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Original Article

Improved treatment of recurrent aphthous stomatitis with sodium pentaborate pentahydrate (NaB)

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Abstract

Aim: Chlorhexidine (CHX) and benzydamine hydrochloride (B-HCl) combination treatment (Kloroben™ spray) was compared with sodium pentaborate pentahydrate (NaB, also called boron) treatment with regard to their effects in the recovery of recurrent aphthous stomatitis (RAS).

Materials and Methods: We assessed the treatment results by evaluating ulcer radius and VAS results. Seventy-one patients with clinically diagnosed minor RAS were selected for the study based on inclusion and exclusion criteria. Group 1 was treated with a 3% solution of NaB and group 2 was treated with Kloroben spray (45 mg benzydamine HCl and 36 mg chlorhexidine gluconate) for 1 week.

Results: After the treatments, there were statistically significant decreases in VAS scores in both Group 1 ($p<0.001$) and Group 2 ($p<0.001$). We found that the decrease in VAS score was greater in Group 1 than in Group 2 ($p<0.001$). Similarly, there were statistically significant decreases in ulcer diameters for both groups. The ulcer diameter reduction was also greater in Group 1 than Group 2 ($p<0.001$).

Conclusions: When the specifications of NaB and studies that report its effects are considered, it may be concluded that NaB works well in the healing process of oral aphthae. Our findings show that NaB is better than CHX for the treatment of RAS, which is demonstrated by greater reduction of ulcer diameter and pain score in the NaB group.

Keywords: Chlorhexidine; recurrent aphthous stomatitis; sodium pentaborate pentahydrate

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most frequent among oral mucosal diseases. Recurrent aphthous stomatitis appears as round, shallow, and painful ulcers with a yellowish-gray pseudomembranous base and erythematous halo, and develops recurrently . These painful lesions may affect speech, eating and oral hygiene negatively. Thus, the lesions may affect quality of life (QoL) more severely than just the pain they cause (2). Minor RAS is the most prevalent form. The lesions are typically seen as several, round and superficial ulcerations that have less than 10 mm radius and are accompanied by an erythematous halo and a gray pseudomembrane base. Small aphthae are mostly limited in the area including the lips, tongue and buccal mucosa (3). Although the lesion is usually self-limited, the pain caused by the aphthae leads to significant morbidity. Therefore, treatment has three goals: reducing pain, accelerating ulcer healing and increasing the duration of ulcer-free periods (4).

Many treatment options are available for aphthous stomatitis. However, a curative treatment option is lacking. The first-line treatment options comprise of antiseptics and anti-inflammatory drugs/analgesics (5). Chlorhexidine (CHX) is one of the bis-guanide antiseptics that has a wide anti-microbial activity range in addition to its safety, efficacy, adequacy and low toxicity (6). Chlorhexidine is available in various forms, such as dental varnishes, mouthwashes, chips and bioadhesive gels (6,7). It is reasonable to administer chlorhexidine 0.2% rinse to all patients presenting with RAS to decrease the likelihood of superinfection with gram-positive and gram-negative bacteria and fungi. In addition, chlorhexidine is efficacious in eliminating and preventing the formation of biofilms that are commonly found in dental plaque (8). Another agent used in treatment is benzydamine hydrochloride (B-HCl) which is a prostaglandin synthetase inhibitor. In addition to having anti-inflammatory effects, benzydamine HCl has local anesthetic and antimicrobial properties (9). In one of the previous studies, a significantly increased

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mucosal repair rate was found by the use of bioadhesive gel formulation of B-HCl. This agent is considered as a topical treatment option for ulcerative lesions of the oral mucosa (10).

Sodium pentaborate pentahydrate (NaB, also known as boron) may be suggested as a novel option for treatment of oral aphthae owing to its positive affect in the recovery process of wounds. Even though some studies show the positive results of Boron on wound recovery, the literature is not yet sufficient to reveal its promising effects in clinical use. It has been found to exhibit significant antimicrobial properties against a broad range of bacteria, fungi and yeast. In addition, the result of a recent study demonstrated that NaB significantly increased superoxide dismutase activity and migration capability in primary human fibroblasts (11,12). Thus, NaB can be seen as a very good candidate agent to treat aphthous ulcers. A solution of NaB has been produced by the Yeditepe University Biotechnology Laboratory. It is currently being sold under the Dermobor brand name in various forms; however, in this study for comparing the effectiveness of sodıum pentaborate pentahydrate (NaB, also known as boron) molecule with CHX and B-HCl combination we use a sprey which contains only soduım pentaborate pentahydrate prepared in Yeditepe University Biotechnology Laboratory .

