

Effect Of Chlordiazepoxide Oral Tablet On Oral Recurrent Bruxism, A Clinical Trial Human Study

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ABSTRACT

Background: Oral recurrent bruxism is the most common disease of the oral cavity. The underlying etiology remains unclear, and no curative treatment is available. Chlordiazepoxide is essential and useful as anti-anxiety, sedative, appetite-stimulating and weak analgesic actions substance, which recent evidence indicates its involved in emotional responses.

Objectives: The present study aimed to use systemic drug such as Chlordiazepoxide oral tablet (5mg). Illnesses related to the oral bruxism by studying its effects in oral recurrent bruxism, this systemic therapy is not indicated in such situation among other drugs.

Methods: In this study patients presented with oral recurrent bruxism were treated with Chlordiazepoxide oral tablet (5mg) administered orally once daily after night meal. The dispersible tablet was administered orally once daily for 10 days, 66 participants, 7 were excluded due to incomplete records (51 males and 8 females aged 45.0±6 years) with oral recurrent bruxism, divided into two groups; group A, 30 patients were randomly assigned to receive Chlordiazepoxide oral tablet (5mg) once per day at night, and group B; 29 patients with oral placebo daily for 10 days.

Results: The results showed that administering of Chlordiazepoxide oral tablet (5mg) accelerated the healing process within a short time period (10 days) without complications or disfigurement in all patients. Group A, 24 patients, (the healing rate were 0.79%) of 30 patients were used Chlordiazepoxide oral tablet (5mg) doses administered orally had complete healing of oral recurrent bruxism at period time eight days of enzyme-linked immunosorbent assay investigation. Also there will be a decline both in salivary cortisol and salivary alpha-amylase (sAA) levels during the time period of the study, compared with group B, only 6 patients (the healing rate were 0.21%) of 29 placebo-randomized patients.

Conclusion: In this study showed that, the Chlordiazepoxide oral tablet treatment was effective in healing the oral recurrent bruxism and the end-points of the study were complete healing and absence of any discomfort pain while eating within a short period of treatment.

Keywords: Librium tablet, oral recurrent bruxism, clinical trial human study, Chlordiazepoxide oral tablet.

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INTRODUCTION

Bruxism is defined as a nonfunctional activity or a parafunctional habit characterized by the unconscious repetitive motion of clenching. It is considered as one of the most common sleep disorders. It occurs due to unconscious neuromuscular activity of the oral cavity. The person grinds his/her teeth while not chewing. Teeth clenching occurs when a person holds their teeth together and clenches the muscles, however without moving the teeth back and forth. Bruxism is regularly reported by 8% of the general population^(1, 2). Sleep bruxism has characteristically been defined by the American Academy of Sleep Medicine as 'an oral activity characterized by grinding or clenching of the teeth during sleep, usually associated with sleep arousals⁽³⁾. Oral recurrent bruxism is a very common oral condition that remains incompletely understood⁽⁴⁾. These patients may report headaches, temporomandibular disorders (TMD), and pain in muscles of mastication upon awakening, but the exact etiology is unknown and unclear⁽⁵⁾. Treatments are primarily empiric and aimed to reduce symptoms rather than prevention or cure. If grinding of teeth due to stress, so prevention of the problem will be by

learning strategies that promote relaxation, such as medication, muscle relaxants before bedtime and for a short period of time, or Botox injections or medication for anxiety or stress recommend short-term use of antidepressants or anti-anxiety medications⁽⁷⁾. However, there are several methods, both topical and systemic, that can be easily and affordably utilized in the primary care setting⁽⁸⁾. Oral recurrent bruxism is characterized by the appearance of initially facial pain, and headache, tooth attrition, fractured cusps of entire teeth, shiny spots on restorations are well-known to be the most frequently occurring effects, in particular, on the dental hard tissue, with well-defined limits temporomandibular disorders^(9, 10, 11, 13, 14). Bruxism is teeth grinding, its cause can be determined by asking questions about patient general dental health, medications, daily routines and sleep habits. To evaluate the extent of bruxism, we check for: tenderness in the patient jaw muscles, obvious dental abnormalities, such as broken or missing teeth, other damages to the teeth, the underlying bone and the inside of the cheeks, usually with the help of X-rays. Dental exam may detect other disorders that can cause similar jaw or ear pain, such as

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temporomandibular joint (TMJ) disorders⁽⁹⁾. The Bruxism manifests in the form of outbreaks, with a chronic and self-limiting course in most cases, oral recurrent bruxism is the most frequent stereotyped sleep-related movement disorder of the oral cavity, its prevalence ranges from 5% to 8% in general population⁽¹⁵⁾. It is more common in patients between 40-50 years of age, and there is not gender difference for oral recurrent bruxism⁽¹⁾. The underlying etiology is not clear, though a series of factors are known to predispose to the appearance of bruxism, including genetic factors, local trauma, endocrine alterations (menstrual cycle), stress and anxiety⁽¹⁶⁾.

