NITROUS OXIDE OR MIDAZOLAM TO TOOTH EXTRACTION? A SYSTEMATIC REVIEW

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ABSTRACT: Aim: This systematic review aimed to evaluate the use of midazolam and nitrous oxide in conscious sedation for dental extraction procedures. Methods: A search was conducted in electronic searches Medline/PubMed, Embase, Cochrane Library, Web of Science, grey literature, and the main scientific journals in the area, following PRISMA. Booleans operators were used for the combinations of terms and the search strategy was adapted to each of the databases, ("tooth extraction" OR "molar, third" OR "tooth, impacted" OR "surgery, oral" OR "exodontics" OR "wisdom tooth" AND "nitrous oxide" OR "anesthetics, inhalation" OR "conscious sedation" OR "laughing gas" OR "moderate sedation" AND "midazolam" OR "benzodiazepines" OR "hypnotics and sedatives" OR "sedative effect"). Study Selection and Data Extraction: The inclusion criteria were parallel and crossover RCTs involving patients of any age submitted to tooth extraction at a dental office under local anesthesia. No language restrictions have been imposed until 2023. The exclusion criteria were studies involving patients submitted to extraction in the hospital setting, studies that did not measure anxiety or sedation and studies for which the full text was not available. Results: Where within the eight articles that met the eligibility criteria, no significant differences were found between the methods, in relation to sedation or anxiety. Conclusion: In conclusion, nitrous oxide and midazolam safely ensure good levels of sedation and anxiety control, being pharmacological approaches possible to be used in dental care, even in those more invasive such as, tooth extraction.
KEYWORDS: Dental Anxiety; Tooth Extraction; Anesthetics; Conscious Sedation;

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ÓXIDO NITROSO OU MIDAZOLAM PARA EXTRACÇÃO DENTÁRIA? UMA REVISÃO SISTEMÁTICA

RESUMO: Objetivo: Esta revisão sistemática visava avaliar a utilização de midazolam e óxido nitroso na sedação consciente para procedimentos de extração dentária. Métodos: Foi realizada uma pesquisa nas pesquisas electrónicas Medline/PubMed, Embase, Cochrane Library, Web of Science, literatura cinzenta, e nas principais revistas científicas da área, seguindo o PRISMA. Foram utilizados operadores booleanos para as combinações de termos e a estratégia de pesquisa foi adaptada a cada uma das bases de dados, ("extração dentária" OU "molar, terceiro" OU "dente, impactado" OU "cirurgia, oral" OU "exodontia" OU "dente do siso" OU "óxido nitroso" OU "anestésico, inalação" OU "sedação consciente" OU "gás do riso" OU "sedação moderada" OU "midazolam" OU "benzodiazepinas" OU "hipnóticos e sedativos" OU "efeito sedativo"). Seleção do estudo e extração de dados: Os critérios de inclusão foram RCTs paralelos e cruzados envolvendo pacientes de qualquer idade submetidos a extração dentária num consultório dentário sob anestesia local. Não foram impostas restrições linguísticas até 2023. Os critérios de exclusão eram estudos que envolviam pacientes submetidos a extração no ambiente hospitalar, estudos que não mediam ansiedade ou sedação e estudos para os quais o texto completo não estava disponível. Resultados: Nos oito artigos que preenchiam os critérios de elegibilidade, não foram encontradas diferenças significativas entre os métodos, em relação à sedação ou ansiedade. Conclusão: Em conclusão, o óxido nitroso e o midazolam garantem, com segurança, bons níveis de sedação e controle de ansiedade, sendo abordagens farmacológicas possíveis de serem usadas nos cuidados odontológicos, mesmo naqueles mais invasivos como, a extração dentária.
PALAVRAS-CHAVE: Ansiedade Odontológica; Extração Dentária; Anestésicos; Sedação Consciente.

