A Six-Month Beta Glucan Treatment and Six-Months Follow Up of Recurrent Aphthous Stomatitis

Rekürrent Aftöz Stomatit'in Beta Glukan ile 6 Aylık Tedavi ve Takibi

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ABSTRACT Objective: Immunomodulating agents, zinc, vitamins B1, B2, B6, and B12, topical analgesics, and topical and systemic glucocorticoids have been the mainstay of treatment for recurrent aphthous stomatitis (RAS). However, their clinical value remains unproven and has been controversial. The aim of this study was to investigate the use of beta-glucan, which is a primer immune activator, as an alternative treatment modality. **Material and Methods:** Twenty-eights subjects (18 female, 10 male) with minor aphthous ulcer were included in this study. As the treatment modality, 10 mg of beta-glucan was administered once a day for six months. The number of ulcers and the degree of pain experienced were recorded before and after two- month period of the treatment. Illness severity scores for each patient were calculated by the sum of the product of the number of ulcers and their pain degree. The illness severity scores before the treatment were compared with those at the end of the treatment. **Results:** There were significant statistical differences between the mean illness severity scores of the patients before and after 2, 4, and 6 months of treatment ($p< 0.001$). **Conclusion:** These results suggest that beta-glucans can be used in the treatment of minor RAS.

Key Words: Beta-1,3-D-glucan; stomatitis, aphthous

ÖZET Amaç: İmmünomodülatör ajanlar, çinko, B1, B2, B6 ve B12 vitaminleri, topikal analjezikler ve topikal ile sistemik glikokortikoidler rekürrent aftöz stomatit (RAS)'ın tedavisi için başlıca kaynaklardır. Bununla birlikte bu ilaçların klinik değerleri hâla tartışmalıdır. Bu çalışmanın amacı alternatif bir tedavi modeli olarak primer immün aktivatör olan beta glukanın kullanımını incelemektir. **Gereç ve Yöntemler:** Minör aftöz ülserasyonlu 28 olgu (18 kadın, 10 erkek) bu çalışmada yer aldı. Tedavi modeli olarak 10 mg beta glukan 6 aylık bir sürede günde bir kez verildi. Ülserlerin sayısı ve hissedilen ağrı dereceleri tedavi öncesinde ve tedaviden sonraki her iki aylık periyodun sonunda kaydedildi. Daha sonra her hastanın hastalık şiddet skoru, ülserlerin sayısı ve onların ağrı derecelerinin çarpımı şeklinde hesaplandı. Tedavi öncesi ülser skorları tedavi sonundakiler (2, 4, 6 ay) ile karşılaştırıldı. **Bulgular:** Hastaların tedavi öncesi ile tedavinin 2, 4 ve 6 aylık dönemleri sonundaki hastalık şiddet skorları arasında istatistiksel olarak anlamlı farklılıklar bulundu ($p< 0.001$). **Sonuç:** Bu sonuçlar beta glukanların minör RAS'ın tedavisinde kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Beta 1,3 D glukan; stomatit, aftöz

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Recurrent aphthous stomatitis (RAS) is a common oral lesion characterized by painful recurring ulcerations and is observed in more than 10% of the general population.[1-3] Although the specific etiology of RAS is unknown and probably multifactorial, most evidence suggests that it is a noninfectious inflammatory disease of the oral mucosa.[4] In addition, some predisposing factors may play a contributing role, such as deficienci-

es in iron, folic acid, zinc, and vitamins B1, B2, B6 and B12, and trauma and stress.[5-7]

Although there is no specific treatment, immunomodulating agents such as zinc, vitamins B1, B2, B6, and B12, topical analgesics, and topical and systemic glucocorticoids have been the mainstay of treatment for RAS. However, their clinical value remains unproven and has been controversial.[2,8]

Beta-glucans (β- glucans) are polymers of β-(1,3)-D-glucose, with or without β-(1,6)-D-glucose side chains, found in the cell walls of many bacteria, plants and yeasts.[9] β-1,3;1,6- glucans from fungi (e.g., mushrooms) and yeast are well-known biological response modifiers that function as immunomodulaters against infectious disease and cancer. The broad spectrum of immunopharmacological activities of glucan includes not only the modification of certain bacterial, fungal, viral and parasitic infections, but also the inhibition of tumor growth.[8] These glucans function through stimulation of granulocytes (neutrophils and eosinophils), monocytes, macrophages and NK cells.[10,11] They also induce inflammatory mediators (IL-1, TNF, leukotrienes).[12]

Various types of glucans can be isolated from almost every species of yeast. However, glucan derived from *Saccharomyces cerevisiae* (*S. cerevisiae*) has been the most extensively studied and has produced the most significant biological effects.[13] Several studies have demonstrated the effects of a polysaccharide obtained from the cellular wall of *S. cerevisiae* (baker's yeast) on cellular immunity, humoral immunity, and neutrophil function.[14] While various soluble and particulate β-glucans have been used in pharmaceutical applications, particulate β-glucan preparations derived from the yeast *S. cerevisiae* are widely used as over-the-counter nutritional supplements.[9]

The purpose of this open study was to evaluate the clinical efficacy of β-glucans, as an immunomodulatory agent, in reducing the severity of pain and number of ulcers associated with RAS.

