Evaluation of cyclobenzaprine sedative effects in third molar surgeries: pilot study

Avaliação dos efeitos sedativos da ciclobenzaprina em cirurgias de terceiros molares: estudo piloto

Evaluación de los efectos sedantes de ciclobenzaprina en cirugías de terceros molares: estudio piloto

Thaísa Tamires Fortaleza Spinelli de Freitas
ORCID: 0000-0003-4099-8568
DDS, Oral and Maxillofacial Surgeon at private practice. Recife, Pernambuco, Brazil.
E-mail: thaisa.spinelli@hotmail.com

Emerson Filipe de Carvalho Nogueira
ORCID: 0000-0002-4560-7733
DDS, MSc. Department of Oral and Maxillofacial Surgery, University of Pernambuco. Pernambuco, Brazil.
E-mail: emersonctbmf@gmail.com

Marcelo Soares dos Santos
ORCID: 0000-0001-7262-6035
DDS, MSc. Department of Oral and Maxillofacial Surgery, University of Pernambuco. Pernambuco, Brazil.
E-mail: marcelo.sd.soares@gmail.com

Victor Hugo Nogueira Moura
ORCID:0000-0001-7569-7955
DDS, private practice. Recife, Pernambuco, Brazil.
E-mail: victorhugo_moura@hotmail.com

João Victor Mesquita Souza Santos
ORCID: 0000-0002-0005-2447
DDS, resident at Oral and Maxillofacial Surgery at Hospital Oswaldo Cruz. Recife, Pernambuco, Brazil.
E-mail: joao_santos11@outlook.com.br

Ricardo José de Holanda Vasconcellos
ORCID: 0000-0002-7934-5743
DDS, MSc, PhD. Department of Oral and Maxillofacial Surgery, University of Pernambuco. Pernambuco, Brazil.
E-mail: ricardo.holanda@upe.br

ADDRESS CORRESPONDENCE
Emerson Filipe de Carvalho Nogueira
University of Pernambuco, Av General Newton Cavalcanti, 1650, 54753-220 Camaragibe, Pernambuco, PE, Brazil;
Phone: + 55 (81) 3184-7659
+ 55 (81) 3184-7660
E-mail: emersonctbmf@gmail.com

ABSTRACT

Background: Patients with anxiety require the use of special methods to enable dental treatment, in order to minimize the stress of the professional in relation to the patient, besides making the procedure more comfortable. The aim this research was evaluate of the sedative effectiveness of the muscle relaxant, Cyclobenzaprine Hydrochloride 10mg in patients submitted to removals of third molars. **Material and methods:** A randomized, triple-blind, placebo-controlled clinical trial involving 10 patients was conducted. Participants received 10mg of Cyclobenzaprine or placebo given the night before and 1 hour before surgery. The split-mouth method was used, and for each patient two third molars were removed, in two different surgical times. Anxiety was evaluated subjectively through scales. **Results:** Patients presented scores that showed low dental anxiety and slightly reduced pressure variables. The Verbal Anxiety Scale presented lower values for cyclobenzaprine (1.20 ± 0.92) compared to placebo (1.30 ± 1.06), suggesting a reduction in anxiety level. The Visual Analogue Scale did not present reduced values for cyclobenzaprine (3.51 ± 2.38) compared to placebo (3.20 ± 2.36) or baseline (3.42 ± 2.35). The Spielberger Inventory presented higher results for cyclobenzaprine (40.5) when compared with placebo (39.00). The Trieger Test showed higher results and longer execution time when patients took cyclobenzaprine, suggesting a greater cognitive alteration when submitted to sedation by muscle relaxant. However, there was no statistically significant difference between the analyzed variables. **Conclusions:** The use of Cyclobenzaprine was not effective in the control of anxiety in patients submitted to third molar extraction. **Keywords:** Anxiety; Oral Surgery; Third Molar Tooth

