Comparative Evaluation of The Efficacy of Topical Hyaluronic Acid (0.2%) and Topical Triamcinolone Acetonide(0.1%) in The Treatment of Recurrent Aphthous Stomatitis

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Abstract

Background: Recurrent aphthous ulcers are the most common oral lesion. They are classified into minor, major, and herpetiform ulcers. More than 85% of recurrent aphthous stomatitis presents as a minor ulcer. Hyaluronic acid is a biomaterial and it is a major carbohydrate component that can be found in many tissues and recently introduced as an alternative approach to enhance wound healing. Triamcinolone acetonide is a synthetic corticosteroid and it has two forms for topical use cream (0.1%) and ointment (0.1%).

Objective: To make a comparison between the effectiveness of hyaluronic acid (0.2%) and triamcinolone acetonide (0.1) in the management of recurrent aphthous ulcer.

Patients and Methods: We recruited eighty patients who had a history of recurrent aphthous stomatitis and when presented with current oral ulcer and randomly divided into two groups, one group received hyaluronic acid, and the other group received triamcinolone acetonide. The instruction was given to all patients to apply the agent to the aphthous ulcer 4 times per day for 6 days (day 0 to day 6). The severity of pain was assessed by using VAS and the change of the ulcer surface area measured.

Results: Eighty patients with aphthous ulcers have participated in the study, 43 were treated with hyaluronic acid, 37 were treated with triamcinolone acetonide. There was a significant difference between the two groups regarding ulcer surface and after three and six days, the diameter of the ulcer in the hyaluronic acid group was significantly reduced in comparison with those of the triamcinolone acetonide group ($p < 0.001$). Regarding VAS for pain, there was a significant difference after three and six days, hyaluronic acid group had significantly less VAS than those of the triamcinolone acetonide group ($p = 0.004$ and $p < 0.001$ respectively).

Conclusion: Hyaluronic acid is more effective than triamcinolone acetonide when used in the treatment of recurrent oral ulcers in reducing pain and surface area of the ulcer.

Keywords: Hyaluronic acid (HA), Triamcinolone acetonide (TA), Recurrent aphthous stomatitis (RAS), comparative evaluation

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Introduction

Recurrent aphthous ulceration or recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease known to human beings. The term "aphthous" is derived from the Greek word "aphthae" which means ulceration [1]. RAS is prevalent in 5%–25% of the population presenting frequently between the second to fourth decades of life [2]. The incidence is slightly higher in females than in males [3]. There are three subtypes of RAS, RAS major (MaRAS), RAS herpetiform (HeRAS), and RAS minor (MiRAS), the most common among them is MiRAS which accounts for 75%–85% [4].

The underlying etiology is not clear but genetic factors, local trauma, endocrine alterations (menstrual cycle), food allergens, stress and anxiety, smoking cessation, certain chemical products, and microbial agents are known to be predisposing factors [5,8,9,10]. The diagnosis is based on the patient's history and clinical manifestations and has no specific diagnostic test. It is advisable to discard possible underlying systemic cause particularly in adults who suffer sudden outbreaks of RAS by requesting a complete series of laboratory tests, including a complete blood count, vitamin B12, folic acid, and evaluating serum ferritin. As biopsy shows unspecific inflammatory lesion, it is only recommended in cases where the diagnosis is uncertain [6,7,11].

The therapeutic choice depends on the severity of the condition, including the frequency of ulcer recurrence, the number of ulcers present, their location, duration, and the level of associated orofacial pain [12]. Triamcinolone acetonide (TA) is a synthetic corticosteroid and is available in two forms for topical use ointment (0.1%) and cream (0.1%). Different parts of the body show varies absorption rate ranging from 1% to 36% and this rate is more in damaged and inflamed skin [13,14]. For the treatment of RAS topical TA ointment was shown to be effective. Hyaluronic acid (HA) is a major carbohydrate component of the extracellular matrix that can be found in many tissues and it is an alternative approach for enhancing wound healing [15,16]. HA reduces the pain and discomfort resulted from the ulcers, enhances the process of healing, and significantly decreases the recurrence of the lesion. The inflammations are also controlled by HA as well as tissue rehydration [17]. The aim of the study was to make a comparison between the effectiveness of topical hyaluronic acid (0.2%) and triamcinolone acid (0.1) in the management of recurrent aphthous ulcers.