We compared CHX and B-HCl combination treatment with NaB treatment with regard to their effects on the recovery of RAS. We assessed the treatment results of CHX and B-HCl and Sodium pentaborate pentahydrate by evaluating ulcer radius and VAS results.

MATERIALS and METHODS

Study design

This is an observational drug study that was aimed at comparing the efficacy of CHX and B-HCl combination (Kloroben spray) and NaB for the treatment of oral aphthous ulcerations. Spray versions were selected to enable compliance to treatment and consistency of dosage. The efficacy of treatment was evaluated by measuring VAS and ulcer diameter after 7-day treatment with each of the medications.

Ethical approval

Ethical approval was obtained from Istanbul Yeniyuzyil University Medical Faculty Ethical Committee (approval date: 27.11.2017, approval number: 046). All phases of the work were carried out in accordance with the Helsinki Declaration and Good Clinical Practice guide. Informed consent was obtained from all individual participants included in the study.

Study group

Power analysis was performed with the following parameters: 5% alpha error, 80% power and 36% lifelong prevalence of RAS (13). We determined that each group should consist of at least 27 subjects. Thus, at least 54 patients with minor oral aphtha had to be included and adjustments were made for age, sex and ulcer radius in the grouping of patients. The patients were randomized and grouped according to date of hospital application. Patients who did not meet inclusion criteria were excluded from the study.

Detailed case history was obtained and intraoral examination was performed on all patients. Seventy-one patients with clinically diagnosed minor RAS were selected for the study based on inclusion and exclusion criteria from December 2017 to July 2018. The majority of patients had previously been assessed in the rheumatology and/or ophthalmology departments; those that had not been evaluated were referred for examination to these clinics. None of the patients were identified to have any symptoms or findings associated with other diseases or conditions. Patients between 18-50 years of age were included in the trial if they presented with 1-2 minor recurrent Aphthous ulcers which had been present for less than 48 hours. The patients which had aphthous ulcers less than 10 mm in diameter that were found at accessible areas, such as the labial mucosa, buccal mucosa or the tongue, were selected.

Patients were selected from those who did not have the following conditions: active upper respiratory tract infection, chronic systemic disease with changes in normal hemoglobin biochemistry and vitamin levels, history of medications which could have impact on formation of RAS, teeth and breathing problems with caries and gastritis. Exclusion criteria were: pregnancy and lactation, boron (NaB) allergy, CHX and B-HCl allergy, systemic corticosteroid use, herpetic aphthous lesion, uncontrolled DM, HT, tuberculosis, and smoking. Additionally, we performed complete blood count and measured zinc, vitamin B12, folic acid and vitamin D levels. Any patients with values not in the respective reference ranges were excluded from the study.

Patients who came to the clinic were firstly diagnosed as having a minor oral ulcer. Minor ulcer definition was: ulcers smaller than 1 cm in diameter with non-keratinized and distinct borderline, covered with oral mucosa. Then, oral histories of the patients were obtained. VAS pain scales were filled and aphthous lesion diameters were measured on the first visit and after the first week of treatment.

Group 1: A 3% solution of NaB was applied to the aphthous area locally (via spraying) for three times daily for 1 week.

Group 2: 45 mg benzydamine HCl and 36 mg chlorhexidine gluconate was applied locally (via spraying) three times daily for 1 week.

Measurements

The patients were requested to score the pain intensity on a 100 mm VAS which was a 100 mm line marked at one end as “no soreness” and another end as “worst possible soreness”. Ulcer diameters were measured at diagnosis and on the seventh day with a flexible ruler. An author who was blinded to the randomization measured the ulcer diameters.

Statistical analyses

All analyses were performed on SPSS v20. For the normality test, the Shapiro-Wilk test was used. According

to normality of distribution, continuous variables were given as mean, median and standard deviation (minimum - maximum). The comparison of independent continuous variables was performed via the independent samples t-test or the Mann Whitney U test, depending on normality of distribution. Comparison of categorical variables between groups was performed with Chi-squared tests. Within group comparisons were made using the Wilcoxon Signed Rank Test. The amount of change seen in VAS score and ulcer diameter was calculated in each group and these differences were compared between groups using the Mann Whitney U test. p≤0.05 values were accepted as statistically significant.