RESUMO

Introdução: Pacientes com ansiedade requerem a utilização de métodos especiais para viabilizar o tratamento odontológico, a fim de minimizar o estresse do profissional em relação ao paciente, além de tornar o procedimento mais confortável. O objetivo desta pesquisa foi avaliar a eficácia sedativa do relaxante muscular Cloridrato de Ciclobenzaprina 10mg em pacientes submetidos a exodontias de terceiros molares. **Materiais e métodos:** Foi realizado um ensaio clínico randomizado, triplo-cego, controlado por placebo envolvendo 10 pacientes. Os participantes receberam 10mg de ciclobenzaprina ou placebo na noite anterior e 1 hora antes da cirurgia. Foi utilizado o método de boca dividida, e para cada paciente foram removidos dois terceiros molares, em dois tempos cirúrgicos diferentes. A ansiedade foi avaliada subjetivamente por meio de escalas. **Resultados:** Os pacientes apre-

ISSN 1808-5210 (Online)
ISSN 1679-5458 (Linking)

sentaram escores que mostraram baixa ansiedade odontológica e variáveis de pressão ligeiramente reduzidas. A Escala Verbal de Ansiedade apresentou valores menores para ciclobenzaprina (1,20 ± 0,92) em relação ao placebo (1,30 ± 1,06), sugerindo redução do nível de ansiedade. A Escala Visual Analógica não apresentou valores reduzidos para ciclobenzaprina (3,51 ± 2,38) em relação ao placebo (3,20 ± 2,36) ou basal (3,42 ± 2,35). O Inventário de Spielberger apresentou resultados superiores para a ciclobenzaprina (40,5) quando comparado ao placebo (39,00). O Teste de Trieger apresentou resultados superiores e maior tempo de execução quando os pacientes tomaram ciclobenzaprina, sugerindo maior alteração cognitiva quando submetidos à sedação por relaxante muscular. No entanto, não houve diferença estatisticamente significativa entre as variáveis analisadas. **Conclusões:** O uso da Ciclobenzaprina não foi eficaz no controle da ansiedade em pacientes submetidos à extração de terceiros molares. **Palavras-chave:** Ansiedade; Cirurgia Bucal; Terceiro Molar.

RESUMEN

Introducción: Los pacientes con ansiedad requieren el uso de métodos especiales que permitan el tratamiento odontológico, con el fin de minimizar el estrés del profesional en relación con el paciente, además de hacer más cómodo el procedimiento. El objetivo de esta investigación fue evaluar la eficacia sedante del relajante muscular Ciclobenzaprina Clorhidrato 10 mg en pacientes sometidos a extracciones de terceros molares. **Material y métodos:** Se realizó un ensayo clínico aleatorizado, triple ciego, controlado con placebo en 10 pacientes. Los participantes recibieron 10 mg de ciclobenzaprina o placebo la noche anterior y 1 hora antes de la cirugía. Se utilizó el método de boca dividida, y para cada paciente se extrajeron dos terceros molares, en dos tiempos quirúrgicos diferentes. La ansiedad se evaluó subjetivamente a través de escalas. **Resultados:** Los pacientes presentaron puntajes que mostraron ansiedad dental baja y variables de presión levemente reducidas. La Escala de Ansiedad Verbal presentó valores más bajos para la ciclobenzaprina (1,20 ± 0,92) en comparación con el placebo (1,30 ± 1,06), lo que sugiere una reducción en el nivel de ansiedad. La Escala Visual Analógica no presentó valores reducidos para ciclobenzaprina (3,51 ± 2,38) en comparación con placebo (3,20 ± 2,36) o basal (3,42 ± 2,35). El Inventario de Spielberger presentó resultados superiores para la ciclobenzaprina (40,5) en comparación con el placebo (39,00). El Test de Trieger mostró mayores resultados y mayor tiempo de ejecución cuando los pacientes tomaban ciclobenzaprina, sugiriendo una mayor alteración cognitiva cuando se sometían a sedación con relajante muscular. Sin embargo, no hubo diferencia estadísticamente significativa entre las variables analizadas. **Conclusiones:** El uso de Ciclobenzaprina no fue efectivo en el control de la ansiedad en pacientes sometidos a extracción de terceros molares. **Palabras clave** Ansiedad; Cirugía Bucal; Tercer Molar.

INTRODUCTION

Not only is dental anxiety a psychologically traumatic experience, it is also a frequent disorder that ranges from a suppressed fear of pain to a phobia, which can lead to unpleasant situations for the patient and the professional. According to Malamed, "going to the dentist" ranks second among the most frequent fears of the population. It should be noted that 75% of the medical emergencies at the dental clinics are related to anxiety, and that their incidence has increased in recent years, as well as the judicial demands for negligence in attention to these cases[1].