Patients and Methods

Study setting: This randomized clinical study was on patients with recurrent aphthous stomatitis from January to June 2020. This study was approved by the research ethical committee of the Kurdistan board of medical specialty and the patients were seen in Khanzad teaching center in Erbil city. The protocol of this article have been discussed and approved by the scientific committee of oral and maxillofacial medicine in the Kurdistan board of medical specialty before starting work.

Study design: The study was a randomized clinical study for the topical effect of

triamcinolone acetonide (0.1%) oral paste compared to hyaluronic acid (0.2%) oral paste for the treatment of (RAU). Eighty patients were enrolled and divided into two groups randomly. Each patient signed a detailed informed consent form. All patients instructed orally and on written paper to apply oral triamcinolone acetonide or hyaluronic acid to that identified ulcer. With the randomized technique, patients with RAU (minor or major) were assigned to study group triamcinolone acetonide or standard comparison group hyaluronic acid group.

Inclusion Criteria

1.Males and females aged ranged between 16–60 years old.

2.Patients with ahistory of recurrent aphthous stomatitis at least three times a year for at least one year [18].

3.Patients with a history of 48hours duration and less of pain and burning sensation secondary to the ulcer and with the characteristic clinical feature of recurrent oral aphthous ulcers.

4.Patients who were willing to undertake the treatment until complete healing of the ulcer takes place.

Exclusion criteria

1.Patients with known allergy to drugs.

2.Patients with any other associated oral mucosal diseases (eg. Lichen planus, fungal infections, chronic ulcer).

3.Patients who were on any other medications for aphthous ulcers.

4.Patients with a history of major systemic diseases that may affect healing of ulcer (eg. Crohn’s disease, celiac disease).

5. Patients with Behcet’s syndrome.

6. Smokers.

Clinical examination: Every patient was seated on a dental chair, and information regarding interference of ulcer with eating, speaking, brushing, drinking, the interval from last occurrence and duration of onset of the ulcer have been taken from each patient. The site, shape, and type of the ulcer were examined clinically. The baseline parameters recorded on the first visit including ulcer surface area in (mm^2), and pain (using VAS score). Evaluations and measurements of ulcer surface area and pain, a photograph of aphthous ulcer of each patient were taken before treatment started (baseline) and after treatment finished (after 6 days of follow up).

Patient Grouping

Eighty patients with (RAU) participated in the study were randomly divided into two groups:

Group I: Consists of 37 patients who administered triamcinolone acetonide (0.1%).

Group II: Consists of 43 patients who administered hyaluronic acid oral paste 0.2%.

Method of paste administration: All Patients advised to apply a small amount of triamcinolone acetonide cream 0.1% and hyaluronic acid oral gel (0. 2%) by the tip of a clean finger to the ulcer completely, 4 times daily (every six hours), 3 times half hour before a meal to avoid contamination with food and 1 time before bed. The patients were advised to wash the mouth entirely before the application of treatment.

Efficacy Evaluation

Ulcer surface area: by using a graduated periodontal probe the index ulcer's diameters measured on treatment days (baseline 3 and 6). The diameters of each ulcer measured by measuring the length and width of the ulcer

and then the two measurements were multiplied to represent the surface areas of the ulcer in (mm^2) [19].

Intensity of Pain: To measure the intensity of the pain, Visual analogue scale (VAS) is used a 10 cm line containing equidistant subdivision that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured, and has following associated notations: no pain, mild pain, discomforting pain, distressing pain, horrible pain, and excruciating pain.

