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An Evaluation of the Efficacy of Clonazepam in Patients with Burning Mouth Syndrome in comparison with Lycopene: A Double-Blinded clinical Study

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ABSTRACT:

Burning mouth syndrome (BMS) as defined by the International Association for the Study of Pain is the burning pain in the tongue or other oral mucous membrane that are associated with normal signs and laboratory findings lasting at least 4 to 6 months. This study was designed to evaluate the clinical efficacy of clonazepam in comparison with lycopene in treating patients with burning mouth syndrome (BMS). Thirty patients were randomized into two groups equally. Group-1 was administered with Clonazepam at a dose of 0.25mg before bed for 1 week, with escalation of the dose by no more than 0.25 mg each week to a maximum dose not greater than 3.0 mg per day in 3 divided doses. Group-2 was administered with lycopene 4 mg twice daily for a period of 8 weeks. The patients were evaluated by the severity of burning sensations using a 10-point visual analog scale (VAS: 0-10; 0=no burning sensation and 10= worst possible burning sensation) and follow-up visits at 2, 4, 6 and 8 weeks to assess the score. The subjects comprised of 10 males and 20 females with an average age years. The results of this study showed that there was reduction in burning sensation significantly at subsequent follow up visits at 2nd, 4th, 6th and 8th weeks in both the groups but these changes were much more pronounced in patients receiving Clonazepam compared to patients receiving Lycopene Clonazepam has been found effective on pain in patients with burning mouth syndrome and there has been no major side effects that would severely restrict its application.

Key words: Burning mouth syndrome, Clonazepam, Lycopene

Introduction

The most difficult problem encountered in oral medicine is one of the patients who consistently complains of pain or burning sensations of oral cavity with no convincing physical explanation (Brightman, 1984).[1] These conditions can occur due to several local , systemic or psychiatric conditions that must be ruled out prior to making diagnosis of burning mouth syndrome.[2] Burning mouth syndrome (BMS) as defined by the International Association for the Study of Pain, is the burning pain in the tongue or other oral mucous membrane that are associated with normal signs and laboratory findings lasting at least 4 to 6 months.[3] BMS is a diagnosis of exclusion (Task Force 1994; Headache Classification Committee 2013) with complex and likely multi-factorial etiology. There is evidence demonstrating disturbances in taste, nervous and endocrine functions that may precipitate or exacerbate the disease.[4]

Clinical studies have shown that the burning sensations can affect the tongue, the buccal mucosa, the palate, the denture bearing areas

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and the throat. There are two forms of burning mouth syndrome (BMS) that has been discussed clinic-pathologically: ‘‘true” or primary BMS, the idiopathic form, and secondary BMS, resulting from local or systemic disorders that may respond to appropriately directed therapies (Scala et al., 2003).[5] Undiagnosed cases like diabetes mellitus, hematological deficiencies, decreased salivary gland flow, candidal infection, allergy and parafunctional habits might also play an important role in the undermined causes of the symptoms of spontaneous burning sensations that should be considered during consideration of the treatment protocols.[6,7,8] Therefore, once BMS has been diagnosed, treatment is often symptomatic with a number of interventions that include psycho-logic counselling and various psychotropic medications like low dose tricyclic antidepressants. [9]

Recently there has been interest in the benzodiazepine class of drugs for the treatment of oro-facial pain, including BMS such as chlordiazepoxide and clonazepam.[10] Gorsky et al [11] found reduction in pain of BMS patients in approximately 67% at daily doses of 15 to 30 mg of chlordiazepoxide. Studies have shown benefit using clonazepam in the treatment of BMS at doses (0.5 to 6 mg daily), with an average reported daily dose of 2 mg.[10]

The purpose of this study was to evaluate the clinical efficacy of clonazepam in comparision with lycopene in treating patients with BMS.