¿ÓXIDO NITROSO O MIDAZOLAM PARA LA EXTRACCIÓN DENTAL? UNA REVISIÓN SISTEMÁTICA

RESUMEN: Objetivo: Esta revisión sistemática pretendía evaluar el uso de midazolam y óxido nitroso en la sedación consciente para procedimientos de extracción dental. Métodos: Se realizó una búsqueda en las bases de datos electrónicas Medline/PubMed, Embase, Cochrane Library, Web of Science, literatura gris y en las principales revistas científicas del área, siguiendo PRISMA. Se utilizaron operadores booleanos para las combinaciones de términos y se adaptó la estrategia de búsqueda a cada una de las bases de datos, ("tooth extraction" OR "molar, third" OR "tooth, impacted" OR "surgery, oral" OR "exodontia" OR "wisdom tooth" OR "nitrous oxide" OR "anaesthetic, inhalation" OR "conscious sedation" OR "laughing gas" OR "moderate sedation" OR "midazolam" OR "benzodiazepines" OR "hypnotics and sedatives" OR "sedative effect"). Selección de estudios y extracción de datos: Los criterios de inclusión fueron ECA paralelos y cruzados que incluyeran pacientes de cualquier edad sometidos a extracción dental en un consultorio dental bajo anestesia local. No se impusieron restricciones de idioma hasta 2023. Los criterios de exclusión fueron estudios que incluyeran pacientes sometidos a extracción en el ámbito hospitalario, estudios que no midieran la ansiedad o la sedación y estudios para los que no estuviera disponible el texto completo. Resultados: En los ocho artículos que cumplían los criterios de elegibilidad, no se encontraron diferencias significativas entre los métodos con respecto a la sedación o la ansiedad. Conclusión: En conclusión, el óxido nitroso y el midazolam garantizan con seguridad buenos niveles de sedación y control de la ansiedad, siendo abordajes farmacológicos posibles de ser

utilizados en la atención odontológica, incluso en aquellas más invasivas como, la extracción dentaria.
PALABRAS CLAVE: Ansiedad Dental; Extracción Dental; Anestésicos; Sedación Consciente.

1. INTRODUCTION

The adrenal stress response is greatest for surgical procedures, such as tooth extraction, and may result in a vasodepressor syndrome, hyperventilation or cause systemic decompensations[1-6] even with the use of anaesthetic drugs and preconditioning[7-10]. Anxiety in dental care could be minimized with guidelines and information on approaches to minimize the painful sensation in more invasive procedures[11].

Conscious sedation is a safe method that provides comfort and minimizes the need for hospitalization[1]. For these purposes, benzodiazepines are considered one of the drug uses of choice. Midazolam is a representative of this group however midazolam sedation is not titratable and has a variable level of absorption in the body and may not achieve the desired level of sedation[3,4,8,9,12,13].

Another method widely used for conscious sedation is nitrous oxide associated with oxygen administered through a face mask, sometimes not accepted by the patient. It is a method that presents rapid onset, titration capacity, low incidence of side effects, and allows a rapid return to normal activities, allowing considerable safety[4,6,8,14]. Then, this systematic review aimed to evaluate the use of midazolam and nitrous oxide in conscious sedation for dental extraction procedures.

2. METHODS

2.1 Study design

The present systematic review of randomized controlled trials (RCTs) was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15-17] and received approval from the institutional review board. (CRD42020181442)

2.2 PICO question

Which method is better for conscious sedation (outcome) in patients submitted to tooth extraction (population): nitrous oxide (intervention) or midazolam (comparison)?

2.3 Eligibility criteria

The inclusion criteria were parallel and crossover RCTs involving patients of any age submitted to tooth extraction at a dental office under local anesthesia in which sedation with nitrous oxide was compared to sedation with midazolam for the control of anxiety, regardless of the administration route employed. No language restrictions have been imposed until 2023. The exclusion criteria were studies involving patients submitted to extraction in the hospital setting, studies that did not measure anxiety or sedation and studies for which the full text was not available.

2.4 Sources of data

Electronic searches were performed in four databases: Medline/PubMed, Embase, Cochrane Library and Web of Science. A search of the grey literature was performed in ClinicalTrials, OpenGrey, Digital Library of Theses and Dissertations (BDTD) and the Brazilian Registry of Clinical Trials (ReBEC). Hand searches were also performed for publications in the main scientific journals in the field of oral and maxillofacial surgery for articles on this topic: *Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery* and *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. Hand searches were also performed of the references cited in the articles included in the present systematic review.

2.5 Search strategy

Searches were conducted using controlled MeSH terms for Medline and Emtree terms for Embase as well as keywords. Booleans operators were used for the combinations of terms and the search strategy was adapted to each of the databases. The following strategy was used in MEDLINE/PubMed: (“tooth extraction” [MeSH Terms] OR “molar, third” [MeSH Terms] OR “tooth, impacted” [MeSH Terms] OR “surgery, oral” [MeSH Terms] OR “exodontics” OR “wisdom tooth”) AND (“nitrous oxide” [MeSH Terms] OR “anesthetics, inhalation” [MeSH Terms] OR “conscious sedation” [MeSH Terms] OR “laughing gas” OR “moderate sedation”) AND (“midazolam” [MeSH

Terms] OR “benzodiazepines” [MeSH Terms] OR “hypnotics and sedatives” [MeSH Terms] OR “sedative effect”).