The intensity of pain was assessed with the following grades:

0: To represent no pain
2: To represent mild pain
4: To represent discomforting pain
6: To represent distressing pain
8: To represent horrible pain
10: To represent excruciating pain [19]

Statistical analysis

The data was analyzed using the Statistical Package for Social Sciences (SPSS, version 25). A test of normality of data (Shapiro-Wilk) showed that the data were not normally distributed Therefore, the non-parametric tests were used. The Mann Whitney test was used to compare the mean ranks of the two groups. Wilcoxon signed ranks test was used to compare the medians before the study with the medians three and six days after the study. A p-value of ≤ 0.05 was considered statistically significant.

Results

Eighty patients with aphthous ulcers have participated in the study, 43 (53.7%) were treated with HA, and the rest (46.3%) were treated with TA. The mean age ± SD of the patients was 28.7 ± 10.1 years, ranging from 16 to 60 years. The median was 28 years.

Table (1) shows that the highest proportion of the sample (31.3%) was aged 20-29 years, and only 20% were aged ≥ 40 years. More than half (60%) of the sample were females. The most common sites of the ulcers were buccal mucosa (37.5%), labial mucosa (23.8%), lateral border of the tongue (12.5%), and floor of the mouth (8.8%). The other sites are presented in (table1) which shows also that the majority (91.2%) of the ulcers were minor.

Table (1): Basic characteristics of the sample study

	No.	(%)
Age (years)		
< 20	19	(23.8)
20-29	25	(31.3)
30-39	20	(25.0)
≥ 40	16	(20.0)
Gender		
Female	48	(60.0)
Male	32	(40.0)
Site		
Buccal mucosa	30	(37.5)
Labial mucosa	19	(23.8)
Lateral border of tongue	10	(12.5)

Floor of mouth Tip of tongue Soft palate	7 6 4	(8.8) (7.5) (5.0)
Dorsum of tongue	3	(3.8)
Ventral surface of tongue	1	(1.3)
Type of ulcer		
Minor	73	(91.2)
Major	7	(8.8)
Total	80	(100.0)

It is evident in Table (2) that there was no significant difference between the two treatment groups in the diameters of the ulcer before the start of the study (p = 0.131), but after six days all the parameters of the ulcer in the HA group were significantly less than those of the TA group (p < 0.001). The same pattern can be observed for the VAS where no significant difference between the two groups was detected before the start of the study (p = 0.549), but after three and six days, all the VAS parameters of the HA group were significantly less than those of the TA group (p = 0.004 and p < 0.001m respectively).

able (2): Surface area of ulcers and VAS parameters at different times of the study by type of treatment

	Type of treatment						
	HA			**TA**			
	Mean	**Median**	**Mean rank**	**Mean**	**Median**	**Mean rank**	**P***
Surface area before (mm)	1.55	0.80	(44.10)	1.12	0.70	(36.31)	0.131
Surface area after 3 days (mm)	0.38	0.30	(35.44)	0.66	0.50	(46.38)	0.033
Surface area after 6 days (mm)	0.06	0.00	(32.79)	0.45	0.20	(49.46)	< 0.001
VAS before	7.70	8.00	(41.88)	7.54	7.00	(38.89)	0.549
VAS after 3 days	2.16	2.00	(33.72)	3.70	4.00	(48.38)	0.004
VAS after 6 days	0.02	0.00	(34.80)	1.05	0.00	(47.12)	< 0.001
***By Mann Whitney test**							

The decrease in the diameter and VAS were calculated, then their means have been compared between the two groups Table (3). After three days, the mean decrease in the surface of the ulcer in the HA group (1.17 mm^2) was higher than that (0.47 mm^2) of the TA group (p = 0.001). After six days, the mean decrease of the surface area in the HA group (1.49 mm) was higher than that (0.68 mm) of the TA group (p = 0.002).

The mean decrease in the VAS after three days in the HA group (5.53) was higher than that (3.84) of the TA group (p = 0.001). After six days, the mean decrease of VAS in the HA group (7.67) was higher than that (6.49) of the TA group (p = 0.001). These results indicate that the response to HA was significantly better than the TA Table (3).