Activation of the autonomic nervous system with a combination of both sympathetic and parasympathetic innervation of the salivary glands leads to high activity of the salivary enzyme "alpha-amylase"⁽¹⁷⁾. Salivary alpha-amylase is variable and sensitive to psychosocial stress. (Nater et al., 2005), pronounced increment following induction of stress compared to the rest condition anxiety⁽¹⁸⁾. Since salivary cortisol became the standard indicator of hypothalamic-pituitary-adrenal (HPA) axis activity, a comparably easy-to-use salivary measure for activity of the sympathetic adrenal medullary system ((SAM))S is highly desired. First evidence that stress-induced changes in salivary alpha-amylase (sAA) activity in humans may be dependent on beta-adrenergic transmission came from a study in which an increase in ((sAA)) activity in response to a cold water stressor was prevented by beta-adrenergic antagonists^(19, 20, 21).

In 1960 Chlordiazepoxide (Librium) was introduced as a specific anti-anxiety substance. The original **chlordiazepoxide HCl and prototype for the benzodiazepine compounds**, was synthesized and developed at Hoffmann-La Roche Inc. It is a versatile therapeutic agent of proven value for the relief of anxiety. Librium is among the safer of the effective psychopharmacologic compounds available, as demonstrated by extensive clinical evidence. Librium is available as capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Each capsule also contains corn starch, lactose and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, Chlordiazepoxide hydrochloride is 7-chloro-2- (methylamino) -5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride, also the capsule contains a white crystalline substance which is soluble in water, and unstable in solution. The powder must be protected from light. The molecular weight of chlordiazepoxide HCl is 336.22.⁽⁷⁾

The Clinical pharmacology of Librium (chlordiazepoxide HCl) has anti-anxiety, sedative, appetite-stimulating and weak analgesic actions. The precise mechanism of action is not known. The drug blocks EEG arousal from stimulation of the brain stem reticular formation. It takes several hours for the peak in blood levels to be reached and the half-life of the drug is between 24 and 48 hours. After the drug is discontinued, plasma levels decline slowly over a period of several days. Chlordiazepoxide is excreted in the urine, with 1% to 2% unchanged and 3% to 6% as conjugate waste⁽²²⁾.

The drug has been studied extensively in many species of animals and these studies are suggestive of action on the limbic system of the brain, which recent evidence indicates its involved in emotional responses. Chlordiazepoxide is the member of a new chemical class of compounds which lacks the vegetative nervous system blocking action of phenothiazines, but possesses similar tranquilizing action on laboratory animals⁽⁷⁾.

Treatment used is multifocal and varies according to the predisposing factors. In all cases, the management is symptomatic, and seeks to reduce oral recurrent bruxism and afford pain relief by administering topical or systemic treatments such as **muscle relaxants, botox injections, medication for anxiety or stress**⁽²³⁾. The present study treatments for oral recurrent bruxism with use of systemic drug Chlordiazepoxide oral tab oral dispersible tablet (5mg) doses administered orally once daily after meal at night.

MATERIALS AND METHODS

Study population

From **66** patients complain from oral recurrent bruxism collected, **7 were excluded** due to incomplete records, a double blind, stratified-randomized clinical case-control study was performed between March 2018 and October 2019, were selected for this study patients of the outpatient Dental Clinic of the of Dental Collage \ University of Babylon. Only 39 included to participate in this study (51 males and 8 females aged 45.0±6 years) were completed study for 4 time period recall. Also, they were randomly divided into two groups; GA: 30 patients used Chlordiazepoxide oral tab oral dispersible tablet (5mg) (26 males and 4 females) and GB:29 patients (25 males and 4 females) were randomized to used placebo oral dispersible tablet.

All patients were informed of all the details of this investigation and signed a consent form prior to their participation. Preoperative evaluation included a complete medical and dental history. In this study, collection patients met the entry criteria similar to those for the oral ulcer⁽²³⁾.

in the study the Included 59 patient, had symptoms of pain for 2 days. patients were a clinical find of oral recurrent bruxism that revealed symptoms.

Among the exclusion criteria were:

- 1- patient Severe Bilateral peripheral neuropathy.
- 2-patient who used Chlordiazepoxide oral tab within two week before study entry.
- 3- Tabaco use patients.
- 4- For female participants, the date of the period was recorded without the current cycle phase,
- 5- **pregnancy** cases.

Treatment regimens

Study participants were randomly assigned in a double-blind fashion. All patients with clinical confirmed oral recurrent bruxism were randomly divided into two groups, group A (GA), assigned to receive Chlordiazepoxide oral tablet 5mg/day (study medications were provided by ((SAM))arra Drug Iraq SDI, and group B (GB) with oral placebo dispersible tablet, 5mg/day. All doses had administered orally once daily after meal for 10 days. Study protocol

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specified that at a reduced dose. The adverse effects, should permanently discontinued by stop taking the drug.

Criteria for response: The primary end point of the study was the complete remission or absence of the oral recurrent bruxism.

Evaluation of patients and follow-up:

After the screening and baseline evaluations, the patients were examined daily and by awaring the **patients' side** effects of the medication. At baseline and at each visit, a quality-of-life questionnaire was administered to assess pain by food eating ability. Repeat oral diagnosis for presenting of oral recurrent bruxism. It was performed after each time period of study treatment to assess the healing of oral recurrent bruxism by the clinical evaluations follow-up.

