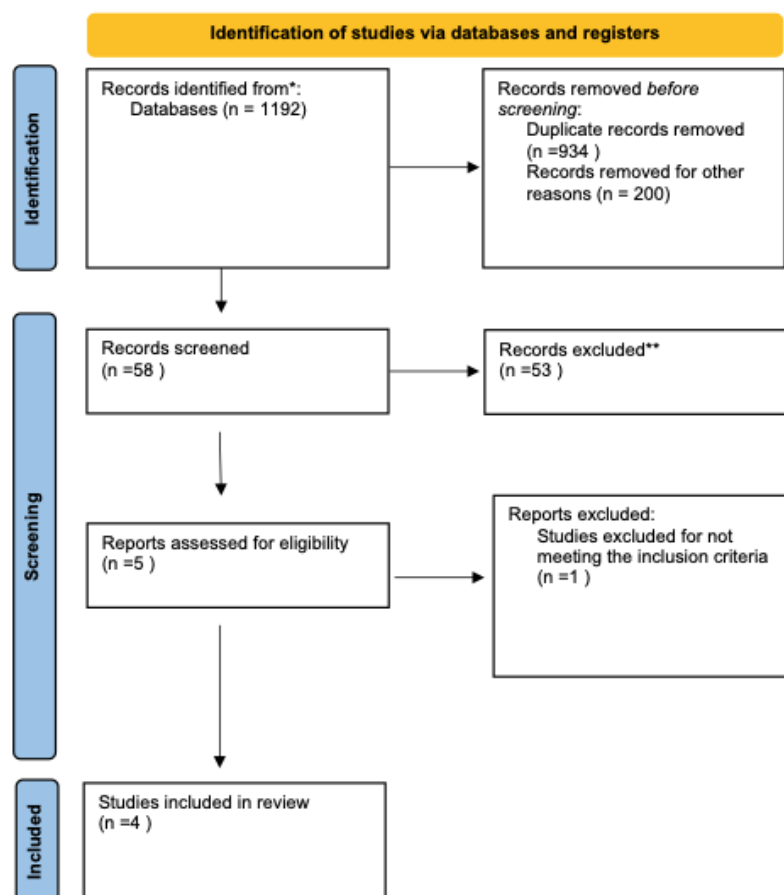
After reading the articles, data from each study were organized into tables according to the year of publication, author, type of study, number of patients, method for assessing anxiety (objective and/or subjective), type of benzodiazepine, route of administration, dose administered, result obtained and reporting of side effects. Subsequently, the results were analyzed to answer the main question of this systematic review.

Results

This systematic review followed the criteria defined by the PRISMA system (Preferred Reporting Items for Systematic Reviews and Meta-analyses) as shown in Figure 1.

In the initial search, 1192 articles were found in the databases selected for this review, 28.10% in the PubMed database (335 articles), 21.98% in the Embase database (262 articles), 20.39% in the Scopus database (243 articles); 16.86% in the VHL database (201 articles) and the remaining 12.67% in the WOS database (151 articles) (**Table I**).

Figure 1 -The PRISMA 2020 flowchart for new systematic reviews only included database and registry searches



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After reading the titles and abstracts, 58 articles (4.86% of the total) that could meet the eligibility criteria for this review were selected. Forty-nine articles (84.48%) were in the PubMed database, 4 (6.90%) in the WOS database, 3 (5.17%) in the VHL database, and 2 (3.45%) in the SCOPUS database. None was selected from the Embase database (**Table I**). However, after careful reading of the abstracts by two different examiners, only 4 articles met all the eligibility criteria proposed in this systematic review. Considering the 1192 studies initially found with the keywords, only 0.3% of them were selected for this investigation (**Table I**).

Table I- Distribution of the articles identified in the initial search in the different databases

Database	Articles found	Selection by title	Selection by abstract	Articles eligible for this research
PUBMED	335	49	5	4
WOS	151	4		
BVS	201	3		
SCOPUS	243	2		
Embase	262	0		
Total	1192	58		

Table II - Variables analyzed in the articles selected for this review and their respective frequency

ANALYZED VARIABLE	FREQUENCY	
Type of study	4 randomized controlled trials	-----
Number of the sample	3 studies - more than 50 patients	1 study - less than 50 patients
Benzodiazepine used	3 studies - midazolam only	1 study - midazolam and diazepam
Route of administration	3 studies – oral route	1 study – intravenous route
Dose administered	2 studies used 7.5 mg	1 study - inconclusive 1 study - more than 7.5 mg
Side Effects	1 study	-----

Table III - Type and method of assessing anxiety used in the articles selected for this review

