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ORAL DISEASES

A prospective, randomized study on the efficacy of tongue protector in patients with burning mouth syndrome

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6 **patients with burning mouth syndrome**
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10 **Short title:** Burning tongue
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12 Original Article type

13 **Key words:** Burning mouth syndrome; **primary; secondary**; parafunctional habits;
14 tongue; treatment.
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ABSTRACT

Objective: was to apply a tongue protector with habit-modifying therapy through self-control, in the patients with burning mouth syndrome (BMS).

Methods: A prospective, randomized study was made of 65 consecutive patients with BMS. Fifty subjects were randomized to two groups: group A (informed) and group B (informed and the application of a tongue protector). The symptoms were evaluated by VAS, while the psychological profile was assessed using the HAD, with application of the quality of life questionnaires SF-36 and OHIP-49. The duration of treatment was two months.

Results: Fifty patients (46 females and 4 males) completed the study. The VAS scores in group B were 8.2 at baseline and 4.5 after two months. The respective scores in group A were 7.1 and 5.6 - the differences between the two groups being significant ($p < 0.001$). In group B the OHIP-49 yielded lower scores for most of the scales, with significant differences versus group A. In group B the SF 36 yielded significant differences versus group A in physical role, bodily pain, general health and emotional role.

Conclusions: Parafunctional traumatism of the tongue should be taken into account in the pathogenesis of BMS with a view to exploring new therapeutic options.

Key words: Burning mouth syndrome; primary; secondary; parafunctional habits; tongue; treatment.

INTRODUCTION

Burning mouth syndrome (BMS) is characterized by a subjective sensation of burning or itching of the oral mucosa, in the absence of clinical and laboratory test data capable of accounting for the symptoms, and with a duration of at least 4-6 months (Grushka *et al.*, 2006; Klasser *et al.*, 2008; Fedele *et al.*, 2007). The prevalence of BMS varies between 0.7-4.5% (Scala *et al.*, 2003; Maltsman *et al.*, 2007). It is mainly seen in postmenopausal women (Baker *et al.*, 2005). There is debate in the medical literature regarding the etiopathogenesis of the disorder, and several factors and concepts have been proposed (Scala *et al.*, 2003; Lamey 1998; Bergdahl *et al.*, 1995; Patton *et al.*, 2007; Danhauer *et al.*, 2002; Rojo *et al.*, 1994; López-Jornet *et al.*, 2008, Sardella *et al.*, 2006; Zakrzewska *et al.*, 2003). The postulated causal factors have been grouped into local factors (infections, irritants, etc.), systemic factors (diabetes mellitus, anemia through iron or folic acid deficiency, etc.), and psychogenic factors; but these causal factors contradict the definition of BMS and so constitute another disease condition separate from BMS. Burning mouth syndrome is considered to be idiopathic/primary when the cause is impossible to determine (Klasser *et al.*, 2008) and secondary when it is possible to identify etiologic factors for the syndrome. Some investigators have suggested that the disorder may be a manifestation of somatization, while others have reported it to be more closely related to neuropathic pain than to somatoform chronic pain syndromes. Parafunctional habits such as tongue thrusting or certain tics in the form of continuous rubbing of the teeth or dentures, lip, cheek or tongue nibbling, compulsive movements and hyperactivity of the tongue may contribute to induce and maintain the syndrome (Lopez-Jornet *et al.*, 2009a). Pain in BMS is most often bilateral and symmetrical in the anterior two-thirds of the tongue (71-78%), followed by the dorsal and lateral surfaces of the tongue, the anterior portion of the hard palate, and the lip mucosa and gingiva. The condition often manifests in several locations (Scala *et al.*, 2003). Considering the chronic nature of BMS and its prevalence, optimum treatment must be established, since no effective therapies have been developed to date. Many treatments have been tested with a view to securing symptoms relief, including benzodiazepines, tricyclic antidepressants, gabapentin, serotonin reuptake inhibitors, lipoic acid and cognitive behavioral therapy – with variable results. It is therefore important to study and understand the physiopathological mechanisms of stomatodynia in order to select the best possible treatment (Klasser *et al.*, 2008; Maina *et al.*, 2005; Minguez Serra *et al.*, 2007; Gremeau Richard *et al.*, 2004; Femiano *et al.*, 2004; Lopez-Jornet *et al.*, 2009 b;

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3 Carbone *et al*, 2009).