MATERIAL AND METHODS

This open study included 28 patients (18 female, 10 male) with a mean age of 28.6 years (range 18-50 years). Clinical diagnosis was made on the basis of clinical appearance and patient history. This study was approved by the ethical committee and informed consent was obtained from all patients.

Inclusion Criteria:

- Over 18 years old.
- Only minor ulcers
- Suffering from RAS for at least two years with a frequency of at least six recurrences per year
- Normal complete blood counts and iron, B12, folate and blood glucose levels.

Exclusion Criteria:

- Known systemic diseases concurrent with lesions in the mouth (Behcet's disease, rheumatoid arthritis, malabsorption, Crohn's disease, celiac disease, ulcerative colitis, Reiter's disease, hemorrhoids, and erythema multiforme).
- Patients who receive other treatment for RAS.
- Pregnant or nursing mothers.
- Patients suffering from psychosis.

All of the patients received oral therapy with β-glucan (Imuneks 10 mg cps, Mustafa Nevzat Company, TURKEY) at one dose of 10 mg daily for six months. The number of ulcers and the degree of pain experienced were recorded before treatment and after every two months of treatment for six months. Ulcers have been divided into 3 groups according to their pain degree, which was determined by the visual analog scale to be mild, moderate or severe. Ulcers with mild pain were graded as one, moderate pain as two, and severe pain as three points. Illness severity score for each patient was calculated as the sum of the product of the number of ulcers and their pain degree. For example, if a patient had two ulcers with mild, one ulcer with moderate, and one ulcer with severe pain, his/her illness severity score would be calculated as [(2 x 1) + (1 x 2) + (1 x 3)= 7].

STATISTICAL ANALYSIS

The collected data were analyzed using the SPSS 10.0 program. The Wilcoxon Signed Rank Test was

used to compare the data recorded before treatment and after every two-month period of treatment. All results were expressed as mean ± standard deviation (m ± SD). *P*-values lower than 0.05 were considered significant.

RESULTS

The distribution of the patients according to gender and age is shown in Table 1. Of the 28 subjects in total, 18 (64.3%) were female and 10 (35.7%) were male. RAS was observed most frequently in the age group of 21 to 30 years and decreased after age 40 in both sexes. Most of the ulcers were localized in tongue (28.6%), buccal mucosa (23.8%) and alveolar mucosa (21.4%) (Table 2).

The number of ulcers according to pain degree before and during treatment is shown in Table 3. Before treatment, 42 painful ulcers were observed in all subjects: 9 were mild, 15 were moderate, and 18 were severe pain. In the treatment period, there was a significant and steady decline in the number of ulcers. It was approximately 50% after two months and 86% after four months of medication. After six months, only one ulcer with severe pain was reported. Additionally, patients were followed up for 6 months after treatment and RAS did not recur in any of the 28 patients.

TABLE 1: Distribution of the patients according to sex and age.

	Female		Male		Total	
Age groups	**n**	**%**	**n**	**%**	**n**	**%**
11-20	5	17.80	2	7.15	7	24.95
21-30	7	25.00	5	17.80	12	42.80
31-40	4	14.30	2	7.15	6	21.45
41-50	1	3.60	0	0	1	3.60
51–60	1	3.60	1	3.60	2	7.20
Total	18	64.30	10	35.70	28	100.00

TABLE 2: The location types and numbers of the ulcer.

Location of ulcers	Number of ulcers	%
Tongue	12	28.60
Buccal m	10	23.80
Alveolar m	9	21.40
Labial m	5	11.90
Flour of m	3	7.10
Hard palate	1	2.40
Attached g	1	2.40
Soft palate	1	2.40
Total numbers	42	

There were significant differences between the mean illness severity scores of the patients before treatment and after 2, 4, and 6 months of treatment (Table 4). The mean illness severity scores before treatment were significantly higher than all values obtained after treatment (after 2 months: Z= 3.83, p< 0.001; after 4 months: Z= 4.68, p< 0.001; after 6 months: Z= 4.65, p< 0.001). The mean illness severity scores after 2 months were significantly higher than the values obtained 4th (Z= 3.99, p< 0.001) and 6th months of the treatment (Z= 4.14, p< 0.001). The mean illness severity scores after 4 months was significantly higher than the values obtained 6th month of the treatment (Z= 3.36, p< 0.001).