Statistical analysis

The data is entered and analyzed with SPSS version 13.1.220 (Stata Corp LP, Texas, USA). In the first place the Shapiro-Wilk normality test is applied to test normality (where $n < 30$). The data was normal disruption with P-value 0.578. The planned study was

59 patients, the study was analyzable and the results in these patients are presented. All analyses were performed on an intention-to-treat basis. Two-by-two classifications of ulcer-related lesion end points were tested by use of stratified exact tests^(24, 25). (Randomization was stratified according to whether a patient volunteered to be in a pharmacokinetic sub-study). The P values for end of complete ulcer healing are exploratory and not confirmatory.

RESULTS

Study population

The patients with the exclusion criteria were not included in this analysis. From 66 patients only 66 patients included in the analysis were enrolled in the oral recurrent bruxism between March 2017 and October 2018, and 7 patients were excluded from the analysis because they were randomized inadvertently and never received study treatment, all patients had the ((SAM))e baseline characteristics of the two groups which were similar as in (Table 1)

Table 1 :data of the group A, and group B.

	Group	mean	S.D	Std. Error	t-value	P-value	Sig
Group A	Before treatment	81.08	7.95	1.180	51.13	0.000	HS
	After treatment	78.98	3.52	1.120	44.79		
Group B	Before treatment	81.42	7.32	1.122	58.11	0.540	N.S
	After treatment	80.96	6.93	1.046	55.61		

DISCUSSION

In most cases, the aim of oral recurrent bruxism treatment is believed to prevent more tooth damage and relieve jaw pain or discomfort and to reduce the tenderness in jaw muscles, in addition to reduce dental abnormalities, such as broken or missing teeth and frequency of relapses⁽²³⁾. This double-blind, randomized, placebo-controlled study shows that Chlordiazepoxide oral tablet 5mg/day is effective in reducing oral recurrent bruxism by 8 days in 22 patients (73.4%) of group A, this agree with study of Azima H.et.al, that Librium is an adequate anti-anxiety and anti-tension substance in neurotic patients, solely in anxiety reactions⁽⁷⁾.

Compared with 8 patients were reduced the oral recurrent bruxism (26.6%) of group B reduce the symptoms by 10 days. These results are consistent with those who were reported previously regarding the effectiveness of Chlordiazepoxide oral tablet 5mg/day in treating patients who have oral recurrent bruxism. Quality-of life measures indicate the reduction of the symptoms such as pain and relieve jaw pain or discomfort, to reduce the tenderness in jaw muscles which were improved markedly in group A (Table 1).

The salivary cortisol has been used as a measure of free circulating cortisol levels ((SAM)). Salivary alpha-amylase (sAA)has also emerged as a novel biomarker for psychosocial stress responsiveness within the sympathetic adrenomedullary system ((SAM))Cortisol is a major steroid hormone secreted by fascicular zone of the adrenal cortex⁽¹⁶⁾. The data

were tested in this study and showed the effect of the Librium oral dispersible tablet on the level of (sAA)and (SAM)**(Tabel.1)**. The group A: had high significant impact P -value (0.000). Also there was a strong **positive** correlation between reduced symptoms (such as pain) and the level of (sAA)and (SAM)**($r = -0.91$)**. In addition to (sAA), the reduced symptoms duration or reduced pain, lead to the most important goals in dentistry and healing increase the rate by **(0.66%)**.

The group B: the result showed no significant impact whereas p-value is (0.540).Also there is **zero correlation** between treatment and symptoms (**$r = 0.00$**).This mean there were no significant effect. In addition, results showed the the level of (sAA) and (SAM)decrease rate by **(0.35%)**.Moreover the results showed that there was no impact effect in the pain and the level of (sAA)and (SAM)rate by (0.21%).

Two researchers investigated the topic and abstract in terms of the inclusion criteria. From total of 66 patients, only seven of patients had been out of this study due to the following reasons:

Discontinuing of study medication because of rash induced three days after administering the medication.

Dose reduction or forgetting to take the medication in the exact time.

CONCLUSION

With the condition of this study, showed that Chlordiazepoxide oral tablet proved to be effective in reducing symptoms duration and reducing pain of the

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patients. Frequent clinical diagnosis and the level of (sAA)and (SAM)should be performed on patients who are not responding to Chlordiazepoxide oral tablet treatment to exclude oral recurrent bruxism that may not have been diagnosed by the initial study. The Chlordiazepoxide oral tablet shortens the duration of the bruxism outbreaks, as well as reducing pain of the level of (sAA)and (SAM)and frequency of the patients.

Ethical Clearance

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and the subject informations and consents were reviewed and approved by a local Ethics Committee.

Conflicts of interest

None of the authors have any conflicts of interest relevant to what is written.

Funding source

University funding was provided for: data collection, analysis, and interpretation; trial design; patient recruitment. No public funding was received.

ACKNOWLEDGMENTS

Authors would like to express their thanks and gratitude to (University of Babylon\ Dental Collage) for their cooperation of this research in their providing of outpatient clinic.

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