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5 The proposed pharmacological protocols have not consistently proved to be predictable
6 and effective in all BMS subjects, in this sense the aim of the present study was to apply
7 a tongue protector with habit-modifying therapy through self-control, and to evaluate
8 the symptoms and quality of life in the patients with burning mouth syndrome (BMS).
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10 11 12 **METHODS**

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14 A prospective, randomized study was made of 65 consecutive patients with BMS seen
15 in the Department of Oral Medicine (University of Murcia, Spain). The study was
16 carried out during the period between March 2007 and June 2009, and was authorized
17 by the Bioethics Committee of the University of Murcia. A sample size was not
18 calculated before starting the trial, as we were not able to predict the effect of the
19 investigated treatment.
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24 Inclusion criteria for participating in the study were a clinical history of continuous
25 symptoms of oral burning or pain on a daily or almost daily basis, during all or part of
26 the day for more than 6 months, without paroxysms, and independent of the nervous
27 pathway. Likewise, the included patients presented no clinical abnormalities that could
28 account for the symptoms. Furthermore, the patients had to present normal blood test
29 findings (complete blood count, blood glucose, serum iron and transferrin levels, serum
30 vitamin B12 and folate), and were required to provide informed consent (Gremeau
31 Richard *et al*, 2004). Patients with pain attributable to other conditions (angiotensin-
32 converting enzyme inhibitor use, candidiasis, lichenoid reactions, sores, tongue atrophy,
33 etc.) were excluded, as were those presenting problems with dentures, biochemical
34 anomalies and a history of hypersensitivity or allergy to the material used. Patients with
35 known neurological disorders and those previously treated, even irregularly, with
36 antidepressants, anticonvulsants, other psychotropic drugs, or psychological therapy
37 were also excluded from the study. Patients occasionally using anxiolytics to induce
38 sleep were accepted. Subjects with signs of lingual and labial parafunctional activity
39 were also considered (tongue rubbing, lip or cheek nibbling) (Figure1).
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44 Primary outcome variable: oral symptoms were registered using a visual analog scale
45 (VAS) consisting of a 10-cm vertical line marked from 0 (= no pain) to 10 (= most
46 severe pain experienced) (Maina *et al*, 2005). Patients were asked to indicate the mean
47 pain intensity for the two weeks preceding the consultation. The difference between
48 baseline and the endpoint scores numerically expressed symptoms variation.
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3 The Hospital Anxiety and Depression scale (HAD) was used to evaluate the patient
4 psychological profile. The HAD comprises two subscales relating to anxiety and
5 depression. Each subscale contains 7 items pertaining to mood disorder. On analyzing
6 the HAD scales, scores of over 10 indicated the probable presence of anxiety or
7 depression, scores of 7 or less indicated no significant anxiety or depression, and scores
8 of 8-10 were taken to be of borderline significance (Bjelland *et al*, 2002).

9
10 The Oral Health Impact Profile (OHIP-49) is an instrument used to measure oral health.
11 With the OHIP-49, each item was scored as follows: 0 = "never", 1 = "hardly ever", 2 =
12 "occasionally", 3 = "fairly often", and 4 = "very often". The OHIP-49 is divided into 7
13 different domains, and the possible score range for each domain is: "functional
14 limitation" (9 items), from 0-36; "physical pain" (9 items), from 0-36; "psychological
15 discomfort" (5 items), from 0-20; "physical disability" (9 items), from 0-36;
16 "psychological disability" (6 items), from 0-24; "social disability" (5 items), from 0-20;
17 "handicap" (6 items), from 0-24; and finally "overall OHIP score" (49 items), from 0-
18 196. In this instrument, higher scores indicate a poorer state of health (Lopez and
19 Baelum 2006) .

20
21 The Short Form 36 (SF-36) Health Survey Questionnaire in turn has been designed to
22 evaluate quality of life. The standard version of the SF-36 contains 8 areas (Alfonso *et*
23 *al.*, 1995): "physical functioning", "physical role limitations", "bodily pain", "general
24 medical health", "vitality", "social functioning", "emotional role limitations", and
25 "mental health". The scoring system is designed in such a way that higher scores
26 indicate better health; thus, 0 is the worst state of health and 100 the ideal state of
27 health.

28
29 Every new patient seen at the Oral Medicine Unit who met the eligibility criteria was
30 asked to enter the trial. After being informed about the scope and methods of the study,
31 the subjects who accepted signed the written informed consent form, and then were
32 randomly allocated to one of the two arms of the study. The random allocation sequence
33 was generated using software available online at
34 <http://graphpad.com/quickcalcs/randomize1>. All the patients were instructed not to use
35 any product for BMS during inclusion in the study.