Patients with anxiety require the use of special methods to enable dental treatment, in order to minimize the stress of the professional in relation to the patient, besides making the procedure more comfortable[2]. For these reasons, sedative procedures have attracted the attention of dentist surgeons and researchers. "Minimal sedation" is a drug-induced condition in which patients respond normally to verbal commands, whereas cardiovascular systems and spontaneous breathing are not affected, and have shown satisfactory results in a dental environment[3]. The use of anxiolytic drugs favors patient cooperation during dental treatment because they act by minimizing stress, in addition to facilitating the work of the dentist leading to satisfactory results.

Cyclobenzaprine Hydrochloride is a central muscle relaxant that has been widely used for over 40 years to treat tension headache, fibromyalgia, and muscle spasms of the lumbar and cervical regions. This medication does not present reports of association with symptoms of dependence after abrupt withdrawal from long-term administration, and is well tolerated by the body, with few adverse effects reported in the literature[1]. Although drowsiness is described as one of the most frequent side effects of this medication, there are still no studies that measure this effect, nor research studies that use this drug for this purpose in oral surgeries.

ISSN 1808-5210 (Online)
ISSN 1679-5458 (Linking)

In this way, this research evaluated the effects of Cyclobenzaprine, with the aim of trying to provide the dentist surgeon with a new option in the control of anxiety and sedation of patients who will undergo oral surgeries.

MATERIAL AND METHODS

An analytical study was performed, of the type randomized clinical trial, of dependent and triple blind samples, where the patient, the surgeon and the evaluator of the results were unaware of the medication used in each case. The research was carried out at the Center for Clinical Research in Maxillofacial Surgery and Traumatology of the Dentistry School of Pernambuco. This research was approved by the Research Ethics Committee of the institution under the number 2.197.230, where all the patients were informed about the research content and signed a free and informed consent term. Patients with planned bilateral extraction of third molars were selected. These patients should have the same number of teeth on each side and similar angulation and degree of inclusion in relation to the classification of Pell and Gregory.

The masking of the drugs was performed and the medications received a codification, and this fact was known only by one professional who did not participate directly in the research. The pills were handled in a handling pharmacy and had standardized outer color and size. They were packed into containers of the same color and were randomly allocated to form the groups and randomized using the RANDOM.ORG program. Each patient underwent two surgical procedures, with the extraction of the same number of teeth on each side during each session.

The patient was asked to complete the identification form and to answer the questionnaire proposed by Corah, which evaluates "dental anxiety" by four questions with five alternatives. Score less than 11 indicates low anxiety, between 11 – 15 moderate anxiety and greater than 15 indicates high anxiety. This step was followed by the Spielberger questionnaire which assesses state anxiety (STAI-S), whose final score ranges from 20 to 80. Individuals were considered to have high or low state anxiety if the score was greater than 49 and less than 33 respectively[4]. Subsequently, the patient responded to the Verbal Anxiety Scale, whose value ranges from zero to four, where zero means no anxiety, and four severe anxiety. He also responded to the Visual Anxiety Scale which ranges from 0 to 100mm, so that the patient can express the intensity of his anxiety, where zero means no anxiety and 100 means severe / intense anxiety.

Finally, the Trieger Test was applied to the patient, which corresponds to a motor cognition test. The Trieger Test consists in connecting dots of a pre-established figure that was applied in two moments: in the initial consultation and in the immediate preoperative period after the use of the randomized medication. The results were compared on the basis of the number of missed points and the time taken to complete the dots.

The first surgical intervention took place two weeks after the initial consultation. During the surgical procedure, all patients underwent local anesthesia with articaine 4% associated with epinephrine 1:200,000, obeying routine procedures for third molar extraction. The second extraction was performed three weeks after the first surgical intervention, following the same protocol previously used.

A database was generated and analyzed in the statistical package SPSS version 23 (Statistical Package for the Social Sciences). F (ANOVA) test for repeated measurements or the Friedman test were used for the comparison between baseline and the conditions of placebo and Cyclobenzaprine. The tests paired t-Student or Wilcoxon were used for the evaluated variables only in conditions A and B. The margin of error used in the statistical test decisions was 5%. The "p" values less than 0.05 were considered statistically significant.

