Original Article

Therapeutic Effects of "Ibuprofen, Diphenhydramine and Aluminium MgS" on Recurrent Aphthous Stomatitis: A Randomized Controlled Trial

Katayoun Borhan-Mojabi[1], Faezeh Mirmiran[2], Marjan Nassiri-Asl[3], Pantea Nazeman[4], Hassan Jahanihashemi[5]

[1]Associate Professor, Dental Caries Prevention Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
[2]Assistant Professor, Dental Caries Prevention Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
[3]Associate Professor of Pharmacology, Department of Pharmacology, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran
[4]Dentist, Research Center, School of Dentistry, Qazvin University of Medical Sciences, Qazvin, Iran
[5]Associate Professor of Biostatistics, Department of Biostatistics, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

Abstract

Objective: Recurrent aphthous stomatitis (RAS) is the most common and painful oral inflammatory lesion with an unknown etiology. This study aims to determine the therapeutic effects of ibuprofen, diphenhydramine and aluminum magnesium simethicone (AlMgS) syrup on reducing oral aphthous ulcer pain.

Materials and Methods: Thirty-one patients with RAS participated in this double-blind clinical trial. Subjects were randomly divided into two groups. The control group (n=14) received drug mixture as drug A (diphenhydramine and AlMgS) and the case group (n=17) received drug B (ibuprofen, diphenhydramine and AlMgS). Drugs were topically applied on ulcers by the patients three times a day for 3 days. Patients were re-examined for the symptoms on the fourth day following their first visits using VAS (Visual Analogue Scale) tool. Statistical analysis was performed using paired t-test, independent t-test and chi-square test.

Results: The mean of pain reduction was 3.17±2 (P<0.001) and 3.82±1.79 (P<0.001) in the case and control group, respectively. The difference in pain reduction between both groups was not statistically significant. In addition, no significant difference was detected between the two groups regarding the duration of pain or burning sensation (P=0.57).

Conclusion: The results of this study demonstrate that in comparison with diphenhydramine and AlMgS syrup, the studied mixture did not effectively reduce the level of pain, duration and burning sensation.

Key Words: Stomatitis, Aphthous; Ibuprofen; Treatment Efficacy

Corresponding author:
P. Nazeman, Research Center, School of Dentistry, Qazvin University of Medical Sciences, Qazvin, Iran

pnazeman@yahoo.com

Received: 25 July 2013
Accepted: 7 December 2013

Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2014; Vol. 11, No.2)

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most painful oral lesion with a considerable prevalence (a mean of 20%) characterized by recurring ulcers confined to the oral mucosa with no other signs of disease [1].

A mature ulcer possesses a yellow necrotic center and a smooth clear margin circumscribed by erythematous haloes. Chiefly the buccal mucosa and lip are infected. Keratinized mucosa of the palate and gingiva are less often involved [2].

Of the etiologic point of view, aphthous stomatitis is a multifactorial lesion; however, the main etiology still remains unknown [3]. Trauma, [4] infectious agents, [5] hormonal factors, [4] genetic susceptibility, [6] hematologic factors, [7] immunologic abnormalities, [8] stress [9] and allergy [10] are considered as the predisposing factors [11].

Treatment of RAS is symptomatic and chiefly empirical [12]. The most common aphthous ulcer treatments include applying topical agents such as antibiotics [13] and analgesics [14] to immunosuppressive agents. [11] Corticosteroids are routinely prescribed for the treatment of these lesions, while the consumption of this medication is eliminated due to the several side effects of this drug [15, 16]. Diphenhydramine and aluminum magnesium simethicone (AlMgS) syrup have long been prescribed as analgesic mouthwash in order to decrease a great number of the symptoms of oral ulcers such as aphthous ulcers [16]. Ibuprofen is a potent non-steroidal anti-inflammatory drug (NSAID) with fair anti-inflammatory potential prescribed in dental pain [17].

A double-blind study conducted by Collier *et al.* (1992) that had assessed 22 patients affected by RAS suggested that 5-aminosalicilic acid (5-ASA) cream should be considered as an effective therapeutic approach for aphthous ulcers. [18] Saxen *et al.* (1997) studied 60 patients affected by RAS and they demonstrated that a single dose of 3% diclofenac in 2.5% hyaluronan resulted in a significant decrease in pain [19].

Therefore, we studied the therapeutic efficacy of ibuprofen, diphenhydramine and AlMgS syrup in the treatment of recurrent aphthous stomatitis.

MATERIALS AND METHODS

This double-blind randomized clinical trial was established in the oral medicine department of dental faculty in Qazvin University of Medical Sciences, Qazvin, Iran**.** This clinical trial was registered in clinicaltrials.gov with NCT01293968 identifier.