2.6 Article selection

The articles retrieved from the databases were managed using the EndNote program to remove duplicates and assist in the article selection process, which was performed by two researchers (T.S. and L.B.) in an individual, independent, and blinded manner. After each step, divergences regarding the inclusion or exclusion of a given article were resolved by consensus. In the first step, the titles and abstracts were read to eliminate articles that did not meet the eligibility criteria. Kappa testing was performed as an additional analysis for each database after reading the titles and abstracts to determine the level of agreement between the reviewers. Pre-selected studies were then subjected to full-text analysis with the application of the eligibility criteria.

2.7 Outcomes

Sedation was assessed using the Brietkopf and Buttner classification and the Ramsay Scale, on which a score is attributed to each state of sedation evaluated by the surgeon immediately after the administration of the drug, 40 minutes after administration, after the completion of the procedure and in the recovery room. On both these assessment tools, the most desirable levels of sedation for the execution of dental surgical procedures are scores of 2 and 3. The score chosen was always the highest found throughout the session.

Corah’s Anxiety Scale was used for the assessment of dental anxiety. This scale has scored items that are used to classify patients as non-anxious, mildly anxious, moderately anxious, or extremely anxious. Spielberger’s State-Trait Anxiety Inventory (STAI) was also used for the assessment, which has scored items, the total of which ranges from 20 (mildly anxious) to 80 (extremely anxious). The Children’s Fear Survey Schedule was used in two studies18,19 for the assessment of anxiety, which has scored items, the total of which ranges from 15 to 75 points, with scores of 38 or more associated with clinical fear.

One study8 used the visual analogue scale ranging from 0 (very calm) to 10 (very anxious). Independently of the means of evaluation, anxiety was assessed in the preoperative period and the immediate postoperative period. Vital signs (blood pressure,

oxygen saturation, heart rate and respiratory rate) were measured before, during and after the surgical procedure.

2.8 Data collection

Data extraction was performed by two researchers with the aid of a table. The following items were extracted from each article: author, year of publication, type of study, sample size, demographic variables (sex and age), intervention group and control group, concentration of drugs, midazolam administration route, surgical procedure performed, outcomes investigated, form of assessing outcome, evaluation times and results of evaluations.

2.9 Appraisal of risk of bias

The risk of bias of the randomized clinical trials was appraised with the aid of the Cochrane Risk of Bias 2 (ROB 2) tool[20]. This instrument is used to appraise methodological quality in five domains: Bias arising from randomization process; bias due to deviation from intended intervention; bias due to missing outcome data; bias in measurement of outcome; and bias in selection of reported results. Each study received an overall judgment of high risk, low risk or uncertain risk.

2.10 Data synthesis

A qualitative synthesis of the results was performed for all outcomes of interest. The meta-analysis[21] was not possible for the outcomes due to clinical heterogeneity finding.

2.11 Appraisal of quality of evidence

The appraisal of the quality of the evidence and degree of confidence for each outcome (sedation, anxiety and altered vital signs) was performed using the Grading Recommendations Assessment Development and Evaluation (GRADE) approach[22].

3. RESULTS

3.1 Search results

The searches of the databases led to the retrieval of 784 potentially eligible articles; the search of the Grey Literature led to the retrieval of one potentially eligible article and no articles were found during the hand search, totaling 785 studies. After the

exclusion of duplicates, 662 records were submitted to the first stage of the selection process (reading of titles and abstracts), which led to the exclusion of 644 records. Thus, 18 articles were submitted to full-text analysis. The Kappa test revealed a good level of agreement between the reviewers for each database (K = 0.914 for Cochrane, 0.875 for Medline, 0.821 for Embase and 0.785 for Web of Science). Ten of the articles submitted to full-text analysis were excluded for not meeting the eligibility criteria (supplementary file) and eight were included in the present systematic review as shown in the Prisma Flowchart (Fig 1).

