RESEARCH ARTICLE

RESPONSE TO TOPICAL CLONAZEPAM IN PATIENTS WITH BURNING MOUTH SYNDROME: A CLINICAL STUDY.

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Summary
Burning Mouth Syndrome (BMS) is a difficult disease for patients and clinicians. Moreover, there is not a general consensus on how to treat the disease. The main objective of this paper is to evaluate BMS patients' response to topical clonazepam treatment.
A double blind study was performed. Among a total of 66 patients, 33 were treated with tablets of clonazepam and another 33 were treated with a placebo. Symptoms were evaluated after 1 month and 6 months of treatment and scored on an analogical scale from 0 to 10.
Among the 33 patients treated with clonazepam, 23 showed at least a 50% reduction in symptoms after 1 month of treatment. On the contrary, only 4 in the placebo group exhibited significant improvement. After 6 months, significant differences were observed again, as 23 of the 33 patients treated with the drug reported at least a 50% reduction in symptoms, whereas only 2 among those treated with the placebo significantly improved.
However, when measured in terms of a complete cure (lack of symtoms), the differences were not significant: 5 drug-treated patients and one belonging to the placebo group were asymptomatic after one month of treatment. In summary, it seems that clonazepam applied topically was effective in treating BMS in a large proportion of patients.

Resumé
La stomatodynie ou Syndrome des sensations de la brûlure buccale *(Burning Mouth Syndrome, BMS)* est une maladie difficile pour les patients et les cliniciens. En outre, il n'y a pas un consensus général sur la façon de traiter la maladie. L'objectif principal de cette étude est d'évaluer la réponse des patients atteints de BMS à un traitement topique avec clonazépam.
Une étude en double aveugle a été réalisée à l'aide d'un total de 66 patients, dont 33 ont été traités avec des comprimés de clonazépam et 33 avec du placebo. Les symptômes ont été évalués après 1 mois et 6 mois de traitement moyennant une échelle analogique allant du 0 à 10.
Parmi les 33 patients traités par le clonazépam, 23 ont montré au moins une réduction de 50% des symptômes après 1 mois de traitement. Au contraire, seulement 4 patients du groupe placebo présentaient une amélioration significative. Après 6 mois, des différences significatives ont été observées à nouveau, puisque 23 des 33 patients traités avec le médicament ont signalé au moins une réduction de 50% de leurs symptômes, tandis que seulement 2 des les patients traités avec le placebo ont noté une amélioration clinique. Toutefois, lorsqu'on mesure les résultats en termes de guérison complète (absence de symptômes), les différences n'étaient pas significatives: 5 patients traités par le médicament et un seul appartenant au groupe placebo étaient asymptomatiques après un mois de traitement. Ceci nous permet d'affirmer que l'application topique du clonazépam a été efficace dans le traitement de BMS dans une proportion importante des patients.

Introduction
Despite the fact that its causes, pathogenesis and even definition are poorly understood, Burning Mouth Syndrome (BMS) is a cause of

concern for both clinicians and patients, and subsequently its treatment is a topic of clinical research (1-5).

The main symptom is a continuous, painful, burning sensation in the oral or pharyngeal mucosa, without apparent clinical alterations (3, 4). This is usually accompanied by some other dysesthesia in the mouth, such as a sandy feeling or dryness; however, salivary flow is often unaffected (4-10). Moreover, patients frequently report altered taste, such as the perception of a metallic or bitter taste (11, 12). The sensation of burning or stinging can be produced in any part of the oral mucosa, especially the tongue (on the tip and sides) and the lips (6, 12).

Up to now, there has been no recognized treatment for BMS (13). Most affected people are postmenopausal women, with strong symptoms of anxiety or depression, who are often being treated with anxiolytics, antidepressants, hypnotics or psychotherapy (7, 8, 14-16).