Of the total number of patients affected by RAS referring to this faculty in the second half of 2010, individuals fulfilling the conditions of the trial including possessing at least one painful apththous ulcer detected in the last three days, age older than 10 years, lack of any systemic disorder or specific syndrome (such as Behcet's) in which aphthous ulcers are considered as the signs of disease , women not experiencing breastfeeding or pregnancy, no history of allergy to NSAIDs, no history of asthma, peptic ulcers, hepatic and renal failures and hemorrhagic disorders, no consumption of anti-inflammatory medications in the last 24 hours, no history of systemic corticosteroid consumption in the last 2 weeks were included in the study. After examination and approving the diagnosis of aphthous stomatitis, each subject signed a detailed informed consent form to participate in the study; meanwhile, the ethical issues and principles of the study were approved in Iran Ethics Committee that were accordant with Helsinki Declaration of 1975 as well. Thirty one patients were randomly allocated to case and control groups by an epidemiologist. This randomization was based on building homogeneous unit blocks (two red and blue beads). If possible, a homogeneous block was generated and the items were randomly allocated to the case and control groups. In lack of homogeneous blocks, each sample was randomly allocated to the groups. Afterwards, a questionnaire was filled for each patient based on personal data and examination results. In this questionnaire, after recording personal data, such as age, gender, education and systemic situation, the state of the aphthous ulcers was evaluated and the level of pain and irritation was assessed by

VAS scale. According to the pharmacist's category, medication A (100 ml diphenhydramine 25 mg and 100 ml AlMgS 550 mg) and medication B (5 ml ibuprofen 100mg, 10 ml diphenhydramine 25 mg and 10 ml AlMgS 550 mg) were randomly prescribed to the patients while the investigators where blinded to these agents. Meanwhile, carboxy methyl cellulose was recruited as the vehicle in the mixture and the medications A and B were randomly numbered as well. All patients were instructed to apply the gel on the site of the ulcer 30-60 minutes before meals, three times daily. On the fourth day, while the medication was applied for 3 days, the patients were clinically assessed and the questionnaires were completed.

Data analysis was performed by paired t-test, independent t- test and chi-square test. In this study $P<0.05$ was considered as statistically significant. On the other hand, out of the total number of 37 patients fulfilling the conditions of the trial, six patients (four cases and two controls) were excluded due to non-compliance.

RESULTS

Thirty-one patients were enrolled in this study. The demographic data and clinical characteristics are illustrated in Table 1.

To assess intra group reduction in pain and irritation after treatment (VAS1 – VAS2), paired t-test was administered and the results suggested significant pain alleviation in both groups (details illustrated in Table 2).

To compare VAS alternations before and after treatment between the two groups, independent t-test was administered and the results demonstrated no statistically significant difference between the level of pain and irritation reduction ($P= 0.358$). In order to compare the duration of pain and irritation reduction between the groups, the history of pain duration and irritation of the previous ulcers were taken into consideration on the day of examination.

After the intervention, duration of pain and irritation reduction was 0.35±3.3 and 0.29±2.7 days in the case and control groups, respectively while the difference was not statistically significant ($P=0.57$).

Table 1. Baseline Demographic and Clinical Characteristics of the Two Groups

Index	Case (n=14)	Control (n=17)	P-Value
Age	33.71±9.7	30.43±10.5	0.374
Gender (%)	Female: 11 (64.7%) Male: 6 (35.3%)	Female: 7(50%) Male: 7(50%)	0.409
VAS_1	6.65±2	5.71±2.2	0.23
Pain Duration (day)	6.35±3.4	5.71±2.6	0.564

Table 2. Mean of Pain Reduction in Case and Control Groups Before and After Treatment

Index	Case (n=17)		Control (n=14)	
VAS	**Before**	**After**	**Before**	**After**
	6.65±2	3.47±2.7*	5.71±2.2	1.89±1.6*

*= $P<0.001$

The power of the study was calculated as 72.19% in comparing the means of pain and irritation reduction in the case and control groups.

DISCUSSION

In this study, ibuprofen, diphenhydramine and AlMgS syrup were effective in alleviating the pain and irritation in aphthous ulcers and VAS was significantly decreased by the fourth day in the case group. While comparing the therapeutic efficacy of this syrup with diphenhydramine and AlMgS, no considerable change was detected in the decrease of irritation, duration and level of the pain in aphthous ulcers; consecutively, this result is inconsistent with the results of the study conducted by Collier et al. on 5-ASA medication [18] and the study carried out by Saxen et al. on the mixture of diclofenac in hyaluronan [19]. It is assumed that lack of a mixture as placebo in this assessment accounts for the inconsistency with Collier's study [18]. In fact, our suggested mixture was compared with the most routine syrup and the first choice in the treatment of patients affected by aphthous oral ulcers. There might be the possibility to detect significant statistical differences if the study was based on comparison of drug and placebo.In the study performed by Saxen et al., [19] the efficacy of diclofenac in hyaluronan was assessed and the dosage form administered in their study was gel, similar to our study, although their method was different. In their study unlike our study, the single dose effects were assessed and VAS was evaluated 10 minutes after applying gel. In another study conducted on children affected by Behcet's disease, prior to the diagnosis of Behcet's disease, NSAID was prescribed and consecutively some joint symptoms improved while no improvement was observed in the other symptoms [20]. The other issue that must be taken into consideration is that ibuprofen was administered in aphthous ulcers therapy for the first time in our study and to our knowledge, no other study has been conducted on the prescription of this medication, either as a single drug or in combination with other drugs in the treatment of aphthous. Furthermore, the dose prescribed through our study was 20 g/L, while we assume that by increasing the dose of ibuprofen and applying different concentrations, the results might change.