ANXIETY ASSESSMENT			
STUDY	METHOD	SUBJECTIVE	OBJECTIVE
Bell et al.	Subjective	- Corah's Scale and Memory test	_____
Jerjes et al.	Objective/ Subjective	Anxiety Scale	Hemodynamic parameters and salivary cortisol
Morais et al.	Objective	-----	Hemodynamic parameters
Torun et al.	Objective / Subjective	- Visual Analogue Scale for Anxiety, Trail Making Test, and Digit Symbol Substitution Test	_____

Only the study conducted by Bell et al., (2000), evaluated the possible side effects of benzodiazepines on anterograde amnesia (**Table II**). The results showed some degree of amnesia in the first 25 minutes, after reaching an adequate level of sedation. This effect did not last for more than 40 minutes. Another study (TORUN et al., 2019) evaluated the psychomotor and cognitive functions through subjective tests showing that midazolam significantly decreases such abilities (**Table III**).

Two studies that evaluated patients subjectively using scales showed a significant reduction in anxiety in the benzodiazepine-treated group (BELL et al., 2020; TORUN et al., 2019) (**Table IV**). One of the studies that also used subjective scales (JERJES et al., 2005) found no difference in anxiety scores when comparing patients who received midazolam or placebo (**Table IV**).

Table IV - Data collection and anxiety results based on the assessment methods

Author	Study	Patient	Molars	Benzodiazepine	Dose / Route	Assessment	Other Effects	Results
GW Bell et al., al 2000	Randomized Clinical Trial	60	85	Midazolam	Increments of 1 to 2 mg/min, I.R. until reach sedation level	- Corah's Scale - Memory test	Anterograde amnesia	--The dose of midazolam required for sedation did not correlate with body mass index ($r = 0.05$; $P = 0.68$). -Preoperative anxiety does not correlate with the drug dose required for sedation ($r = 0.16$, $P = 0.21$). - Significant reduction in postoperative anxiety in the 60 patients who were sedated ($P < 0.001$). -There was no significant correlation between decreased anxiety and memory of the surgery ($r = 0.03$, $p = 0.6$). -Correlation between the degree of amnesia and the time of operation ($p < 0.001$), up to 25 minutes after surgery
Jerjes et al., 2005	Randomized Clinical Trial	38	-	Midazolam	7.5 mg O.R.	- Hemodynamic parameters - Cortisol - Hospital Anxiety and Depression Scale	Not assessed	-Mean HAD scores for depression and anxiety show no significant differences between the control and treatment groups ($P = 0.673$ and 0.628 , respectively). -After administration of sublingual midazolam there was a marked decrease in cortisol levels compared to samples taken from the placebo group ($p < 0.000$). -No statistical significance was observed in vital signs measurements
Morais et al.,2015	Randomized Clinical Trial	120	240	Midazolam Diazepam	7,5 mg O.R 10 mg O.R.	Hemodynamic parameters	Not assessed	No statistically significant differences were found in the hemodynamic parameters studied (HR, BP, PO ₂ , RR), in Groups 1 (diazepam x placebo) and 2 (midazolam x placebo), at any of the evaluation moments.
Torun et al., 2019	Randomized Clinical Trial	90	90	Midazolam	0,2mg/kg O.R.	- Visual Analogue Scale for Anxiety - Trail Making Test - Digit Symbol Substitution Test	Not assessed	VAS, DSST, and TMT-A and -B scores were evaluated before and after medication. No relevant differences were observed between the groups before medication. The results show that anxiety was significantly reduced in the midazolam group ($P < 0.001$) with no statistically significant difference from the other groups (melatonin and placebo).

When the effects of the benzodiazepines were objectively assessed using hemodynamic parameters, two studies (JERJES et al., 2005; DE MORAIS et al., 2015) showed no benefit on anxiety when compared to premedicated placebo groups (**Table IV**). Only the study conducted by Jerjes et al. (2005) demonstrated that the level of salivary cortisol found in patients medicated with midazolam was significantly lower than that found in patients who received placebo (**Table IV**).

Discussion

Probably, due to its action on the Central Nervous System, its interaction with alcoholic beverages, and its ability to cause dependence with prolonged use, the sale of these drugs is controlled in almost all countries of the world, requiring a special prescription to be purchased in drugstores. These actions could cause some fear regarding the preoperative use of benzodiazepines. Certainly, much of this fear is based on the possible adverse reactions of benzodiazepines, including respiratory depression, anterograde amnesia, reduced psychomotor skills, and psychic dependence (PENG et al., 2022).

In postulating this systematic review, our intention was to verify in the scientific literature the use of benzodiazepines in a surgical model widely used in dental research (lower third molar extraction), as well as to analyze reports of possible side effects when using them clinically. We know that anxiety is a reality that makes dental treatment difficult and that it also contributes to the deterioration of oral health.