3.2 Study and patient characteristics

The eight clinical trials that composed the present review had a total of 415 male and female patients with ages ranging from five to 65 years. Only two clinical trials reported following the guidelines of the Consolidated Standards of Reporting Trials (CONSORT-statement)[23]; And three studies were performed with adult patients[6,10,24] and the other five involved pediatric patients (Table 1)[8,12,18,19,25].

The intervention groups were submitted to nitrous oxide at concentrations ranging from 30 to 50% in combination with oxygen. The comparison groups were submitted to midazolam with varying concentrations depending on the weight of the patient and different administration routes, leading to clinical heterogeneity. Wilson et al.[12] and Venchard[10] used the intravenous administration of midazolam; Wilson[18] used transmucosal administration and the other studies administered the drug orally[6,8,18,24,25].

The authors recorded the time required for each drug to obtain the maximum level of sedation as well as the time until complete recovery and discharge Except the Venchard[10] that did report only the time to recovery. Nitrous oxide achieved a faster onset of action and faster recovery (Table 2). Therefore, the patients submitted to midazolam had a longer overall appointment, except for the study by Gamba[24], who reported a longer overall appointment in the nitrous oxide group N2O/45 (20-50 minutes) and Midazolam/24 (11-35 minutes).

3.3 Sedation and Anxiety

The patients in both the interventions were adequately sedated for the procedure. Most patients in the nitrous oxide group were maintained with a score of 2, whereas those in the midazolam were maintained with a score of 3. Thus, midazolam achieved greater sedation, including patients with a sedation score of 4 (Table 2). In all studies, anxiety

levels diminished significantly in the postoperative period compared to the preoperative period, independently of the drug employed (Table 3).

3.4 Change in vital signs

No significant difference in blood pressure and in the qualitative analysis of oxygen saturation and respiratory rate were found between the patients. Higher blood pressure was always recorded in the immediate preoperative period, independently of the drug employed and after the administration, blood pressure diminished in both groups (Table 4).

For heart rate, it was possible to observe that the Mhatre study[8] showed higher values for midazolam at the time of surgery. However, it was not possible to perform a meta-analysis of the results due to clinical heterogeneity. A high risk of bias was found regarding the deviation of data from the intended intervention and missing outcomes (Fig 2). Deviation from the intended intervention was found in one study[24], in which the number of patients in each group could not be determined due to lack of notification of dropouts. Missing outcome data were found in two studies[12,25], in which outcomes were demonstrated in graphs and without reporting of standard deviation data.

The articles appraised as having a low risk of bias described adequate randomization and allocation methods and reported all data studied. Regarding the quality of evidence assessed using the GRADE approach, very low quality was found for the anxiety outcome, low quality of evidence was found for the sedation outcome and moderate quality of evidence was found for the outcomes related to vital signs.

4. DISCUSSION

The most common tools for assessing sedation are the Brietkopf and Buttner classification and the Ramsay scale. With both instruments, a score of 2 (patient is awake, cooperative, and calm) and 3 (patient responds to commands, drowsy and inactive) are the most desirable for extractions performed in the dental office, as the patient is able to respond to the surgeon's command and therefore can help during surgery by opening the mouth or turning the head when requested, while remaining calm and sufficiently relaxed, avoiding interference from anxiety.

In the qualitative analysis of the included articles, midazolam achieved a score of 4 (the patient is drowsy, without reactions, responding only to touches on the glabellum); reaching deeper levels of sedation, which should be considered with caution as it may

offer risk. Nitrous oxide, on the other hand, allows an assessment of the depth of sedation; it can be titrated and adjusted, thus avoiding overdosage and allowing greater control over the patient's level of sedation[10,26]. In the evaluation by GRADE there is a low degree of confidence for the result, demonstrating the need for more clinical trials and standardization in the assessment measures.

As regards the times required to achieve maximum sedation and recovery, a greater speed was found with nitrous oxide. On average, the time required to achieve maximum sedation with nitrous oxide is approximately 5 minutes, and 30 minutes for midazolam; and the recovery time on average is 30 minutes with nitrous oxide compared to 60 minutes with midazolam[27]. A fact can be justified by nitrous oxide being a poorly soluble gas with minimal metabolization.

In addition to these characteristics, it was possible to compare both drugs as to route of administration and patient acceptance. Administration requires only a nasal mask, offering no bad taste, does not require venous access, and because it concomitantly offers oxygen, it guarantees the maintenance of adequate saturation levels[14]. Midazolam may use the route which offers a fast onset, but has the inconvenience of requiring venous access, which is seen as a negative point by patients. As well as the oral route, with the inconvenience of the taste, and the transmucosal route which presents as an adverse effect, increased salivation.