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37 All the patients in group A were informed in detail about their illness, and were
38 instructed not to rub their tongue against their teeth and/or dentures. A self-control
39 technique was used to this effect, the patients being given 10 printed habit-modifying
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3 reminder points to be placed in visible places. The same measures were adopted in
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5 group B, though in this case the patients were moreover programmed for tongue
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7 protector placement. The protector consisted of a transparent, low-density polyethylene
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9 sheath covering the tongue from the tip to the posterior third. These tongue protector s
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11 were single-use devices measuring 0.1 mm in thickness, with a standard size (67 mm in
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13 length and 66 mm wide), and were custom manufactured by our group (figure 2). Each
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15 patient received a kit with the protectors and the reminder points for treatment.
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17 Instructions were provided on their use – the protector being worn during the daytime
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19 for a period of two months. We recommended use of the protector 15 minutes / three
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21 times a day with the therapeutic aim of avoiding continuous rubbing against the teeth
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23 and/or dentures.

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25 The patients in both groups were examined at the start of treatment and again after two
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27 months. One month after inclusion, the investigator called the patients in both groups by
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29 telephone as a reminder and to reinforce motivation. All patients completed the HAD
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31 questionnaire and the quality of life instruments OHIP 49 and SF-36 on each of the
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33 visits (after 0 and 2 months). On these visits the subjects were also questioned about
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35 tolerability and possible adverse effects.

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37 The data were analyzed using the SPSS version 12.0 statistical package (SPSS® Inc.,
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39 Chicago, IL, USA). A descriptive study was made of each variable. The associations
40
41 between the different qualitative variables were studied using Pearson's chi-squared
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43 test. We used the Student t-test for two independent samples in application to
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45 quantitative variables - in each case determining whether the variances were
46
47 homogeneous. A probability of less than $p \leq 0.05$ was accepted as significant.

48 RESULTS

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50 Sixty-five patients referred to the Department of Oral Medicine for oral burning
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52 sensation were assessed for eligibility: 12 failed to meet the inclusion criteria and three
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54 refused to participate in the study. A total of 50 subjects were therefore finally included:
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56 46 females and 4 males, aged 61.18 ± 12.27 years (range 37-84). Table 1 shows the
57
58 homogeneity of the two patient groups on the day of inclusion in the study. During the
59
60 two-month duration of the study there were no dropouts in either group, and no adverse
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62 effects were observed.

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64 The VAS scores in group B (tongue protector group) were 8.2 at baseline and 4.5 after
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66 two months. The respective scores in group A were 7.1 and 5.6) - the differences

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3 between the two groups being significant ($p < 0.001$) (Table 2). Regarding the HAD, the
4 scores showed no significant differences for either of the groups during the course of the
5 study.
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9 In group B the OHIP-49 (Table 3) yielded lower scores (i.e., better quality of life) in all
10 domains, with significant differences between the two study time points (day 0 and after
11 two months). Thus, the total OHIP-49 score in group B was 62.9 ± 34.0 on day 0 and
12 44.5 ± 28.1 after two months. In contrast, group A showed only minimum changes, with
13 a total score of 55.4 ± 4 on day and 53.7 ± 35.3 after two months. On comparing the two
14 patient groups, significant differences were observed in the scales or domains
15 corresponding to functional limitation, bodily pain, psychological discomfort, physical
16 disability, psychological disability, and total score.
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20 Lastly, as refers to the SF-36 (Table 4), the patients subjected to tongue protector
21 treatment (group B) showed improvement in the scores between day 0 and the end of
22 treatment (2 months) in practically all the subscales, while only minimal changes were
23 observed in group A. On comparing the two groups, significant differences were
24 recorded for physical functioning, physical role, bodily pain, general health and
25 emotional role (Table 4).
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33 DISCUSSION