In 2003, Zakwreska et al (15) evaluated previous research in which patients suffering from BMS were treated with antidepressive drugs, analgesics, hormonal reposition therapy, vitamins or cognitive therapy; their results showed that only cognitive therapy had a significant effect. In contrast, some authors have reported improvement with low doses of tricyclic antidepressants (4, 12, 13). In other papers, improvement after the use of oral benzodiazepines or other anxiolytics (11, 12, 15), including clonazepam (12, 17) has been described. Topical anesthetic solutions can be effective in some cases, while in others symptoms are exacerbated (18). The topical or systemic administration of capsaicin, a desensitizer, has been also recommended (19, 20). In 1998, Woda et al reported a 50% reduction on a pain scale following the treatment of BMS patients by local application of clonazepam tablets (21). They suggested that this local treatment may affect some unknown etiopathogenic factor in the peripheral nervous system. On the basis of these findings, we designed a clinical study for comparative purposes. We treated a group of BMS patients with clonazepam tablets dissolved in the mouth, or with a placebo, and subsequently, a clinical evaluation of the symptoms in both groups was performed.

The main purpose of this study was to evaluate BMS patients' response to locally-applied clonazepam treatment.

Material and methods

Patients

Between January 2005 and July 2006, we enrolled 66 adults with BMS to participate in a randomized clinical trial. The primary aim of the study was to examine the effect of locally applied clonazepam. Most patients -64- were females. Some patients attended the clinic to receive dental or medical treatment, while others were referred by colleagues after unsuccessful treatments. All subjects reported oral burning in the absence of apparent oral lesions. None of the patients was treated in the last month before their inclusion in the study.

We excluded patients with disorders in the oral mucosa that could explain the symptoms, those who were receiving treatment for BMS and those who did not attend the follow-up visits.

The study did not exclude any patient who had an accompanying systemic disease, nor those who were receiving treatment for other disorders. Subjects taking anxiolytics or antidepressives were not rejected, since there is a high prevalence of BMS among patients with psychiatric antecedents (21-31).

Methods

A double blind study was performed. Three clinicians, with extensive experience in oral medicine, examined the patients (they belong to the Oral Pathology section, Faculty of Dentistry, University of Barcelona; two of them have an MD and PhD, are specialists in Oral Medicine, and one is a DDS and PhD and also a dermatologist). A table of random numbers was used in order to ensure the randomization of the treatments.

The patients were examined in the Section of Oral Medicine at the Dental Clinic of the University of Barcelona and in private practice. A detailed clinical history was recorded for each patient, and a protocol sheet as the one used by Woda et al was completed (21). During the first visit, the burning presented by the patients was recorded using a visual analogic scale (VAS) from 0 to 10. The protocol was reviewed and approved by the Institutional Review Board.

Six variables were recorded for each patient: age, sex, duration of disease, location of the burning sensation, systemic diseases and drugs consumed.

Before the trial began, the patients were informed of the purposes of the study. When the patients had given their consent, they were provided with the tablets.

Study design: Two groups of patients were established at random: Group A: 33 patients, treatment group. Each patient was given a sealed envelope containing 32 tablets of 0.5mg of clonazepam. They were instructed to take a single tablet at the first sign of discomfort in the morning. The tablet should be dissolved in the mouth for three minutes, and then the remaining saliva should be spat out. The patient should then note his or her sensations and the evolution of the symptoms. If there was improvement, the procedure was to be repeated when the symptoms reappeared. Patients were advised not to exceed four tablets a day (that is, a total dose of 2 mg of clonazepam). Group B: 33 patients, placebo group. They were given 32 lactose tablets, of the same shape and size as those given to Group A. Their instructions were the same as those given to Group A. All the patients were scheduled for a visit after 1 week for the sole purpose of detecting undesirable side effects. They were again scheduled for visits after 1 month and 6 months, which allowed the clinicians to monitor their evolution. At each visit, the burning sensation was measured on a VAS from 0 to 10.

Statistical treatment of data: The data were processed using the SPSS 11.0 for Windows. Results were analyzed using the Chi square test. On the basis of the data recorded, two new variables were created for later analysis: More than 50% improvement after 1 month and 6 months, and remission after 1 month and 6 months, defined as a score of 0 (absence of pain).

Results

Table 1 shows the data corresponding to the VAS before the beginning of the treatment, after 1 month and after 6 months, both for the treatment group and for the placebo group. Table 2 shows the most representative statistical data for both groups. One can observe that the differences between the groups' averages were not statistically significant at the beginning of the treatment. In contrast, after one month, the mean in both groups had decreased; the VAS was significant (P<0,005) in the clonazepam group whereas it was not significant in the placebo group.