RESULTS

The median (min-max) age was 39 (18-54) years in Group 1 and 36 (18-52) years in Group 2. There was no significant age difference between the groups (p=0.243). Baseline findings of the two groups were as follows: in group 1, ulcers were located on the lips in 20 and on the tongue in 19 patients. In group 2, ulcers were on the lips in 18 and on the tongue in 14 patients. VAS score had a median (min-max) value of 8 (6-10) in Group 1 and 8 (7-9) in Group 2. Median (min-max) ulcer diameter was 7.3 (4.8-9.5) mm's in Group 1 and 7.7 (6.3-9.0) in Group 2. Therefore, in the initial analyses, the two groups were determined as homogeneous (Table 1).

Table 1. The characteristics of patients during selection

Variables	Group 1 (n=39)	Group 2 (n=32)	p
Gender			
Female (n)	20	16	1.000
Male (n)	19	16	
Location			
Lips	20	18	0.858
Tongue	19	14	
Age	39 (18-54)	36 (18-52)	0.243
VAS score	8 (6-10)	8 (7-9)	0.531
Ulcer diameter	7.3 (4.8-9.5)	7.7 (6.3-9.0)	0.139

After the treatments, there were statistically significant decreases in VAS scores in both Group 1 (p<0.001) and Group 2 (p<0.001). When the differences between two groups in terms of the amount of change in VAS scores were analyzed, we found that the VAS score decrease in Group 1 was greater than Group 2 (p<0.001). Similarly, there were statistically significant decreases in ulcer diameters for both Group 1 (p<0.001) and Group 2 (p<0.001). The reduction in ulcer diameter of Group 1 was greater than the reduction seen in Group 2 (p<0.001). VAS scores and ulcer diameters before and after the treatment are shown in Table 2 (Table 3).

Table 2. VAS scores and ulcer diameters before and after the treatment

	Group 1		Group 2	
	Median (min-max)	p	Median (min-max)	p
VAS scores				
Before treatment	8 (6-10)	<0.001	8 (7-9)	<0.001
After treatment	1 (0-3)		4 (1-4)	
Ulcer diameter				
Before treatment	7.30 (4.80-9.50)	<0.001	7.70 (6.30-9.00)	<0.001
After treatment	1.00 (0-3.00)		3.45 (2.00-4.30)	

Table 3. The comparison of the amount of change in VAS score and ulcer diameter in each group

	Group 1 Median (min-max)	Group 2 Median (min-max)	p
VAS change	6 (5-9)	4 (3-6)	<0.001
Ulcer diameter change	5.80 (4.10-8.00)	4.45 (2.70-5.20)	<0.001

DISCUSSION

We compared the effectiveness of NaB and benzydamine HCl and chlorhexidine gluconate in oral aphtha. The reason that benzydamine HCl and chlorhexidine gluconate was chosen as a rival to NaB was the fact that It is one of the most frequently used medications for oral aphthous stomatitis. In our study, we found that benzydamine HCl and chlorhexidine gluconate reduces VAS score and ulcer diameters in oral aphthous stomatitis, but according to these measures, NaB treatment was superior to benzydamine HCl and chlorhexidine gluconate treatment.

Combination of B-HCl and CHX is a favorable treatment option (5,14). When these two molecules are assessed separately, it is seen that these ingredients play different roles that complete each other in the treatment process. While CHX is an agent that can reduce RAS time and increase the number of days without aphthous ulcers, B-HCl is a topical agent that has been shown to provide temporary relief of pain without any effect on the actual healing process (15,16). In various studies, CHX was found effective against recurrent oral mucosa ulceration and gingivitis. Chlorhexidine is efficacious against bacteria in the oral flora and organisms that cause oral cavity disease. It is an effective antiseptic and helps treat secondary infection in mucosal ulceration (17,18).

Chlorexidine has been compared with many other treatment options in the literature. In the study of Soylu Özler G et al. (19), CHX and sucralfate were compared and the results were remarkable. After the treatment, the sucralfate group had significantly lower pain scores than the CHX group, but the mean values of pain scores were similar prior to the treatment. On the 7th day following the treatment, the re-epithelialization of ulcers in the sucralfate group was significantly more than in the CHX group. Recovery time

recorded in the sucralfate group was significantly shorter compared to the CHX group (19). Although sucralfate is a safe drug that is used in the treatment of gastrointestinal ulcers and is suggested to increase fibroblast growth factors and prostaglandins in the ulcer area (20), the effect of sucralfate is mostly dependent on its physical barrier effect which prevents further injury of the tissue (21). However, RAS presents in the oral mucosa which is a very active area and the coating effect of sucralfate may be short-lived and efficacy may be reduced. Thus, there is a requirement for a treatment option with better healing properties and lesser side-effects while also being an effective rival to CHX. Sodium pentaborate pentahydrate (NaB) is a very strong candidate agent to treat RAS as shown in our study.