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35 Our results indicate clinical improvement among the patients for burning mouth
36 syndrome (BMS). The VAS scores were modified in both groups during the treatment
37 period (0-2 months), though significant differences were observed between them. On
38 only considering overall improvement, the mean reduction in VAS score observed in
39 group B was from 8.2 at baseline to 4.5 at the end of the study. The mean 1.4-point
40 decrease in pain intensity observed in this study in group A may appear small, but
41 obviously all patients did not respond in the same way to the active treatment.
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48 Burning mouth syndrome is a diagnostic and therapeutic challenge because of its
49 etiopathogenic variability (Patton *et al*, 2007; Kasser *et al*, 2008). The latest studies
50 suggest that psychopathological factors may play an important role in the disorder, in
51 correlation with the multifactorial origin of BMS. A strong psychological component in
52 BMS has been clearly identified in the last decade. It has been suggested that somatic
53 complaints from unfavorable life experiences associated with chronic pain may
54 influence both individual personality and mood changes. Bergdahl *et al*, 1995, studied
55 the effect of cognitive therapy on resistant BMS. Their patients were randomly divided
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3 into two equal groups: a therapy group was subjected to cognitive therapy and an
4 attention / placebo group served as control group. The authors used a visual analog scale
5 to estimate the intensity of BMS, and they found it to be significantly reduced in the
6 therapy group after cognitive therapy was completed (12-15 one-hour sessions once a
7 week).

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11 Gremeau-Richard *et al*, 2004, published a randomized double-blind, multicenter parallel
12 group study in which topical clonazepam improved the stomatodynia symptoms (two-
13 thirds of the included subjects). However, this treatment was not effective in all
14 subjects. Several studies have assessed systemic therapies, including amisulpiride,
15 selective serotonin reuptake inhibitor antidepressants such as paroxetine and sertraline,
16 trazodone and 0.25% capsaicin, with variable results (Patton *et al*, 2007; Minguez Serra
17 *et al*. 2007). The use of lipoic acid in BMS patients was presented as a promising
18 alternative for management of the symptoms, with high levels of improvement - though
19 lipoic acid is not effective in many cases (Lopez Jornet *et al*, 2009b, Carbone *et al*,
20 2009).

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30 Oral parafunctional habits have been widely implicated as factors that intervene in the
31 development and perpetuation of other syndromes (Axel, 2008, Dworkin *et al*, 1992)
32 such as for example temporomandibular joint disorders. Parafunctional activity is
33 defined as the potential lesions (depending on the tolerance of the individual in
34 question) caused by a series of movements that occur in parallel to normal function,
35 though lacking a functional purpose, and which generate traumatic forces characterized
36 by an abnormal direction, excessive intensity, and a frequent and lasting character. Any
37 type of hyperactivity – in this case of the tongue and/or lips – occurring without
38 functional objectives or in a way that proves inadequate for the stomatognathic system,
39 is regarded as parafunctional activity. In this context, the tongue protector used in our
40 study offered protection, since it avoided direct friction or rubbing of the tongue mucosa
41 against the teeth and/or dentures protect the tongue regarding the changes in
42 temperature and taste, **salivary flow (increased)** though its use could also exert a placebo
43 effect.

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The management of BMS symptoms is the greatest challenge related with this
syndrome. Several systemic and local therapies have been suggested to treat these
patients, with frequently unsatisfactory results. Maybe this fact explains the high
receptivity of BMS patients for new therapies and the good adherence to treatment

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3 observed in our study.

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5 A possible confounding factor is represented by occult candidiasis. Some authors
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7 reported evidence for candida-induced burning mouth even in the absence of objective
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9 signs (Terai and Shimahara, 2007), thus suggesting the advisability of routine treatment
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11 with antifungal agents for at least one week before confirming the diagnosis of BMS.
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13 As this issue was not taken into account in the present protocol, some patients may have
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15 had occult candidiasis, and therefore perhaps failed to respond to treatment.

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17 Moreover, as the evaluation of symptoms could be altered by the interpersonal
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19 relationship between the patient and investigator, the same examiner followed-up on all
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21 of the patients in the study, in order to ensure that the results would be comparable.

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23 It is important to consider quality of life in BMS patients, since the impact of the
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25 disease on the different domains or subscales is considerable. Accordingly, in our study
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27 use was made of two validated instruments, the OHIP-49 and SF-36. Our results show
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29 significant improvements in the OHIP-49 score in the group of patients treated with the
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31 tongue protector, in the domains relating to functional limitation, bodily pain,
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33 psychological discomfort, physical disability, psychological disability and in the total
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35 score.

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37 As regards the SF-36, after two months of treatment group B showed improvement in
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39 all the domains, with significant differences versus group A as regards the subscales
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41 used to assess physical functioning, physical role, bodily pain, general health, and
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43 emotional role. Thus, the tongue protector could be an alternative for the management
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45 of patients with BMS. Self-inflicted damage secondary to parafunctional activity of the
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47 tongue should be taken into consideration in the pathogenesis of BMS, with a view to
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49 developing new management strategies.