Information on the systemic diseases and treatments received by the patients is shown in Table 3. As can be seen, the most frequent disorders present were psychological, hormonal, cardio-circulatory and gastrointestinal diseases. A significant number of patients were regular consumers of psychoactive drugs.

Their age average was 64,9 (ranging from 48- to 85-years-old). The patients were divided into three groups: younger than 60, from 60 to 70, and older than 85 (Figure 1).

Information about the pain characteristics, its

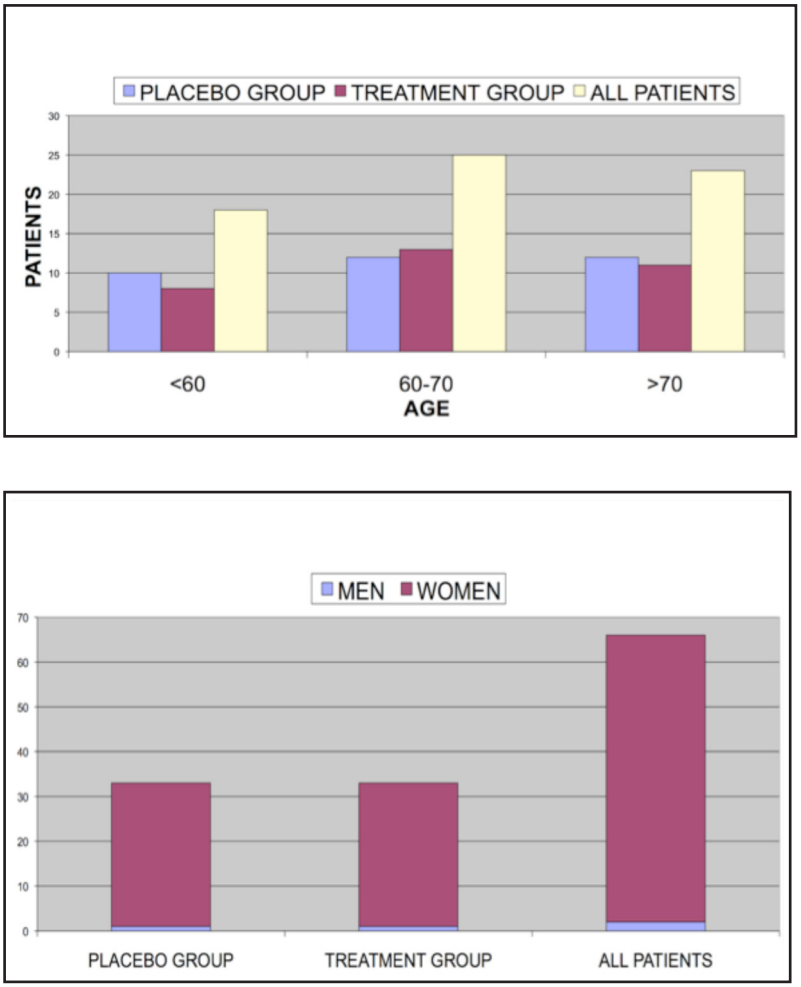

Figure 1. Age and gender of the patients on the treatment and the placebo group.

Clonazepam Patients			Placebo Patients		
First Day	1 month	**6 months**	**First Day**	**1 month**	**6 months**
9	4	3	8	0	2
6	5	4	7	4	4
7	6	5	4	3	3
6	5	3	9	5	5
5	1	2	6	4	4
8	2	5	7	5	5
9	0	2	8	5	5
10	4	4	9	5	5
10	0	0	10	4	6
5	1	3	9	6	6
6	0	2	9	6	6
7	2	3	8	5	5
6	2	4	8	6	6
8	2	3	8	5	5
9	4	3	8	4	6
8	3	3	6	5	4
7	4	3	9	5	5
9	0	0	8	6	5
8	5	3	9	5	5
8	3	4	6	4	4
8	5	6	7	4	4
8	3	3	6	6	6
6	4	4	4	3	3
8	3	3	8	5	5
7	0	0	9	5	5
5	3	3	10	6	6
9	4	3	10	7	6
6	4	5	5	3	3
10	4	2	6	4	4
8	5	4	7	4	4
9	4	3	7	4	4
10	2	3	8	5	5
9	3	2	9	2	3

Table 1. VAS (Visual Analogic Scale) values for the symptoms reported by both patient's groups.

