EFFICACY OF CLONAZEPAM AND NORTRIPTYLINE IN THE MANAGEMENT OF BURNING MOUTH SYNDROME: A COMPARATIVE STUDY

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BACKGROUND

Burning mouth syndrome (BMS) is a syndrome with intra oral burning sensation without clinical cause which occurs daily for more than 2 hours per day persisting for more than 3 months, which may be associated with taste alteration and oral dryness. The etiopathogenesis of BMS remains elusive and the most accepted theory suggests a neuropathic pain condition involved with neurotransmitter GABA in the gustatory system. Clonazepam-GABA agonist has been used in clinical practices for BMS. Nortriptyline, a TCA inhibits the reuptake of serotonin and norepinephrine into the synapse, thereby enhancing signalling via these neurotransmitters and thus used in neuropathic pain of BMS.

METHODS

72 patients of VIMSAR ENT OPD complained of burning mouth sensation without any oral or general pathology and diagnosed as BMS from September 2017 to February 2019 were included in the study. 36 patients were prescribed clonazepam and other 36 patients were treated with nortriptyline. Clinical evaluation after 6 wks. and 3 months of treatment was done and pain evaluated with verbal numerical scale (VNS).

RESULTS

Out of 72 patients, 46 were males and the mean age of presentation was 66 years. At the time of presentation, the mean baseline VNS score for the group (n=36) treated with clonazepam was 7.1 ± 0.9 and for the group (n=36) treated with nortriptyline was 6.8 ± 1.2. After treatment, VNS scores were 4.7 ± 1.3 and 4.5 ± 0.9 respectively at 6 weeks (p=0.510) and 3.3 ± 1.3 and 2.5 ± 0.9 respectively at the end of 3 months (p=0.499).

CONCLUSIONS

Nortriptyline is a better drug than Clonazepam for management of pain in patients with BMS.

KEYWORDS

Burning Mouth Syndrome, Clonazepam, Nortriptyline, Stomatodynia, Glossodynia, Dry Mouth.


BACKGROUND

Burning mouth syndrome (BMS) is an idiopathic condition characterised by abnormal burning sensation of oral cavity involving buccal mucosa, tongue mucosa and soft palate without any evident pathological changes and sometimes associated with oral dryness and odynophagia. It usually occurs daily for few minutes to hours in a day and may persist for more than three months. Synonyms of BMS are stomatodynia, glossodynia, dry mouth, sore mouth or glossopryosis. Its aetiology has still remained unclear. Patton et al. suggested that in a large percentage of patients, BMS probably involves interactions among local, systemic, and psychogenic factors.1 It is a neuropathic pain which may be due to some local causes like chronic irritation of gustatory system which mediate the secretion of GABA, due to systemic causes or it may be due to psychological factors which mediate the secretion of serotonin. According to many recent literatures BMS has a neuropathic aetiology.2-5 BMS aetiology could be due to local factors such as composition of saliva, mucosal blood flow, inflammation, and changes in cell morphology.6-9 According to Lamey and Lewis BMS is of three different types.

BMS type 1: Burning increasing throughout the day and reaching its peak in the evening.
BMS type 2: Characterized by the complaint of continuous sensory disturbances.
BMS type 3: Intermittent symptoms with pain-free periods during the day.
Scala et al. classified BMS as -
1. Primary BMS- Idiopathic condition (no local or systemic cause for the burning identified).
2. Secondary BMS- Presence of organic local or systemic cause for the intra-oral burning sensation.

Prevalence of BMS in the general population is around 0.7% to 15%.

Aims and Objectives
- To compare the efficacy of clonazepam over nortriptiline in managing pain in BMS.
- To compare the efficacy of clonazepam and Nortriptiline in managing BMS.

METHODS
This study was an interventional study done in department of ENT and head and neck surgery, VIMSAR, Burla from September 2017 to February 2019 among the outdoor patients who came with chief complain of burning sensation in oral cavity with or without dryness of mouth for more than three months. Before starting the trial, the examiner was calibrated so as to achieve a minimum kappa value of 0.80 to test interrater reliability. Among these patients 72 nos. of patients were selected who didn’t have any known local or systemic pathological condition. So all patients having systemic pathology like DM, HTN and patients having known oral pathology were excluded from our study. These patients were divided into two groups as group-A and group-B each containing 36 patients each by using proper sampling method. Group A (n=36) patients who were treated with Clonazepam 0.5mg once daily. Group B (n=36) patients who were treated with Nortriptiline 25 mg once daily. Pain in BMS patients were scored according to Verbal Numerical Scale (VNS) (0-10) at the time of presentation (1st visit) and after prescribing the respective drugs to both the groups, pain scoring was done at 6 weeks and 3 months following treatment. Ethical clearance for the same was obtained from the institutional ethical committee.

RESULTS
Out of 72 patients, 46 (63.8%) were males .The mean age of presentation was 66 years. At the time of presentation, the mean baseline VNS score for the group-A (n=36) treated with clonazepam was 7.1 ± 0.9 and for the group-B (n=36) treated with nortriptiline was 6.8 ± 1.2. After treatment with clonazepam and nortriptiline, the 2 groups were followed up at 6 weeks and 3 months as shown in Table 1. There mean VNS score were 4.7 ± 1.3 and 4.5 ± 0.9 respectively at 6 weeks (p=0.510), 3.3 ± 1.3 and 2.5 ± 0.9 respectively at the end of 3 months (p=0.499).