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51 Although our working hypothesis may be supported statistically, we included only a
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53 small patient series treated for a period of two months – a fact that makes it difficult to
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55 draw firm conclusions. Future studies are needed to reproduce our findings in larger
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57 series, over longer periods of time and involving an adequate sample of patients.

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59 It is essential to deepen our understanding of the physiopathological mechanisms of
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burning mouth in order to select the best treatment and develop new therapies which
may use different mechanisms. Future research moreover should focus on the long-term
effects of treatment and on the quality of life of patients with burning mouth syndrome,
in order to establish the clinical impact of such interventions

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Figure 1. Flow diagram

Figure 2. View of the tongue protector .Manufactured by our group with a standard size (67 mm in length and 66 mm wide)



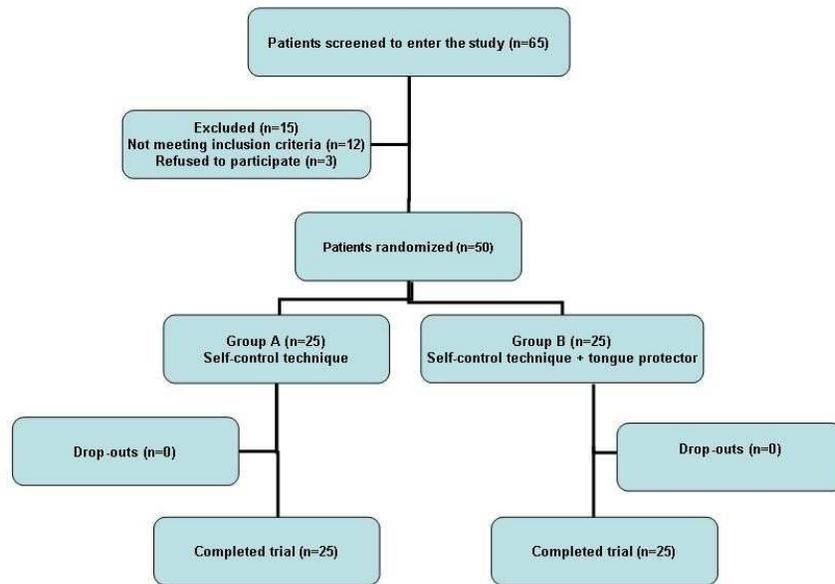


Fig. 1. Flow diagram of the trial

254x190mm (96 x 96 DPI)

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Table 1. Homogeneity of the study groups on day 0 (baseline) in relation to age, gender and the VAS and HAD scores (Student t-test and Pearson χ^2).

Age, gender, VAS, HAD day 0	Group B (n=25)	Group A (n=25)	P-value
Age: mean \pm SD	60.96 \pm 11.97	61.40 \pm 12.81	0.901
Gender			1.000
Male: n (%)	2 (8)	2 (8)	
Female: n (%)	23 (92)	23 (92)	
VAS: mean \pm SD	8.2 \pm 2.1	7.1 \pm 2.1	0.087
HAD: mean \pm SD			
Depression	9.28 \pm 6.00	8.96 \pm 6.09	0.852
Anxiety	11.12 \pm 5.27	11.24 \pm 5.67	0.939

Note: VAS = visual analog scale; HAD = Hospital Anxiety-Depression scale; SD = standard deviation

Table 2. Evolution of the VAS and HAD scores during the two months of the study
(Student t-test).

VAS and HAD	Group B (n=25): mean ± SD	Group A (n=25): mean ± SD	P-value
	Evolution (day 0 - 2 months)	Evolution (day 0 - 2 months)	
VAS	$(8.2 \pm 2.1) - (4.5 \pm 2.2) = 3.6 \pm 2.2$	$(7.1 \pm 2.1) - (5.6 \pm 1.5) = 1.4 \pm 1.6$	<0.001
HAD			
Depression	$(9.28 \pm 6.00) - (8.28 \pm 5.93) = 1.00 \pm 3.73$	$(8.96 \pm 6.09) - (8.92 \pm 6.13) = 0.04 \pm 0.20$	0.205
Anxiety	$(11.12 \pm 5.27) - (11.20 \pm 6.59) = -0.08 \pm 3.39$	$(11.24 \pm 5.67) - (11.04 \pm 5.43) = 0.20 \pm 1.00$	0.694

Note: SD = standard deviation; VAS = visual analog scale; HAD = Hospital Anxiety-Depression scale

Table 3. Evolution of the OHIP-49 score during the two months of the study (Student t-test).