This review showed that, in the period covered by it, 1192 articles reported some use of these drugs in surgical procedures of lower third molars, which seems to demonstrate their great utility in operative procedures in Dentistry. However, only 4 articles met all the proposed criteria, since the studies should be randomized and placebo-controlled, and performed in humans. Studies that associated or compared benzodiazepines with other groups of drugs were excluded from this analysis.

The drug used in all 4 studies was Midazolam, a well-known benzodiazepine with a rapid onset of action and a sedative effect for a short period of time (O'DONNELL; BIES; SHELTON, 2017), most often used orally in the selected articles. Only one of the studies (BELL et al., 2000) used midazolam intravenously, a route of administration not allowed to dentists in Brazil for routine use.

Only one of the studies (DE MORAIS et al., 2015) made a comparison between two different benzodiazepines, midazolam and diazepam, finding no significant

differences between their anxiolytic activities. Unlike midazolam, which has an elimination half-life of around 3 hours, diazepam has a very prolonged effect, with an elimination half-life of around 20 to 100 hours (O'DONNELL; BIES; SHELTON, 2017; PENG et al., 2022). Furthermore, the time required for diazepam to reach peak plasma concentration is almost 2.5 hours, in contrast to midazolam, which can reach peak plasma levels in 15 to 30 minutes (MIDAZOLAM injection, solution; DailyMed – U.S. National Library of Medicine).

The dose of the drugs used (midazolam and diazepam) is also among those recommended by the manufacturers and used in other articles in the literature (PENG et al, 2022; DE MORAES, 2019; DELLOVO et al., 2019, MIDAZOLAM injection, solution; DailyMed – U.S. National Library of Medicine). Bell et al. (2000) state that the amount of midazolam needed to obtain a predetermined level of sedation cannot be reliably predicted. However, Jerjes et al., (2005) state that small doses of midazolam appear to have a significant beneficial effect on preoperative cortisol levels, patient stress and anxiety, without having a noteworthy effect on the cardiovascular and respiratory systems or prolonging the patient's recovery time. Furthermore, Pereira Santos et al. (2013), in a study not selected for this review, reported that a dose of 7.5 mg of midazolam would be the most effective form of sedation to reduce the level of salivary cortisol during the extraction of lower third molars.

Probably, due to these two factors: rapid onset and sedative effect for the adequate time to perform the surgical procedure, midazolam was the drug of choice in the articles selected here. This, however, does not exclude the possible use of other drugs belonging to the same group, since their sedative effects are similar (O'DONNELL; BIES; SHELTON, 2017).

One of the studies Bell et al., (2000) was concerned with evaluating anterograde amnesia after intravenous injection of midazolam showing that this amnesia is of short duration, lasting for only 25 minutes after reaching an adequate level of sedation. In other studies not included in this review, Ganzberg et al., (2005), also using benzodiazepines in third molar surgery, when assessing amnesia through a questionnaire, reported that there was no statistically significant difference when compared to the group treated with zaleplon. Similarly, De Moraes et al., (2019), when comparing two benzodiazepines with nitrous oxide, found no significant difference between the 3 sedation groups for retrograde amnesia. In the articles selected by the inclusion criteria of this review, there is no data regarding amnesia, when the drug is

administered orally. However, because of the reduced elimination half-life of midazolam, this amnesia, if it occurs, does not appear to be of major clinical concern to the dentist.

A study conducted by Torun et al. (2019) showed that midazolam reduces the psychomotor ability and cognitive abilities of patients. Thus, even considering the short elimination half-life of this substance, it seems clear that after the surgery the patient should avoid activities that require a certain manual skill and that may be dangerous, such as driving a vehicle. This data reinforces the frequent clinical recommendation of postoperative rest and also corroborates other findings in the literature (PENG et al., 2022).

Hemodynamic parameters are frequently used in clinical studies of third molar extraction to observe cardiac and respiratory changes at different surgical times (LEITCH et al., 2004, GANZBERG et al., 2005, USTUN et al., 2006, CHEUNG et al., 2007, STUDER et al., 2012, DANTAS et al., 2017, FARAH et al., 2019, CAVALCANTI et al., 2020).

When hemodynamic parameters were used to analyze anxiety, in the articles selected in this review (JERJES et al., 2005 and MORAIS et al., 2015), no significant difference in blood pressure (BP), heart rate (HR), frequency respiratory rate (RR) and partial pressure of oxygen (PO₂) were found when comparing patients who received benzodiazepine with those who received placebo. This fact, although described by only one article, may indicate that, at the doses used in these studies and when used orally, no respiratory depressant effect was observed in medicated patients. This fact is also described in the literature in an article by Ogle & Hertz (2012).