CONCLUSION

Generally, it is concluded that NSAIDs are not truly potent medications for reducing pain and irritation in aphthous ulcers and studies on a larger number of subjects by applying different concentrations may be needed to assess the efficacy of these drugs in improving the signs of these lesions. According to the results obtained from this study, it is demonstrated that compared to diphenhydramine and AlMgS, ibuprofen, diphenhydramine and AlMgS syrup is not a potent medication in reducing the pain level, duration and irritation of recurrent aphthous stomatitis ulcers. Therefore, prescribing this medication to the patients affected by RAS is not suggested until there are more studies conducted on this issue.

REFERENCES

1- Greenberg MS, Glick M, Ship JA. Burket's oral medicine, diagnosis and treatment. 11th ed. India: BC Decker Inc; 2008. p. 57-61.

2- Gonsalves WC, Chi AC, Neville BW. Common oral lesions: Part I. Superficial mucosal lesions. Am Fam Physician 2007 Feb;75(4):501-7.

3- Mimura MA, Hirota SK, Sugaya NN, Sanchez JR JA, Migliari DA . Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. Clinics (Sao Paulo) 2009; 64(3):193-8.

4- Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc. 2003 Feb;134(2):200-7.

5- Marchini L, Campos MS, Silva AM, Paulino LC, Nobrega FG. Bacterial diversity in

aphthous ulcers. Oral Microbiol Immunol. 2007 Aug;22(4):225-31.
6- Guimarães AL, Correia-Silva Jde F, Sa AR, Victória JM, Diniz MG, Costa Fde O, et al. Investigation of functional gene polymorphisms IL-1beta, IL-6, IL-10 and TNF-alpha in individuals with recurrent aphthous stomatitis. Arch Oral Biol. 2007 Mar;52(3):268-72.
7- Compilato D, Carroccio A, Calvino F, Di Fede G, Campisi G. Haematological deficiencies in patients with recurrent aphthosis. J Eur Acad Dermatol Venereol. 2010 Jun;24(6):667-73.
8- Borra RC, de Mesquita Barros F, de Andrade Lotufo M, Villanova FE, Andrade PM. Toll-like receptor activity in recurrent aphthous ulceration. J Oral Pathol Med. 2009 Mar;38(3):289-98.
9- Gallo Cde B, Mimura MA, Sugaya NN. Psychological stress and recurrent aphthous stomatitis. Clinics (Sao Paulo). 2009;64(7):645-8.
10- Wardhana, Datau EA. Recurrent aphthous stomatitis caused by food allergy. Acta Med Indones. 2010 Oct;42(4):236-40.
11- Murray B, Biagione A, Lamey PJ. The efficacy of amelxanox Oradisk on the prevention of recurrent minor aphthous ulceration. J oral Pathol Med. 2006 Feb;35(2):117-22.
12- Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol. 2007 Sep;21(8):1019-26.
13- de Abreu MA, Hirata CH, Pimentel DR, Weckx LL. Treatment of recurrent aphthous stomatitis with clofazimine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Nov;108(5):714-21.
14- Suma GN, M Shukla. Topical analgesia for oral mucosa: An Update. J Oral Health Res. 2010; 1(1): 33-40.
15- Regezi Ja, Sciubba JJ, Jodan RCK. Oral pathology, clinical pathologic correlation. 5th ed. Philadelphia: W.B Saunders Co; 2008. p. 35-9.
16- Domonkos AN, Arnold HL, Odom RB. Andrew's disease of the skin. 8th ed. Philadelphia: W.B Saunders Co; 1990. p. 939.
17- Langlais RP, Miller CS, Nield-Gehrig JS. Color atlas of common oral disease. 4th ed. Maryland: Lippincott; 2008. p. 191.
18- Collier PM, Neill SM, Copeman PW. Topical 5-aminosalicylic acid: a treatment for aphthous ulcers. Br J Dermatol. 1992 Feb;126(2):185-8.
19- Saxen MA, Ambrosius WT, Rehemtula AF, Russell AL, Eckert GJ. Sustained relief of oral aphthous ulcer pain from topical diclofenac in hyaluronan: a randomized double-blind clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Oct;84(4):356-61.
20- Kari JA, Shah V, Dillon MJ. Behcet's disease in UK children: clinical features and treatment including thalidomide. Rheumatology (Oxford). 2001 Aug;40(8):933-8.