DISCUSSION
Many studies of burning mouth syndrome (BMS) have described more epidemiological and etiological aspects than diagnosis and treatment whereas our study discusses about the management of BMS and a comparison between the efficacy of Clonazepam and nortriptiline for treating the disease. The data of this review were materialized in a standard examination protocol which included a thorough clinical examination of the oral cavity for diagnosing BMS and all patients in study group were subjected to two different drugs after being divided in two study groups randomly. The symptoms present in patients with BMS are

a) The triad consisted of:
   1. Oral mucosal pain: burning, scalding, tingling, numb feeling, stinging;
   2. Altered taste (dysgeusia): Altered taste perception;
   3. Xerostomia, with dry mouth.

b) Other symptoms: thirst, headache, pain in temporomandibular joint (TMJ) tenderness, shoulder, and suprahyoid muscles.

According to Scala et al., the fundamental criteria and additional criteria are as follows.

Fundamental Criteria
1. Deep burning sensation of oral mucosa (bilateral) every day.
2. Pain of at least 4-6 months.
3. Constant intensity or increasing intensity during the day.
4. Characteristic symptoms are not getting worse/sometimes there may be an improvement over the ingestion of food and liquid.
5. No interference with sleep.

**Additional Criteria**

1. The occurrence of other oral symptoms (dysgeusia ± xerostomia)
2. Sensory changes/chemosensory alterations
3. Psychopathological alterations/mood changes that translate the patient’s personality disorder

The diagnosis of BMS is done by exclusion.15,16 aetiology of BMS remains unclear and not understood. Although the aetiology of BMS still remains unclear, according to Patton et al. BMS probably involves interactions among local, systemic, and psychogenic factors.1 According to some literatures, BMS might be influenced by local factors such as composition of saliva, mucosal blood flow, inflammation, cell morphology, etc.6,9 but others suggest that BMS is of neuropathic aetiology. Jääskeläinen et al. and Hagelberg et al. shows the involvement of dopaminergic system in BMS2,7 and Lauria et al. observed that changes like axonal degeneration and hypothesized that trigeminal small fibre sensory neuropathy with the help of tongue biopsies.8 Eating often relieves the burning sensation (mainly sweets), suggesting that the decrease in pain may be due to the stimulation of the gustatory system.9 Most commonly affected site in BMS is anterior two thirds of the tongue.8,21 Most of the times, clinical examination does not reveal any changes. So with no clinically evident lesions in oral mucosa, intraoral burning can be due to systemic disorders (such as diabetes mellitus or anaemia, folic acid deficiency, or vitamin B12 – cobalamin deficiency) or could be diagnosis of exclusion.22

**Common Laboratory Tests**

- Complete blood cell counts (CBC).
- Sedimentation rate (ESR).
- Serum iron.
- Serum ferritin concentration.
- Iron binding capacity.
- Concentration of circulating folic acid, vit. B12, zinc, etc.
- Glycaemia (blood glucose level).
- Determination of serum hormone (estradiol) levels in women.

**Other Laboratory/ Clinical Tests**

- Sialometry
- Specific investigations of systemic diseases
- Allergic epicutaneous tests.
- Fungal culture for the isolation of Candida species from oral mucosa.

Our study which included only idiopathic BMS, the therapeutic principles covered a triple purpose: improvement of symptoms, correction of biological and/or morphological disturbances and the therapy of psychoemotional changes (Table 3).

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<tr>
<th>Systemic Therapy</th>
<th>Correction Therapy</th>
<th>Psychopharmacological Therapy</th>
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<tr>
<td>Solution 3% benzodiazepine</td>
<td>Iron</td>
<td>Benzodiazepines</td>
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<td>Anthistamine</td>
<td>Vit. B12/ Folate</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Sucrafate</td>
<td>Vit. B1, B2, B6</td>
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<td>Salivary substitutes</td>
<td>Topical antifungal</td>
<td>Hypnosis</td>
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**Table 3. The Major Therapies Used in BMS**

After 6 months of treatment given to two groups our study found that the VNS Score decreased quite promisingly with nortriptyline rather than Clonazepam. In our study reduction in pain due to BMS was found to be about 53% with clonazepam as compared to Grushka et al. study which reported a 70% reduction in pain levels with the oral administration of Clonazepam, a GABA agonist (0.5–1.5 mg/day in divided doses to a maximum of 3 mg/day).24 According to Heckmann et al clonazepam 0.5 mg/day had reduced pain in BMS significantly in a double blind randomised control study.25 Nortriptyline works by inhibiting the reuptake of serotonin and nor-epinephrine into the synapse thereby enhancing signalling via these neurotransmitters and thus helps treating pain in BMS. In our study administration of oral low dose nortriptyline could reduce 63% of pain due to BMS which can be correlated with another study in which low dose TCA (10-40 mg/day) has reduced pain significantly.26 our study found out the mean VNS score of 7.1 ± 0.9 with clonazepam and 6.8±1.2 with nortriptyline on 1st visit. After 3 months of treatment the mean VNS score with Clonazepam was 3.3±1.3 and 2.5±0.9 with nortriptyline. The mean VNS score at baseline with clonazepam was 7.1±2.0 and 7.5±1.1 with Amitriptyline in another study. The same study showed mean VNS score of 4.4±2.0 with clonazepam and 4.1±2.7 with amitriptyline after 3 months of treatment.27

**CONCLUSIONS**

Nortriptyline was found to be more efficacious than clonazepam in treatment of BMS. BMS remains a challenge for both clinicians and researchers. Uses of electric taste/tingling detection threshold ratio, and biomarker in BMS as reliable tools for diagnosing BMS are being considered recently. Future research should focus on developing a uniform definition, diagnostic criteria and various treatment options with long-term follow-ups.

**REFERENCES**