DISCUSSION

The cause of RAS is incompletely understood but appears to involve immune system dysfunction.[11] Thus, definitive treatment is difficult to determine. Although a variety of treatment modalities have been suggested in RAS, their clinical value remains unproven and has been controversial. Relief of pain and reduction of ulcer duration are the main goals of therapy.[11] Patients with frequent or severe outbreaks of aphthae should be counseled on the advisability of a medical screening for various forms of anemia, gastrointestinal disease, food allergies, and other diseases potentially affecting the immune system. It may also be wise to rule out Behcet's disease through questioning about the presence of lesions of the genital mucosa.[9] None of our patients had any disease or abnormal blood values for the iron, B12, and folate.

Treatment options include no treatment, treatment of associated systemic diseases or conditions (e.g., celiac sprue, vitamin deficiencies), systemic medications, topical medications, conversion of the aphthous ulcer to a wound, and palliative treatments.[11] The American Academy of Oral Medicine has recommended topical treatments for

TABLE 3: The number of ulcers according to pain degree.

		During treatment		
Pain degree	Before treatment	After 2 months	After 4 months	After 6 months
Mild	9	3	0	0
Moderate	15	6	1	0
Severe	18	13	5	1
Total	42	22	6	1

TABLE 4: The mean illness severity scores before and during treatment (m ± SD).

		During treatment		
	Before treatment	After 2 months	After 4 months	After 6 months
Ulcer Score	3.32 ± 2.20	2.57 ± 2.36	1.36 ± 1.66	0.54 ± 1.14

RAS. Topical medications include anesthetics, antihistamines, antimicrobials, and anti-inflammatory agents.[9] A variety of topical medications have been used in the treatment of RAS: however, these do not prevent recurrence and the inability to obtain adequate contact time may limit their effectiveness.[10,11] In fact, most of the medications mentioned above had previously been used in the author's patients, but they did not prevent the recurrence of RAS.

A wide spectrum of agents have been suggested to be beneficial for RAS, but few studies have been performed to assess their efficacy or their adverse effects.[12] Many drugs, including transfer factor, gamma-globulin therapy, sodium cromoglycate lozenges, dapsone, colchicine, pentoxifylline, levamisole, colchicine, azathioprine, prednisolone, azelastine, alpha 2-interferon, cyclosporine, deglycerinated liquorice, 5-aminosalicylic acid (5-ASA), prostaglandin E2 (PGE2), sucralfate, diclofenac, and aspirin have been used successfully in persistent cases: however, recurrances occur when the these drugs are withdrawn.[10,11,15] They also cause side effects such as gastric disturbance, hemorrhagic tendency, renal impairment, teratogenic effect, suppression of inflammatory cells, electrolyte imbalance, hypertension, osteoporosis, and hormonal suppression.[14-18]

β-glucan is the most well-known powerful immunomodulatory agent and is a very powerful antagonist to both benign and malignant tumors; it lowers cholesterol and triglyceride level, normalizes blood sugar level, heals and rejuvenates the skin and has various other benefits.[12,19] Yeast β-glucan, because it is easily purified, and mushrooms β-glucan, because there are a lot of experiments performed in Japan, China, and Korea have been primary types investigated.[12] Despite numerous studies on the biological effects of β–1,3 glucan, no efforts have been made to understand the role of β–1,3 glucan in RAS treatment. In this study, the authors have shown for the first time that a β–1,3;1,6-D- glucan isolated from *S. cerevisiae* ranging in size from 2 to 10-μ (Imuneks 10 mg cps) has an important effect on RAS treatment. Oral administration of β- glucan to 28 patients with RAS, for a period of six months resulted in a significant reduction of up to 98% of the ulcers at the end period. Furthermore, the treatment relieved pain in nearly all of the patients with RAS. Despite the β-glucan cessation, during the six months after treatment, no ulcer was observed in any patient. Thus, it is expected that β–1,3;1,6- glucan, through its immunoregulatory effects and because there is no evident toxicity, may be of therapeutic value in RAS.

No known side effects associated with β-glucans have been reported in humans. Beta-glucan isolated from the common baker's yeast *S. cerevisiae* is typically used in a highly purified form to minimize the allergic reaction in yeast-sensitive individuals.[13,20] There is a study demonstrated con-

sumption of concentrated barley -glucan was not associated with any obvious signs of toxicity in Wistar rats even following consumption of large quantities.[21] Since there was no study about the effects of -glucan on RAS, the authors chose to use a low dose (10 mg). However, it may be beneficial to further investigate the drug using a higher dosage regimen.

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