Five of the studies included in this review involved pediatric patients, where one of the major concerns is the risk of adverse effects, such as respiratory depression and the paradoxical reaction, with midazolam. The safety profile in patients up to 17 years of age is achieved when the ideal concentration for the patient's weight is respected[12]. Thus, nitrous oxide is accepted as a safe form of sedation for this age group[25].

Using the GRADE to assess the issue of anxiety a "very low" level of evidence was observed, probably a reflection of the heterogeneity of the studies. A standardization of methods and assessment times are important, as they will allow a homogeneous comparison of studies, and more reliable results[1]. Controlled clinical trials with uniformity in evaluation are necessary to allow more reliable estimation of effects.

The use of these drugs precedes a preoperative clinical evaluation of the patients because scientific evidence shows that the use of midazolam is associated with a reduction in blood pressure[6] and an increase in heart rate[9]. In the present review, despite the heterogeneity of the sample that prevented a meta-analysis, this influence was noticeable, but oxygen saturation and respiratory rate remained within the normal range[6,8,12,24,25]. For

this result the level of evidence regarding outcome related to vital signs was considered moderate using the *GRADE* approach.

Another form of administration would be the combination of midazolam and nitrous oxide to achieve more efficient sedation[10]. For Sivaramakrishnan[28] this association allowed a lower dose of midazolam and a faster recovery of the patient. However, the combination of midazolam and other drugs is risky and requires stricter monitoring[3]. In the present review, the response to midazolam and nitrous oxide was performed independently, and both ensured adequate sedation.

5. CONCLUSION

In conclusion, nitrous oxide and midazolam safely ensure good levels of sedation and anxiety control, being pharmacological approaches possible to be used in dental care, even in those more invasive such as, tooth extraction. However, midazolam proved to have a more profound level of sedation and less control over heart rate, which requires more attention and control in vital signs.

The review considers that the use of safe drugs that provide better anxiety control for people who fear more invasive dental procedures represents a continuous search for more humanized care and concern for the well-being of patients.

The meta-analysis was not possible for the results due to the finding of clinical heterogeneity. With this result, there is a need for more studies, with more established methodologies, are carried out in order to enable greater scientific evidence of drugs that present a greater control of anxiety in dental care, and less predisposition to adverse effects

ETHICAL APPROVAL

Not applicable

COMPETING INTERESTS

The authors declare no conflict of interest.

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AVAILABILITY OF DATA AND MATERIALS

The data listed for this systematic review are available to anyone interested.

PATIENT CONSENT

Not applicable.

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ANEXOS

Figure legends:

Table 1 – Qualitative description of articles included in present review

Author/ year/ type of study	Number of patients (N)	Age and sex	Intervention Group	Control Group	Procedure	Outcome studied	Outcome assessment method	Results
WILSON *et al.* 2002[18] Randomized controlled crossover clinical trial	46	10-16 years Male: 16 Female: 30	Inhaled N20 30% + 70% O2	Midazolam oral 0.5mg/kg	Extraction of 4 teeth for orthodontic reasons	Sedation	Brietkopf & Buttner classification	Midazolam achieved deeper level of sedation. Patients less anxious at first appointment and more anxious at second appointment regardless of sedation method.
						Anxiety	Spielberger's State-Trait Anxiety Inventory + Children's Fear Survey Schedule.	Greater reduction: patients had received nitrous oxide at first visit.
						Tempo	Calculation of time of onset of action and recovery	Faster effect and recovery with N2O.
WILSON *et al.* 2003[12] Randomized controlled, crossover clinical trial	40	12- 16 Years Male: 10 Female: 30	Inhaled N20 30% + 70% O2	Midazolam I.V.: 0.5mg/min, with maximum of 5mg. Mean dose of midazolam: 2.8mg	Extraction of 4 teeth for orthodontic reasons	Sedation	Brietkopf & Buttner classification	Midazolam achieved deeper sedation. All patients less positive about type of sedation at second visit, regardless of method.
						Time	Calculation of time of onset of action and recovery	Both drugs had fast onset. Faster recovery with N2O
VENCHARD *et al.* 2006[10] Randomized controlled trial	40	16-65 years	Inhaled N20 40% + 60% O2, if not sufficient, increments of 5% until maximum of 55% N2O 20 patients	Midazolam I.V.: 2mg slow, increments of 1mg per min until reaching level of sedation. 20 patients	Simple and complex extractions	Anxiety	Corah's Anxiety Questionnaire	
						Vital signs	Reading of vital signs	Lower saturation level with Midazolam, but without significant difference
						Time	Calculation of time of onset of action and recovery	Shorter surgery time with N2O Faster recovery with N2O
WILSON *et al.* 2006[25]	35	5-10 years	Inhaled N20 30% + 70% O2	Midazolam oral: 0.3mg/kg	Extraction of 4 primary teeth	Sedation	Brietkopf & Buttner classification	Midazolam achieved deeper level of sedation.
						Time	Calculation of time of onset of action and recovery	Faster onset of action and recovery with N2O