Clonacepan Patients 1st Day	
Mean	7,6969697
Standard error	0,26644705
Median	8
Mode	8
Standard deviation	1,53062178
Range	5
Minimun	5
Maximun	10
Sum	254
N	33

Placebo Patients 1st Day	
Mean	7,57575758
Standard error	0,27534518
Median	8
Mode	8
Standard deviation	1,58173763
Range	6
Minimun	4
Maximun	10
Sum	250
N	33

Clonacepan Patients 1st Month	
Mean	2,84848485
Standard error	0,29555165
Median	3
Mode	4
Standard deviation	1,697815
Range	6
Minimun	0
Maximun	6
Sum	94
N	33

Placebo Patients 1st Month	
Mean	4,24242424
Standard error	0,20884922
Median	4
Mode	4
Standard deviation	1,19974745
Range	6
Minimun	0
Maximun	6
Sum	140
N	33

Clonacepan Patients 6st month	
Mean	3,03030303
Standard error	0,23631021
Median	3
Mode	3
Standard deviation	1,35749881
Range	6
Minimun	0
Maximun	6
Sum	100
N	33

Placebo Patients 6th month	
Mean	4,42424242
Standard error	0,16872013
Median	4
Mode	4
Standard deviation	0,96922337
Range	4
Minimun	2
Maximun	6
Sum	146
N	33

Table 2. Statistical data of the VAS (visual analogic scale) values reported by both patient's groups.

Pathological history (A)				
	Psycological Diseases	Hormonal Diseases	Cardiocirculatory Diseases	Gastrointestinal Diseases
Placebo group (n=33)	20	12	14	18
Treatment group (n=33)	21	14	17	20
All patients (n=66)	41 (62%)	26 (39%)	31 (47%	36 (55%)

Psycoactive drugs (B)			
	Hypnotics	Anxioltycs	Antidepressants
Placebo group (n=33)	23	25	18
Treatment group (n=33)	23	24	15
All patients (n=66)	46 (70%)	49 (74%)	33 (50%)

Other drugs (C)							
	Digestive	Cardiocir-culatory treatmens	Diabetes pills	Hormonal treatment	Analgesic drugs	Lipid-lowering drugs	Vitamins
Placebo group (n=33)	16	14	4	1	16	6	3
Treatment group (n=33)	18	15	3	3	14	9	2
All pa-tients (n=66)	34 (52%)	29 (44%)	7 (11%)	4 (6%)	30 (45%)	15 (23%)	5 (8%)

Systemic diseases (D)				
	Psycological Diseases	Hormonal Diseases	Cardiocirculatory Diseases	Gastrointestinal Diseases
Placebo group (n=33)	20	15	16	19
Treatment group (n=33)	21	11	15	17
All patients (n=66)	41 (62%)	26 (39%)	31 (47%)	36 (36%)

Table 3. Relevant variables recorded from the anamnesis of the patients: Pathological history (A), Psychoactive Drugs usage (B), Other drugs usage (C) and Systemic diseases (D).

location, duration, altering factors and trigger factors is shown in Table 4. All the patients reported burning on the tongue; the lip area was the second location of the symptoms, followed by the palate. 88% of the patients reported oral dryness, and the majority of them suffered BMS symptoms for more than one year.

Table 5 shows the average number of tablets taken by each group. It is necessary to note that during the first week, consumption in both groups was similar. After the second week, there was a decrease in the number of tablets consumed. This decrease is more apparent, although not significant, in the patients who were taking clonazepam.