Table (3): Means of decrease in the surface area of ulcer and VAS, three and six days after the start of the study, by type of treatment

	HA		TA		
Differences	**Mean(±SD)**	**Mean rank**	**Mean(±SD)**	**Mean rank**	**P***
Surface area before - after 3 days	1.17(±1.84)	48.48	0.47(±0.65)	31.23	0.001
Surface area before - after 6 days	1.49(±2.10)	48.01	0.68(±0.60)	31.77	0.002
VAS before - VAS after 3 days	5.53(±2.14)	48.40	3.84(±2.10)	31.32	0.001
VAS before - VAS after 6 days	7.67(±0.99)	48.01	6.49(±1.63)	31.77	0.001

*By Mann Whitney test

Table (4) shows in the HA group, there was a significant decrease in the median surface area of the ulcer from 0.8 mm2 before the start of the study, to 0.3 mm2 three days after the start of HA treatment ($p < 0.001$). The median became zero after six days ($p < 0.001$). In the TA group, there was also a significant decrease in the median surface area of the ulcer from 0.7 mm2 at the start, to 0.50 mm2 after three days ($p < 0.001$), to 0.20 mm2 after six days ($p < 0.001$).

Regarding the median of the VAS, the HA group shows a significant decrease from 8 at the start, to 2 after three days ($p < 0.001$), and then to zero after six days ($p < 0.001$). In the TA group, it decreased significantly from 7 at the start, to 4 after three days, and then to zero after six days ($p < 0.001$).

Table (4): Comparing the median values of the surface area of ulcers and VAS before the study with the values taken three and six days after treatment in each of the study groups

	HA		TA	
	Median	**P****	**Median**	**P****
Surface area before (mm^2)	0.80		0.70	
Surface area after 3 days (mm^2)	0.30	< 0.001*	0.50	< 0.001*
Surface area after 6 days (mm^2)	0.00	< 0.001*	0.20	< 0.001*
VAS before	8.00		7.00	
VAS after 3 days	2.00	< 0.001*	4.00	< 0.001*
VAS after 6 days	0.00	< 0.001*	0.00	< 0.001*

*Comparing the median with the reading before the study

**By Wilcoxon signed ranks test

Discussion

RAS is considered to be a common disorder with no clear etiopathogenesis. No specific tests for diagnosis arerecognized. Therefore, clinical examination is the only modality for diagnosis [20]. The RAS can affect people of any age group. In this study, the highest percentage (31.25%) was in the age group of [20-29] and the mean of age was 35±13.6 year. Complito et al and Orbak et al [26,31] in their study on adult patients reported that RAS was more common under the age of 38.5 years.

This study revealed a higher number of female patients than male patients in the RAS

group but statistically, there is no significant difference between them like other studies didn't show any significant influence of sex on RAS [33,34]. In other studies, patients with a clinical diagnosis of RAS were significantly more often in males [35,36]. A study suggests that RAS is more common in women [20], which may be due to hormonal change and anemia which may be due to deficiency in vitamin B12, folate, or ferritin. The difference in the result may be due to sample type, size and socioeconomic factors.

The results of this study have shown that aphthous ulcers were mostly located on the buccal and labial mucosa, lateral side of the tongue, the floor of mouth which is consistent with a study [26], which may be due to the majority of patients participated in this study had minor aphthous ulcers and that this type of ulcer mostly locates on the mentioned parts of the mouth. Topical medications should always be the first-line management of RAS. Medium to high potency corticosteroids like TA is widely used in the management of RAS [21-22].

An alternative topical agent that's recently used for the management of recurrent oral ulcers is HA. HA is a glycosaminoglycan with anti-oedematous and anti-inflammatory effects. Several features make HA an ideal agent for wound healing by assisting early granulation tissue formation, preventing the destructive effects of inflammation, stimulating re-epithelization and angiogenesis [23, 24]. The study also found that HA gel reduces RAS pain without causing any clinically observed side effects. Furthermore, easy application and no unfavorable taste made it a good choice [29].