Prospective, Randomised controlled crossover clinical trial				Mean dose of midazolam: 8.6mg			
WILSON *et al.* 2007[19] Randomized-cross-over clinical trial	36	10-16 years Male: 10 Female: 26	Inhaled N20 30% + 70% O2	Midazolam - transmucosal (EPISTAT): 0.2mg/kg- 2 min in mucosa Mean dose of midazolam: 10mg	Extraction of 4 teeth for orthodontic reasons	Sedation	Brietkopf & Buttner classification	Similar level of sedation
						Anxiety	Spielberger's State-Trait Anxiety Scale Children's Fear Survey Schedule Dental Subscale	Significant different in preoperative and postoperative anxiety, regardless of sedation method.
GAMBA, 2008[24] Randomized clinical trial	100	40-60 years Male: 52 Female: 48	N2O: increments of 5-10% every 2 min until ensuring adequate sedation. Mean dose of N2O: 55%	Midazolam oral: 7.5mg	Extraction of three maxillary teeth	Anxiety	Corah's Anxiety Scale	Higher concentration of N2O compared to most studies Procedure time longer with N2O (time with patient in chair)
						Vital signs	Reading of vital signs	N2O ensure lower blood pressure. Midazolam ensured lower heart rate and respiratory rate
						Time	Calculation of time of onset of action, recovery time and total time of appointment	Total appointment time lower with N2O
MHATRE *et al*, 2018[8] Randomized clinical trial	40	5- 12 years	Inhaled N20 50% + 50% O2 (increments of 10%)	Midazolam oral 0.5mg/kg	Extraction of compromised teeth (decayed), alternating methods	Sedation	Ramsay sedation scale.	Midazolam achieved deeper level of sedation.
						Anxiety	Visual analog scale de anxiety.	Lower postoperative level of anxiety with N2O
						Tempo	Calculation of time of onset of action and recovery	Faster time to onset of action and recovery with N2O.
DE MOARES *et al.* ,2019[6] Randomized clinical trial	80	18 - 30 years	Inhaled N20 40% + 60% O2	Midazolam oral: 7.5mg	Extraction of upper third molar	Anxiety	Corah's questionnaire. Visual analog scale de anxiety.	Difference in mean at first appointment and end of surgery for both sedation methods. No significant difference between methods.
			40 patients	40 patients		Altered vital signs	Reading of vital signs	No significant difference between methods

Table 2- Duration and level of sedation of session in nitrous oxide and midazolam groups

AUTHOR/ YEAR	NUM-BER OF PA-TIENTS(N)	TIME TO MAXIMUM SEDATION		MAXIMUMM LEVEL OF SEDATION		ASSESSMENT TOOL	TIME TO RECOVERY		TOTAL TIME OF AP-POINTMENT	
		N2O	**MIDAZO-LAM**	**N2O**	**MIDAZOLAM**		**N2O**	**MIDAZO-LAM**	**N2O**	**MIDAZO-LAM**
WILSON *et al*, 2002[18]	46	5(5-10)	20(5-65)	Score 1: 1 patient Score 2: 37 patients Score 3: 8 patients	Score 2: 1 patient Score 3: 24 patients Score 4: 21 patients	Brietkopf and Buttner Classification	20(20-25)	42.5(15-90)	-	-
WILSON *et al*, 2003[12]	40	6 (2-18)	8 (4 - 20)	-	-	-	23.3 +/- 2.58	51.6 +/- 6.61	-	-
VENCHAD *et al*, 2006[10]	40	10	54	-	-	-	-	-	-	-
WILSON *et al*, 2006[25]	35	6.8 (2-10)	15.9(2-30)	-	-	-	-	-	33.2(24-65)	74.8(60-100)
WILSON *et al*, 2007[19]	36	7.1(2-10)	14.4(2-20)	Score 3: 35 patients	Score 3: 36 patients	Brietkopf and Buttner Classification	-	-	34.1(28-44)	64.7(60-90)
MHATRE *et al*, 2018[8]	40	1.98 +/- 0.73	23.3 +/- 4.42	Score 1: 12 patients Score 2: 26 patients Score 3: 2 patients	Score 1: 6 patients Score 2: 27 patients Score 3: 6 patients Score 4: 2 patients	Ramsay Sedation Score	73.83 +/- 36.15	130.63 +/- 33.74	-	-