Patients who improved reported that they felt the symptoms disappear a few minutes after

Clinic Characteristics of Pain (A)				
	Swelling sensation	Dryness	Sandy feeling	Burning
Placebo group (n=33)	10	30	2	33
Treatment group (n=33)	9	28	3	33
All patients (n=66)	19 (29%)	58 (88%)	5 (8%)	66 (100%)

Location (B)						
	Tongue	Palate	Gum	Oropharyngeal	Lips	Other
Placebo group (n=33)	33	16	10	9	20	3
Treatment group (n=33)	32	17	8	7	22	4
All patients (n=66)	66 (100%)	33(50%)	18(28%)	16 (25%)	42(63%)	7 (11%)

Duration Time (C)			
	< 6 months	6 to12 months	> 12 months
Placebo group (n=33)	2	7	24
Treatment group (n=33)	2	5	27
All patients (n=66)	4 (6%)	12 (18%)	50 (76%)

Altering or Trigger Factors (D)			
	Stress	Temperature (*)	Chewing
Placebo group (n=33)	20	14	21
Treatment group (n=33)	17	15	22
All patients (n=66)	37 (56%)	29 (44%)	43 (65%)

Table 4. Clinic characteristics of pain (A), its location (B), duration time (C) and altering or trigger factors (D) (*) Variation inside the oral cavity).

Patients who improved reported that they felt the symptoms disappear a few minutes after

	Day 1	Day 2	Day 3	Day 4	Day 5
Treatment group	3,1	3,3	3,1	3,3	3,3
Placebo group	3,1	3,4	3,2	3,2	3,5

	Day 6	Day 7	2nd week	First month	6th month
Treatment group	3	3,4	19	70	62
Placebo group	3,7	3	21	95	84

Table 5. Average number of tablets taken by both groups of patients.

the tablet was dissolved in their mouths; even the dryness and taste alterations reduced. Some patients reported a sensation of effervescence and numbness of the tongue when the tablet was dissolved. However, symptoms reappeared after 3 or 4 hours and a new tablet was necessary. This way, patients were able to control the symptoms all day. The only side effect registered was some degree of sleepiness in 5 patients of the clonazepam group, which did not require the clinicians to suspend the treatment.

When the VAS values at the beginning and after one month were compared, it was observed that, of the 33 subjects receiving clonazepam, 23 showed more than a 50% reduction in symptoms, while only 4 out of the 33 individuals treated with the placebo showed such an improvement (Figure 2). This difference was statistically significant ($p<0.05$, Chi square). Again, 5 of the subjects receiving clonazepam were completely cured after one month, while complete disappearing of symptoms occurred in only one subject taking the placebo ($p>0.05$). Similarly, in a comparison between VAS values at the beginning and after six months, of the 33 patients receiving clonazepam, 23 improved more than 50%, while only 2 of those receiving the placebo improved ($p<0.05$). In this case, only 3 of the 33 patients who were receiving clonazepam were totally asymptomatic, while none among those receiving the placebo was asymptomatic ($p>0.05$).

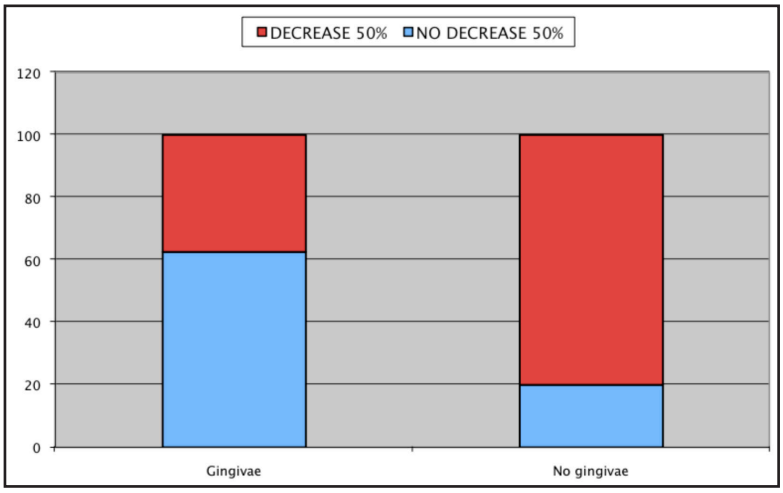

Figure 2. Distribution of the diminution of 50% of the symptoms after one month of treatment, according to location.

Discussion

Regarding the descriptive data, both groups

appear to be homogeneous (Table 3, 4 and Figure 1), and our population group is comparable to those described by Woda et al (21), Browning et al (22), Brailo et al (23) and Gorsky et al (24). Although data referring to symptom reduction are valuable in respect to the cure, the number of patients was too small (n=5); thus, it seems that data concerning the disappearance of symptoms should be regarded as a suggestion for future studies.