When the pain-relieving property of benzydamine hydrochloride, was examined, its effectiveness raised doubts. In a study with limited evidence, no difference was found between placebo and benzydamine hydrochloride mouthwash in reducing ulcer count or pain in recurrent aphthous ulcers (22). Thus, treatment-wise, our study may be considered to show the difference between CHX and NaB in the management of RAS.

The way NaB interferes with microbial metabolism makes it an interesting agent for the treatment of oral aphthous stomatitis. Boron was found to increase extracellular matrix turnover, metalloproteinase activation, keratinocyte migration and at the same time, boron is also involved in ion transport, calcium metabolism and hormone synthesis (23). Therefore, considering these effects of NaB, we believe the mechanism of action is associated with its mediation of a number of factors involved in tissue repair, such as replenishment of the extracellular matrix, keratinocyte migration and ion transport in tissues. There are a few studies showing the change of wound recovery activity after use of boron and derivatives. In a study by Demirci et al. (23), a gel containing NaB was found to display remarkable antimicrobial properties. This study presented the healing effects of boron containing gel by wound closure, increased epithelization, and angiogenesis (23). Increased epithelialization may also be one of the critical mechanisms by which NaB contributes to healing, especially considering the fact that the oral mucosa is a very active area. In addition, Aysan et. al. (11) evaluated whether boron is effective on radiation-induced skin reactions (RISR) in breast cancer patients. In conclusion, they reported that RISR was diminished after the use of boron-based gel. Its mechanism of action is not clear, but it is thought that it may be associated with wound recovery, thermal degradation and antioxidant effects of boron (11). Furthermore, in an animal study, the effect of boric acid use on recovery of the Achilles tendon was investigated. They found that the healing process was positively affected by boric acid. They suggested that this effect was associated with stimulation of TNF-α levels that caused production of collagen and proteoglycans required for the repair process of wounds. Although this study is focused on tendon healing, the results are important to understand the effects of boric acid (24). Furthermore, a study by Benderdour et al. showed that boron was not mitogenic and was non-toxic until 1% (w/v) concentration in tissues (25), which is an extremely high level and is practically impossible to obtain with spray treatment in the oral mucosa.

Absorption of boron occurs in the respiratory and digestive system, and is thought to be processed into boric acid, which has a tissue distribution of 90%. In the study of Tepedelen et al, results indicated that boric acid not only reduced the occurrence of DNA double helix breaks caused by agents, but also improved wound recovery. It was suggested that boric acid had significant therapeutic efficacy and might be added into treatment recommendations for inflammatory diseases in which wound recovery and oxidative stress play key roles (26).

Our study has two major strengths. Firstly, we used a relatively new agent which is considered to be promising for wound treatment in a condition which does not have a curative treatment and observed successful results compared to a widely used treatment. Secondly, the groups were appropriately randomized and the pre-treatment characteristics of groups were similar. There are also limitations to our study. Firstly, we only included patients with minor ulcers; thus our study may not capture the whole picture of RAS cases. However, minor ulcers were chosen because major oral ulcers take a longer time to heal and recur much more frequently which may have caused problems in the evaluation of the efficacy of treatment. Secondly, we did not determine the time of full recovery. Instead, improvements in ulcer diameter and VAS scores were evaluated which are important factors in the morbidity of RAS. Finally, due to ethical considerations, we did not include a group without treatment.

CONCLUSION

When the specifications of sodium pentaborate pentahydrate (NaB) and studies that report its effects are considered, it may be concluded that NaB works well in the healing process of oral aphthae, possibly by stimulating the production of various compounds necessary for repair and increased epithelialization. Indeed, the main target of this study was to determine if NaB treatment could be an alternative to CHX and B-HCl combination (Kloroben) in the treatment of minor oral aphtha. Our findings show that NaB is better than Kloroben for the treatment of RAS, which is demonstrated by greater reduction of ulcer diameter and pain score in the NaB group after a week of treatment.

Conflict of interest : The authors declare that they have no competing interest.

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