RESULTS

A total of 10 patients, 8 females and 2 males, ranging in age from 16 to 28 years, were the sample of the research. The authorization of those responsible was obligatory, allowing the participation of patients under the age of 18. However, 3 of these patients did not return to the second surgery to remove contralateral third molars.

With the values obtained in the initial consultation, the patients showed an average score of 7.40 on the Corah Scale and in addition the systolic and diastolic blood pressure variables were slightly reduced, 115.00 and 75, 00 respectively (Table 1). The Verbal Scale showed lower values for cyclobenzaprine (1.20 ± 0.92) compared to placebo (1.30 ± 1.06), while the Visual Scale had a higher average value for cyclobenzaprine (3.51 ± 2.38) compared to placebo (3.20 ± 2.36) and baseline (3.42 ± 2.35). The Spielberger Inventory showed higher results for cyclobenzaprine (40.5) compared to placebo (39.00) (Table 2), and the average time of execution of the questionnaire was higher when patients were under the effect of cyclobenzaprine,

(approximately 1.55 minutes) compared to placebo (1.39 minutes). However, for the fixed margin of error (5%), no statistically significant difference was found between the three evaluations in any of the analyzed variables.

Table 1 - Statistics of the evaluated variables only at the baseline: systolic blood pressure, diastolic blood pressure and Corah-anxiety scale.

Variable	Mean ± DP (Median)
Systolic blood pressure	115,00 ± 9,26 (115,00)
Diastolic blood pressure	75,00 ± 9,26 (75,00)
Corah-anxiety scale	7,40 ± 3,44 (6,50)

It was also observed that the average of the Trieger Test variable presented a higher score when patients took Cyclobenzaprine (73.00) than placebo (62,00), in addition the average time to the execution of the test when under they were under muscle relaxant effect was 1.38 minutes and when under placebo effect was 1.31 minutes (Table 2). However, the differences between the results obtained were not statistically relevant (P> 0.5).

Table 2 - Statistics of the numeric variables according to the condition.

Variable	Baseline Mean ± DP	Placebo Mean ± DP	Cyclobenzaprine	p-valor
Visual scale – anxiety	3,42 ± 2,35 (2,85)	3,20 ± 2,36 (3,30)	3,51 ± 2,38 (3,45)	p (1) = 0,851
Verbal sclale	1,30 ± 0,95 (1,00)	1,30 ± 1,06 (1,50)	1,20 ± 0,92 (1,00)	p (1) = 0,959
I. Spiel-anxiety	41,60 ± 4,50 (43,00)	40,20 ± 5,71 (39,00)	40,00 ± 4,83 (40,5)	p (1) = 0,471
I.SPIEL time (min)	2,15 ± 1,36 (1,83)	1,67 ± 0,87 (1,39)	1,72 ± 0,58 (1,55)	p (1) = 0,437
T.TRIEGER-motor coordination	75,20 ± 18,90 (72,00)	59,70 ± 15,81 (62,00)	78,10 ± 28,31 (73,00)	p (1) = 0,064
T. Trieg time – baseline (min)	1,58 ± 0,70 (1,40)	1,63 ± 1,00 (1,31)	1,56 ± 0,92 (1,38)	p (1) = 0,803

(1) test F (ANOVA) for repeated measurements.

DISCUSSION

Fear and anxiety are common symptoms observed in patients in the preoperative period. According to studies[5], it was observed that anxiety is an extremely important factor to be considered during the removal of impacted third molars, as well as age, impaction depth, tooth angulation and proximity of the root canal, dental anxiety is also related to the degree of surgical difficulty, which can generate behavioral alterations of the patients. In addition, patients with a high degree of trace or state anxiety tend to require longer surgery time and have a slower postoperative recovery[6].

Cyclobenzaprine Hydrochloride is a centrally acting muscle relaxant that has been widely used to relieve muscle spasms associated with acute and painful musculoskeletal conditions[1,7]. Borenstein and Scott[8] collected the results of two clinical trials which evaluated three therapeutic regimens for the treatment of muscular pain with the use of cyclobenzaprine hydrochloride, and concluded that the often used therapeutic regimen of 10mg three times a day is effective in the improvement of muscle spasms, reduction of local pain and sensitivity, and increased range of motion. In addition, sedation was the most common adverse event associated with the use of this drug at the usual dosage of 10mg. However, cyclobenzaprine is generally well tolerated and has been associated with few serious adverse effects. In this research, the same dosage of 10mg was used and no significant change was observed in somnolence of the evaluated sample.