After one month of treatment with clonazepam, 70% of our patients showed at least a 50% reduction of symptoms. In contrast, the proportion of patients showing complete remission (15%) is less encouraging.

Although most of the patients had been suffering from BMS symptoms for more than one year, those suffering from BMS for a shorter period of time experienced a more remarkable reduction of the symptoms. This is consistent with the results obtained by Woda et al (21), who also reported better results in patients with shorter evolution times. This author described a reduction in the pain scale average, from 6.2 +/- 0.3 to 3 +/-0.5, after 1 month of treatment. According to their research, one-half of their patients were cured, while a third experienced remarkable improvement; the rest remained as they were at the beginning of the study.

It is also significant that the patients who were not suffering from any psychological problems had a greater proportion of cures. Numerous authors (25-32) have associated BMS with certain types of psychiatric disorders, such as depression or anxiety. The studies by Lamey and Lamb (25) and Lamey and Lewis (33) in 1989 found that the patients who were suffering from chronic anxiety were the least likely to improve during the treatment. In 1996, Lamey claimed an improvement rate of 70% among patients in whom diagnosis and treatment of other factors were effective (34). Other authors (30-32) concur with Lamey; they believe that psychiatric, social or personal problems are poor prognostic factors in terms of a cure. So, our results are in agreement with those of Lamey, who found that patients suffering from psychological problems and chronic anxiety are more difficult to treat.

On the other hand, the rapid activity of the topical clonazepam, seems to indicate that this drug acts locally while dissolving in the mouth, acting on some of the peripheral etiopatogenic factors of the BMS.

The same hypothesis is supported by Gremeau-Richard et al (35).. In a controlled and double blind study, they achieved similar results and, therefore, suggested that clonazepam acts locally, affecting one or more of the etiopathogenic mechanisms responsible for BMS. This would validate the proposal of Grushka et al (36), who stated that BMS originates with an alteration in neuronal transmission. These authors note that the sensitive endings of the tongue responsible for the perception of the burning sensation are closely related to the taste receptors and to the sensation of dryness. The main explanation could be that, in some patients, the dryness and altered taste improved simultaneously with the clonazepam treatment.

However, it should be noted that the effectiveness of the clonazepam could be partially attributed to its sublingual absorption, since some of the patients experienced sleepiness, as we mentioned before. Nevertheless, the rapid reduction of discomfort (in less than 10 minutes) and the duration of the period in which the patient was asymptomatic (3-5 hours) are not consistent with data on the pharmacokinetic properties of systemic clonazepam. When administered orally, clonazepam has a half–life of 25 to 60 hours and a serum peak between 3 and 12 hours due to its hepatic degradation. Normally, it takes 3 to 4 hours to exert its pharmacological effect, which lasts 7-8 hours.

Both groups of patients showed improvement, which was partially due to the psychotherapy. The management of patients with BMS should be focused on two aspects. On one hand, clinicians could treat the symptoms; on the other hand, they could use basic psychotherapy customized to each person, which can be carried out in our dental office. The aforementioned psychotherapy is focused on listening to the patient, emphasizing affectivity, security and tranquility, and transmitting the feeling that we know exactly what the patient is going through as well as the difficulties we face in giving him/her solutions to his/her problems.

Our personal experience has shown us that, if we manage to calm the patient with our attitude, the possibility of improvement increases; this is particularly true in patients who are relatively stable from an emotional point of view. The improvement was significant at the beinning of our study, but we noted that, in the control performed after six months, there was a high degree of heterogeneity. There were periods of exacerbation of the disease, during which time the subjects did not respond in the

same way to the medical treatment. Similarly, we also have observed periods of improvement, in which taking the drug was not necessary. Looking at the clinical history, it becomes clear that most periods of exacerbation coincided with phases of emotional unbalance. Due to these aspects, in the control performed after six months, we asked the patients to provide us with the average VAS value corresponding to the days immediately before their visit. Taking into account the results obtained in this study, we can conclude that clonazepam applied topically was beneficial for the treatment of , in our group of studied patients. Further investigations should be carried out to explore the etiopathogeny of BMS. These studies could lead to the discovery of new and more effective treatments.

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