TIME TO MAXIMUM SEDATION, TIME TO RECOVERY AND TOTAL TIME OF APPOINTMENT IN MINUTES

Table 3- Level of anxiety at different evaluation times in nitrous oxide and midazolam groups

AUTHOR/ YEAR	NUMBER OF PA-TIENTS(N)	EVALUATION TIME		ASSESSMENT TOOL
		N2O	**MIDAZOLAM**	
WILSON *et al*, *2002*[18]	46	1st surgery: 30(15-46) 2nd surgery: 26(15-43) 1st Surgery: 44 (20-67) 2nd Surgery: 35 (20-64)	1st surgery: 32(17-61) 2nd surgery: 30(15-59) 1st Surgery: 47 (23-73) 2nd Surgery: 40 (20-68)	Children's Fear Survey Schedule Spielberger's State-Trait Anxiety Inventory

VENCHARD *et al*, 2006[10]	40	Before surgery: Mean: 15.48 (5-20) (extremely anxious)		Corah's Anxiety Scale
WILSON *et al*, 2007[19]	36	Before: 31.9 (15-61) After: 27.1 (15-52)		Children's Fear Survey Schedule
		Before: 45.5 (20-73) After: 39.4 (20-66)		Spielberger's State-Trait Anxiety
GAMBA *et al*, 2008[24]	100	Before surgery: -19 patients mildly anxious -50 patients moderately anxious -31 patients extremely anxious		Corah's Anxiety Scale
MHATRE *et al*, 2018[8]	40	Before: 6.09+/-1.18 After: 4.10+/-0.79	Before: 6.09+/-1.18 After: 4.93+/-1.21	Visual analog scale for anxiety
DE MOARES *et al*, 2019[6]	80	Before: 14.5 +/- 2.2 After: 11.7+/-2.1	Before: 14.5 +/- 2,2 After: 11.5 +/-1,8	Corah's Anxiety Scale

Table 4- Vital signs at different evaluation times in nitrous oxide and midazolam groups

AUTHOR/ YEAR	NUMBER OF PATIENTS (N)	EVALUATION TIME	MEAN BLOOD PRESSURE		OXYGEN SATURATION		HEART RATE (BPM)		RESPIRATORY RATE	
			N2O	**Midazolam**	**N2O**	**Midazolam**	**N2O**	**Midazolam**	**N2O**	**Midazolam**
			(N=20)	(N=20)						
WILSON *et al*, 2003[12]	40	Initial	84.9 (65.6-115.3)	83.3 (65.6-102.3)	97 (92-100)	97 (91-99)	82.2 (59-117)	84.5 (55-117)	19.2 (14-26)	18.3 (14-24)
		Adm of sedation	81.0 (67.1-95.3)	79.2 (60.3-93.6)	100 (97-100)	98 (92-100)	82.0 (56-119)	83.3 (53-115)	18.3 (14-24)	18.6 (14-22)
		Surgery	78.2 (65.8-94.5)	79.4 (67.9-90.2)	100 (97-100)	98 (91-100)	87.6 (62-126)	92.2 (72-122)	19.3 (14-27)	19.0 (14-22)
		Final	79.5 (65.6-93.2)	79.4 (67.7-92.9)	99 (94-100)	99 (94-100)	78.2 (60-99)	83.0 (65-120)	18.5 (14-24)	18.6 (14-22)
		Discharge	78.4 (64.3-91.0)	80.1 (62.0-99.6)	97 (92-100)	97 (92-100)	77.4 (63-106)	82.7 (62-120)	18.2 (12-24)	18.4 (14-22)
			(N=35)	(N=35)						
WILSON *et al*, 2006[25]	35	Initial	77.3 [62–113]	77.9 [63.3–93.3]	99 [96–100]	98 [95–100]	83.7 [58–123]	82.2 [53–107]	20.0 [16–24]	19.6 [16–24]
		Maximum sedation	75.7 [63–100]	75.5 [58–92.6]	100 [97–100]	98 [95–100]	79.8 [56–122]	81.6 [64–104]	20.0 [16–22]	19.4 [16–22]
			75.7 [63.3–92.3]	75.9 [62–100.6]	100 [98–100]	99 [96–100]	82.2 [57–113]	83.2 [60–111]	19.8 [16–24]	19.8 [16–22]
		Local anesthetic	76.7 [59.6–93]	74.9 [63–89.3]	100 [98–100]	99 [96–100]	85.4 [63–109]	93.5 [66–118]	19.9 [16–24]	19.6 [16–22]
		Surgery	76.7 [59.6–93]	74.0 [60.3–86.6]	100 [96–100]	99 [95–100]	81.5 [57–106]	90.1 [57–113]	19.8 [16–24]	19.4 [16–22]
		Final	76.8 [62–95.6]	75.9 [57.6–97.6]	98 [96–100]	98 [95–100]	84.8 [59–123]	87.6 [71–109]	20.0 [14–26]	19.2 [16–20]