Adverse effects on other anxiolytic drugs, such as benzodiazepines, are rare conditions, but some undesirable effects may be reported, such as drowsiness, excessive sedation, disturbance of motor coordination, confusion and transient loss of memory[9]. These adverse effects were not found in our research.

In the present study, according to the results obtained from the Corah Scale applied in the initial consultation, the patients presented on average a score that evidenced low dental anxiety, in addition the pressure variables were slightly reduced. Although the anxiety assessment is quite subjective, when the results of the reapplied tests after the surgical procedure were compared, the Verbal Anxiety Scale presented lower values for cyclobenzaprine compared to placebo, suggesting a reduction in the level of anxiety. The other applied tests presented higher results for cyclobenzaprine compared to placebo, however, it was observed that patients took on average a longer time to respond to the Inventory when they were under the effect of the drug. However, no statistically significant correlations were found between the questionnaires and applied tests to assess dental anxiety.

The Trieger test was used to evaluate the degree of recovery of patients undergoing sedation. When patients took cyclobenzaprine, they had higher results and, in addition, they took longer to execute the test when they were under the effect of muscle relaxant when compared to placebo, suggesting a greater cognitive alteration when submitted to cyclobenzaprine sedation. However,

ISSN 1808-5210 (Online)
ISSN 1679-5458 (Linking)

the differences between the results obtained were also not statistically relevant.

Teixeira and Quesada[9] concluded that the use of benzodiazepines with anxiolytic purpose allows the patient to adapt better to the treatment, treating the symptoms of anxiety, and providing advantages to the dental surgeon such as relaxation of the skeletal muscles, reduction of salivary flow and reflex vomiting, unlike the present study, in which no effectiveness was observed in the control of anxiety by the use of cyclobenzaprine.

CONCLUSION

In our study, although drowsiness was observed as a side effect of cyclobenzaprine, this drug was not effective in controlling the patient's anxiety, since there was no significant difference between the drugs. However, this pilot study included a small sample suggesting that a larger study should be performed, so that more concrete results can be found or maybe alteration of the drug regimen aiming the improvement in anxiolysis.

REFERENCES

1. de Santana Santos T, Calazans AC, Martins-Filho PR et al. Evaluation of the muscle relaxant cyclobenzaprine after third-molar extraction. J Am Dent Assoc. 2011;142(10):1154-62

2. Pereira VZ, Barreto RC, Pereira GS et al. Avaliação dos níveis de ansiedade em pacientes submetidos ao tratamento odontológico. Revista Brasileira de Ciências da Saúde. 2013;17(1):55-64.

3. Chen Q, Wang L, Ge L et al. The anxiolytic effect of midazolam in third molar extraction: a systematic review. Plos One. 2015;10(4).

4. Gorenstein C, Andrade L. Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. Braz J Med Biol Res. 1996;29(4):453-7.

5. Aznar-Arasa L, Figueiredo R, Valmaseda-Castellón E et al. Patient anxiety and surgical difficulty in impacted lower third molar extractions: a prospective cohort study. Int J Oral Maxillofac Surg. 2014;43(9):1131-6.

6. Lago-Mendez L, Diniz-Freitas M, Senra-Riveira C et al. Postoperative recovery after removal of a lower third molar: role of trait and dental anxiety. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108(6):855-60.

7. Winchell GA, King JD, Chavez-Eng CM et al. Cyclobenzaprine Pharmacokinetics, Including the Effects of Age, Gender, and Hepatic Insufficiency. J Clin Pharmacol. 2002;42(1):61-9.

8. Borenstein DG, Scott K. Efficacy of a Low-Dose Regimen of Cyclobenzaprine Hydrochloride in Acute Skeletal Muscle Spasm: Results of Two Placebo-Controlled Trials. Clin Ther. 2003;25(9):1056-73.

9. Teixeira TF, Quesada GAT. Terapia Ansiolítica Para Pacientes Odontológicos. Saúde. 2004;30(1-2):100-3.