OHIP-49	Group B (n=25): mean ± SD	Group A (n=25): mean ± SD	P-value
	Evolution (day 0 - 2 months)	Evolution (day 0 - 2 months)	
Functional limitation	$(10.80 \pm 5.98) - (7.72 \pm 5.53) = 3.84 \pm 5.24$	$(12.36 \pm 6.83) - (12.28 \pm 6.80) = 0.08 \pm 0.64$	0.001
Bodily pain	$(15.80 \pm 8.31) - (11.16 \pm 8.06) = 4.64 \pm 7.43$	$(14.16 \pm 7.65) - (13.56 \pm 8.37) = 0.68 \pm 2.35$	0.014
Psychological discomfort	$(10.40 \pm 5.82) - (6.84 \pm 5.55) = 3.56 \pm 5.07$	$(7.52 \pm 6.49) - (7.52 \pm 6.77) = 0.00 \pm 1.15$	0.001
Physical disability	$(9.08 \pm 6.95) - (6.12 \pm 6.72) = 3.12 \pm 5.36$	$(8.88 \pm 7.16) - (8.88 \pm 7.16) = 0.00 \pm 0.00$	0.005
Psychological disability	$(10.04 \pm 6.26) - (6.76 \pm 6.22) = 3.28 \pm 6.22$	$(5.08 \pm 5.72) - (4.64 \pm 5.93) = 0.44 \pm 1.35$	0.031
Social disability	$(3.00 \pm 5.38) - (2.52 \pm 4.77) = 0.72 \pm 5.99$	$(3.12 \pm 5.46) - (2.96 \pm 5.49) = 0.16 \pm 0.80$	0.646
Handicap	$(3.84 \pm 6.22) - (2.36 \pm 5.64) = 1.48 \pm 5.16$	$(4.32 \pm 4.66) - (3.88 \pm 4.79) = 0.46 \pm 1.56$	0.358
Total OHIP-49	$(62.96 \pm 34.03) - (44.52 \pm 28.17) = 18.44 \pm 29.53$	$(55.40 \pm 34.33) - (53.72 \pm 35.30) = 1.92 \pm 4.93$	0.008

Note: SD = standard deviation

Table 4. Evolution of the SF-36 score during the two months of the study (Student t-test).

SF-36	Group B (n=25): mean ± SD	Group A (n=25): mean ± SD	P-value
	Evolution (day 0 - 2 months)	Evolution (day 0 - 2 months)	
Physical functioning	(57.40 ± 34.12) – (67.60 ± 38.04) = -10.20 ± 25.26	(54.00 ± 38.78) – (54.20 ± 39.01) = -0.20 ± 1.00	0.054
Physical role	(26.50 ± 42.43) – (58.00 ± 49.23) = -35.50 ± 45.31	(44.00 ± 50.66) – (44.00 ± 50.66) = 0.00 ± 0.00	<0.001
Bodily pain	(24.00 ± 31.38) – (39.50 ± 36.48) = -15.50 ± 26.65	(51.22 ± 28.61) – (54.22 ± 29.11) = -3.00 ± 7.63	0.029
General health	(32.99 ± 29.38) – (44.16 ± 29.34) = -11.16 ± 23.31	(42.33 ± 27.94) – (42.99 ± 29.13) = -0.66 ± 3.33	0.031
Vitality	(39.80 ± 25.55) – (52.00 ± 30.31) = -12.20 ± 23.80	(47.80 ± 27.99) – (50.80 ± 30.40) = -3.00 ± 8.03	0.073
Social functioning	(47.00 ± 39.73) – (59.50 ± 41.02) = -12.50 ± 25.51	(60.00 ± 32.87) – (62.50 ± 34.23) = -2.50 ± 10.20	0.075
Emotional role	(34.66 ± 47.60) – (55.99 ± 48.80) = -21.33 ± 40.68	(42.66 ± 47.64) – (43.99 ± 46.86) = -1.33 ± 6.66	0.019
Mental health	(36.16 ± 27.45) – (51.52 ± 29.08) = -15.36 ± 27.89	(47.04 ± 27.76) – (52.00 ± 30.19) = -4.96 ± 17.40	0.120

Note: SD = standard deviation