When the hyaluronic acid group was compared with triamcinolone acetonide in terms of pain score, the present study showed statistically significant difference. The present clinical trial proved that the pain reduction was seen more in the hyaluronic acid group as compared to the triamcinolone acetonide group within the 3rd day which goes with study done by Koray et al 2016 [28] who states that HA gel reduces the pain of RAS more than TA when comparing the two agents. These results suggest that pain can be successfully control by HA gel in cases of RAS.

In the present study, hyaluronic acid was compared with triamcinolone acetonide with regards to the ulcer surface area. It showed that hyaluronic acid has a significant reduction in ulcer surface area on 3rd day as compared to 1st day which shows the similar results with the study done by Nolan et al in 2006 [29].

This whole process may be attributable to the effect of HA as it stimulates the deposition of collagen and angiogenesis which lead to the healing process [25]. The increased delivery of oxygen and nutrients caused by angiogenesis will lead to local collagen deposition which has a central role in the healing process of wounds.

The study result revealed that hyaluronic acid gel reduces RAS surface area and pain without any clinically recording side effects. Furthermore, because the hyaluronic acid gel was easy to use without any unfavorable taste and odor and it was easy for patients to apply, most of the patients showed a preference for it over other agents and

wanted to use it again at any time they will have RAS.

Due to the presence of a large number of etiological factors, success in the treatment of RAU is difficult. There is no definite curative treatment for RAS. Hence, the goal of treatment is to decrease pain, healing time, size of the ulcer [28].

Not all treatment modalities are successful at obtaining all these goals. Reduction in symptoms seems to be all that most modalities are able to offer. Therefore, it is important to critically evaluate any clinical trial to determine if a medication should be recommended for widespread use.

Limitations of the study

Many previous clinical studies have followed the method of comparative evaluation of two topical therapeutic agents, the results of the present study will be better and more beneficial if the placebo topical agent was added as a control to exclude the role of mechanical protective effect , although such comparison was done by the previous study. The application of topical agent has some limitation regarding drug delivery and retention which may affect the efficacy of the agent.

The limitation of study time has affected the evaluation of long-term improvement in the quality of patients life and epidemic of covid 19 has affected the sample size since there were periods of quarantine.

Conclusions

The topical application of HA gel is more effective in decreasing pain intensity and healing of ulcer than TA, without any orally observed side effects. HA gel could be used in the clinical practice of RUS treatment.

Recommendations

Our recommendation for future studies including:

1.Involving many centers in the study to increase the number of patients.

2.Different socioeconomic levels to study the effect of different social groups.

3.Many topical agents to compare the different effects.

Conflicts of interest

No conflict of interest

References

[1]Wardhana DE, Datau EA. Recurrent aphthous stomatitis caused by food allergy. Acta Med Indones. 2010 Oct;42(4):236-40.

[2] Vincent SD, Lilly GE. Clinical, historic, and therapeutic features of aphthous stomatitis: literature review and open clinical trial employing steroids. Oral surgery, oral medicine, oral pathology. 1992 Jul 1;74(1):79-86.

[3]Preeti L, Magesh KT, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. Journal of oral and maxillofacial pathology: JOMFP. 2011 Sep;15(3):252.

[4]Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. The Journal of the American Dental Association. 2003 Feb 1;134(2):200-7.

[5]Femiano F, Buonaiuto C, Gombos F, Lanza A, Cirillo N. Pilot study on recurrent aphthous stomatitis (RAS): a randomized placebo-controlled trial for the comparative therapeutic effects of systemic prednisone and systemic montelukast in subjects unresponsive to topical therapy. Oral Surgery, Oral Medicine, Oral Pathology, Oral

Radiology, and Endodontology. 2010 Mar 1;109(3):402-7.

[6] Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. Journal of oral pathology & medicine. 2012 Sep;41(8):577-83.

[7]Preeti L, Magesh KT, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. Journal of oral and maxillofacial pathology: JOMFP. 2011 Sep;15(3):252.

[8]Zhou Y, Chen Q, Meng W, Jiang L, Wang Z, Liu J, Lin M, Zhou H, Chen X, Zhao M, Zeng X. Evaluation of penicillin G potassium troches in the treatment of minor recurrent aphthous ulceration in a Chinese cohort: a randomized, double-blinded, placebo and no-treatment–controlled, multicenter clinical trial. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2010 Apr 1;109(4):561-6.