MATERIAL AND METHODS

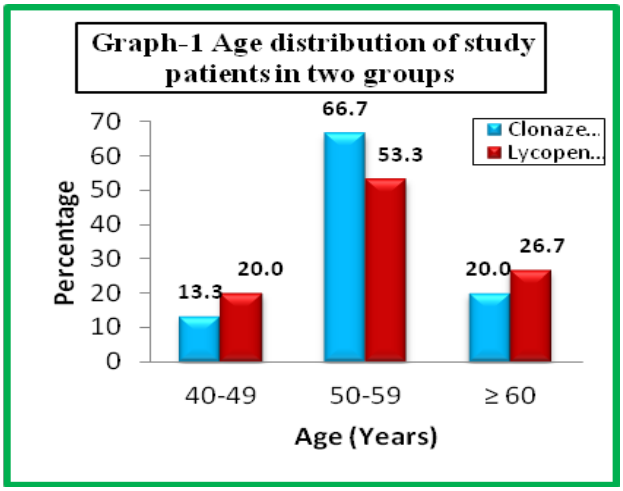
This double-blinded randomized clinical study was done in the Department of Oral Medicine And Radiology, Government dental college Srinagar. The inclusion criteria include 30 patients who reported for the treatment of BMS with a chief complaint of burning sensations of the mouth. Exclusion criteria include patients with geographic tongue, oral candidiasis, lichen planus and systemic diseases like diabetes, HIV, pregnancy and immuno-suppression. After taking written consent, detailed medical history was taken from each participant, thorough clinical examination of the oral cavity and laboratory tests including complete blood cell counts, fasting blood sugar levels were performed. Hematologic examination findings of all the 30 patients were normal, including tests for vitamin B 12, serum ferritin, serum zinc, complete blood cell count, blood film, erythrocyte sedimentation rate, thyroid-stimulating hormone, and blood sugar. Thirty patients attending in our department were randomized into two groups equally. Group-1 was administered with Clonazepam at a dose of 0.25mg before bed for 1 week, with escalation of the dose by no more than 0.25 mg each week to a maximum dose not greater than 3.0 mg per day in 3 divided doses. Dose of clonazepam was increased only until they experienced either significant pain relief or untoward side effects without relief. Group-2 was administered with lycopene 4 mg twice daily for a period of 8 weeks. The patients were evaluated by the severity of burning sensations using a 10-point visual analog scale (VAS: 0-10; 0=no burning sensation and 10= worst possible burning sensation). Side effects were recorded by patient history. The patients were followed at 0, 2, 4, 6 and 8 weeks and scores were assessed.

Statistical Methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as Mean±SD. Graphically the data was presented by bar and line diagrams. Student’s independent t-test was employed for comparing various VAS score between two groups. A P-value of less than 0.05 was considered statistically significant. All P-values were two tailed.

Results

The subjects comprised of 10 males and 20 females with mean age of 55.9 years in case of clonazepam group and 55.7 years in lycopene group with no statistically significant difference ($p > 0.05$). Table-1 shows mean age of the patients and the graph-1 showing age distribution of study patients in two groups. All the patients finished the period of study and there were no side effects reported, that could restrict the progression of treatment.

Table 1: Age distribution of study patients in two groups					
Age (years)	Clonazepam Group		Lycopene Group		P-value
	No.	%age	No.	%age	
40-49	2	13.3	3	20.0	0.933
50-59	10	66.7	8	53.3	
≥ 60	3	20.0	4	26.7	
Total	15	100	15	100	
Mean±SD (Range)	55.9±6.32 (40-67)		55.7±6.61 (45-70)		



The results of this study showed that there was reduction in burning sensations significantly at subsequent follow up visits at 2nd, 4th, 6th and 8th weeks in both the groups but these changes were much more pronounced in patients receiving Clonazepam compared to patients receiving Lycopene (P<0.05). The mean VAS score for two groups before and after treatment are shown in table-2.