Another objective parameter analyzed in the study by Jerjes et al. (2005), was the reduction of salivary cortisol levels in patients who received oral midazolam when compared to patients who received placebo. Cortisol, a hormone produced by cells in the adrenal cortex, is normally used as an indirect measure of stress and anxiety levels since its production is stimulated especially by the activity of the Sympathetic Nervous System during the alarm reaction (CANON, 1929). This fact seems to objectively point to the reduction of anxiety after preoperative medication with benzodiazepines. Pereira Santos et al. (2013), using cortisol as an anxiolytic measure when comparing midazolam with nitrous oxide, reported a significant decrease between the baseline cortisol value and that of the second surgery, a fact that was not observed with the use of nitrous oxide.

The reduction in anxiety assessed by subjective questionnaires, in the articles selected in this review, seems to point to a benefit of the medication in the preoperative period. Only one of the studies showed no difference compared to placebo. The working hypothesis to be addressed in future studies is that calm patients are more easily anesthetized, collaborate better during the surgical procedure, report less postoperative pain, consume fewer analgesics and anti-inflammatory drugs after surgery, facilitate the dentist work, and, considering the low levels of stress and anxiety, would take better care of their oral health.

Conclusion

Within the limitations of this systematic review, we can conclude that anxiety seems to be effectively reduced when benzodiazepines are used in the preoperative phase, when compared to patients who received placebo medication, in double-blind randomized clinical trials. Midazolam was the drug most used in the selected studies and, apparently, at the doses used by these researchers, its side effects were minimal, especially in anterograde amnesia and respiratory depression. However, due to the small number of articles that met all the eligibility criteria, more randomized and comparative clinical studies, subjectively and objectively evaluated, are needed to place this group of drugs as the gold standard in the treatment of dental anxiety.

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ANEXO

ANEXO A - Registro em PROSPERO

PROSPERO
International prospective register of systematic reviews


National Institute for
Health Research

UNIVERSITY *of* York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Anxiety Control with Benzodiazepine in Lower Third Molar Surgery: Systematic Review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Controle da Ansiedade com Benzodiazepina na Cirurgia de Terceiro Molar Inferior: Revisão Sistemática

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

15/03/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

11/05/2021

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

ANEXO B – Coleta de dados

000 fx Quantidade 3o molares inf.				
A	B	C	D	E
Autor	Tipo de estudo	Quantidade de Pacientes		Benzodiazepinico
GW Bell et al., 2000	Ensaio clinico	60		Midazolam
JA Leitch et al., 2004	Ensaio clinico randomizado parcialmente cego	110		Midazolam
Waseem Jerjes et al., 2005	Ensaio duplo-cego randomizado controlado	38		Midazolam
Steven I Ganzberg et al., 2008	Desenho duplo-cego cruzado	14		Triazolam
Yakup Ustun et al., 2006	Estudo duplo-cego, cruzado e randomizado.	20		Midazolam
CW Cheung et al., 2007	Randomizado, duplo-cego, comparativo	60		Midazolam
Hansan Garip et al., 2007	Randomizado e prospetivo	40		Midazolam
Ozgen Goktay et al., 2010	Prospetivo, randomizado, duplo-cego e controlado	60		Midazolam
Steuder FR et al., 2012	Prospetivo, randomizado e duplo-cego cruzado	12		Midazolam
Rubina Gupta et al., 2012	Estudo comparativo	30		Midazolam
Pereira-Santos et al., 2013	Controlado, randomizado	28		Midazolam
Megann K Smiley et al., 2014	Randomizado	24		Midazolam
Araújo de Moraes et al., 2015	Ensaio clinico prospetivo, randomizado e duplo-cego	120		Diazepam / Midazolam
LP Dantas et al., 2017	Ensaio clinico cruzado, randomizado, controlado, duplo-cego	40		Midazolam
AG Devello et al., 2018	Ensaio clinico randomizado, duplo-cego, controlado e cruzado.	30		Midazolam
Torun et al., 2019	Estudo clinico duplo-cego, prospetivo e randomizado	90		Midazolam
Farah GJ et al., 2019	Randomizado, boca dividida, design cruzado	20		Midazolam
Da Cunha et al., 2020	Ensaio clinico randomizado, controlado, triplo-cego e paralelo	200		Midazolam
Cavalcanti et al., 2020	Ensaio clinico randomizado, design de boca dividida	25		Diazepam
Sharma et al., 2018	Estudo prospetivo, aleatório e duplo-cego	50		Lorazepam /Diazepam