		Discharge							
			(N=100)	(N=100)					
		Initial	106.6	106.6	96 (96-97)	96 (96-97)	105.5 (100-113)	108 (100-114)	23 (22-24)	23 (22-24)
		Before entering	100	100	-	-	104 (100-111)	72 (68-75)	23 (22-24)	16.5 (16-18)
GAMBA *et al*, 2008[24]	100	In chair	100	100	96 (96-97)	96 (96-97)	74.5 (70-81)	72 (68-75)	16.5 (16-18)	16.5 (16-18)
		After local anesthetic	100	100	100 (99-100)	94 (93-95)	72 (67-75)	72 (68-75)	16.5 (16-18)	14 (14-15)
			100	100	100 (99-100)	94 (93-95)	68 (65-72)	72 (68-75)	16 (15-17)	14 (14-15)
		Surgery	100	100	97 (97-99)	94 (93-95)	68 (65-72)	72 (68-75)	17 (16-18)	14 (14-15)
		Final								
			(N=40)	(N=40)						
		Initial	72.53+/-6.4	71.3+/-7.38	98.53 +/- 1.26	98.58 +/- 0.84	92.3 +/- 13.4	92.23 +/- 12.23	23.6 +/- 2.87	24.23 +/- 3.21
		Maximum sedation	71.9+/-7.28	69.53+/-7.8	99.28 +/- 0.88	98.85 +/- 1.69	92.08 +/- 13.78	90.7 +/- 10.17	24.75 +/- 3.41	23.85 +/- 3.75
MHATRE *et al*, 2018[8]	40		74.13+/-8.02	75+/-0.89	98.98 +/- 0.92	98.73 +/- 1.55	94 +/- 14.66	97.28 +/- 14.04	26.25 +/- 3.04	25.7 +/- 4.52
		Local anesthetic	75.28+/-9.98	72.95+/-9.48	99.15 +/- 0.95	98.75 +/- 1.66	98.68 +/- 15.24	105.43 +/- 15.09	25.75 +/- 3.63	25.5 +/- 3.5
		Surgery	73.63+/-9.54	70.73+/-8.47	99 +/- 0.93	99.18 +/- 0.68	98.4 +/- 13.61	101.55 +/- 12.95	25.6 +/- 3.01	24.2 +/- 4.05
		Final	71.6+/-7)	72.08+/-8.64	98.85 +/- 0.95	98.95 +/- 1.36	93.35 +/- 12.79	93.35 +/- 13.3	24 +/- 2.81	24.33 +/- 3.53
		Discharge								
			(N=40)	(N=40)					-	-
		Initial	83.71	83.76	97.25 +/- 1.90	97.00 +/- 2.26	81.92 +/- 11.28	82.56 +/-13.82		
DE MOARES *et al*, 2019[6]	80	Surgery	73.61	77.39	98.31 +/- 1.13	97.22 +/- 3.87	77.59 +/- 11.34	80.86 +/- 12.47		
		Final	77.16	77.37	98.02 +/- 1.83	97.90 +/- 1.80	76.56 +/- 13.08	80.85 +/- 13.08		
		Discharge	84.04	83.62	97.85 +/- 1.52	98.22 +/- 1.69	77.20 +/- 11.15	79.56 +/- 13.94		