Table 2: Comparison based on VAS score among two groups at various intervals of time					
Time Interval	Clonazepam Group		Lycopene Group		P-value
	Mean	SD	Mean	SD	
0 Weeks	6.5	1.41	6.3	1.40	0.699
2 Weeks	4.0	1.13	5.6	1.35	0.001*
4 Weeks	3.5	1.13	5.0	1.31	0.002*
6 Weeks	2.3	0.72	4.9	1.30	<0.001*
8 Weeks	2.0	0.65	4.1	1.13	<0.001*

*Statistically Significant Difference (P-value<0.05)

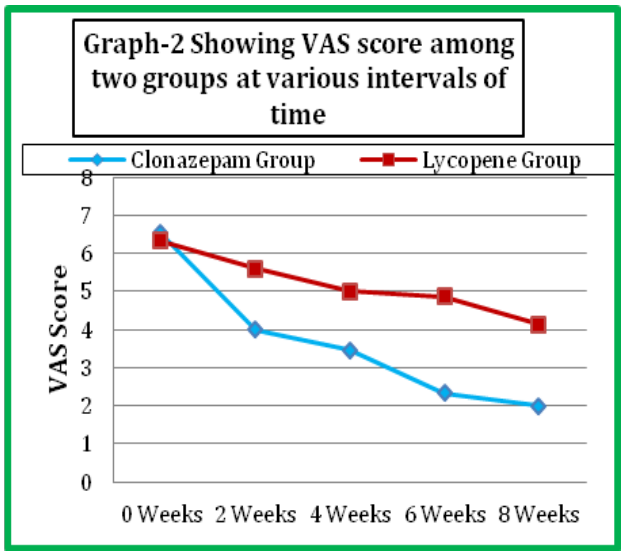
Discussion

BMS is a diagnosis of exclusion (Task Force 1994; Headache Classification Committee 2013) with complex and likely multi-factorial etiology. There is evidence demonstrating disturbances in taste, nervous and endocrine function that may precipitate or exacerbate the disease.[4] Treatment of BMS is often symptomatic with a number of interventions that include psycho-logic counseling and various psychotropic medications like low dose tricyclic antidepressants, benzodiazepines such as chlordiazepoxide and clonazepam. [9]

Clonazepam in the treatment of BMS at doses (0.5 to 6 mg daily), with an average reported daily dose of 2 mg have shown promising results with reduction in burning sensations significantly.[10] It is argued that benzodiazepines such as clonazepam and chlordiazepoxide may be exerting their effect by acting as anxiolytic agents and affect psychogenic changes as they are GABA-receptor agonists binding to both peripheral as well as central receptor sites.[12,13]

Clonazepam used as an anticonvulsant, binds more to central than peripheral benzodiazepine receptor sites with strong effect on the brain's serotonergic system and has a longer half-life compared to other benzodiaze-pines, thereby resulting in fewer withdrawal effects upon discontinuation of the medication.[14] In this study we evaluated the clinical efficacy of clonazepam in comparision with lycopene in treating patients with BMS.

There was reduction in burning sensations significantly at subsequent follow up visits at 2nd, 4th, 6th and 8th weeks in both the groups. The reduction in burning sensations was more pronounced in patients receiving Clonazepam compared to patients receiving Lycopene (P<0.05). There is reduction in mean VAS score for two groups before and after treatment are shown in table-2 and graph-2 showing VAS score among two groups at various intervals of time.



Heckmann et al. conducted a study on clonazepam versus placebo in patients with Burning Mouth Syndrome and concluded that pain ratings changed significantly with much more pronounced effect in patients receiving clonazepam compared to placebo.[14] P. Cano-Carrillo et al. studied efficacy of lycopene-enriched virgin olive oil in comparision to placebo for treating burning mouth syndrome and found that symptoms significantly improved in both groups with no statistically significant differences between the groups.[15] Huang W et al. have found benefit using clonazepam in the treatment of BMS at doses (0.5 to 6 mg daily), with an average reported daily dose of 2 mg.[10]

Conclusion

Clonazepam has been found effective on pain in patients with burning mouth syndrome and there has been no major side effects that would severely restrict its application. It reduces the symptoms of BMS, so could be a novel therapeutic agent for the treatment of BMS.

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