[9] Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, Peleg R, Press Y. Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial. The Journal of the American Board of Family Medicine. 2009 Jan 1;22(1):9-16.

[10]Liang MW, Neoh CY. Oral aphthosis: management gaps and recent advances. Ann Acad Med Singapore. 2012 Oct 1;41(10):463-70.

[11]Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. British Journal of Oral and Maxillofacial Surgery. 2008 Apr 1;46(3):198-206.

[12]Mimura MA, Hirota SK, Sugaya NN, Sanches Jr JA, Migliari DA. Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. Clinics. 2009 Mar;64(3):193-8.

[13]Khandwala A, Van Inwegen RG, Alfano MC. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 1997 Feb 1;83(2):222-30.

[14]Fani MM, Ebrahimi H, Pourshahidi S, Aflaki E, Sarvestani SS. Comparing the effect of phenytoin syrup and triamcinolone acetonide ointment on aphthous ulcers in patients with Behcet's syndrome. Iranian Red Crescent Medical Journal. 2012 Feb;14(2):75.

[15] Hammad HM, Hammad MM, Abdelhadi IN, Khalifeh MS. Effects of topically applied agents on intra-oral wound healing in a rat model: a clinical and histomorphometric study. International journal of dental hygiene. 2011 Feb;9(1):9-16.

[16]Chen WY. AbatangeloG. Functions of hyaluronan in wound repair. Wound Repair Regen. 1999;7(2):79.

[17] Lee J, Jung JY, Bang D. The efficacy of topical 0.2% hyaluronic acid gel on recurrent oral ulcers: comparison between recurrent aphthous ulcers and the oral ulcers of Behçet's disease. Journal of the European Academy of Dermatology and Venereology. 2008 May;22(5):590-5.

[18]Piskin S, Sayan C, Durukan N, Senol M. Serum iron, ferritin, folic acid, and vitamin B12 levels in recurrent aphthous stomatitis. Journal of the European Academy of Dermatology and Venereology. 2002 Jan;16(1):66-7.

[19]Meng W, Dong Y, Liu J, Wang Z, Zhong X, Chen R, Zhou H, Lin M, Jiang L, Gao F, Xu T. A clinical evaluation of amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: a randomized, placebo controlled, blinded, multicenter clinical trial. Trials. 2009 Dec 1;10(1):30.

[20] Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. The Journal of the American Dental Association. 2003 Feb 1;134(2):200-7.

[21]Quijano D, Rodríguez M. Topical corticosteroids in recurrent aphthous stomatitis. Systematic review. ActaOtorrinolaringologica (English Edition). 2008 Jan 1;59(6):298-307.

[22]Elad S, Epstein JB, von Bültzingslöwen I, Drucker S, Tzach R, Yarom N. Topical immunomodulators for management of oral mucosal conditions, a systematic review; Part II: miscellaneous agents. Expert opinion on emerging drugs. 2011 Mar 1;16(1):183-202.

[23] Moseley R, Waddington RJ, Embery G. Hyaluronan and its potential role in periodontal healing. Dental Update. 2002 Apr 2;29(3):144-8.

[24] Koray M, Ofluoglu D, Onal EA, Ozgul M, Ersev H, Yaltirik M, Tanyeri H. Efficacy of hyaluronic acid spray on swelling, pain, and trismus after surgical extraction of impacted mandibular third molars. International journal of oral and maxillofacial surgery. 2014 Nov 1;43(11):1399-403.

[25] Buemi M, Galeano M, Sturiale A, Ientile R, Crisafulli C, Parisi A, Catania M, Calapai G, Impalà P, Aloisi C, Squadrito F. Recombinant human erythropoietin stimulates angiogenesis and healing of ischemic skin wounds. Shock. 2004 Aug 1;22(2):169-73.

[26]Orbak R, Cicek Y, Tezel A, DOGRU Y. Effects of zinc treatment in patients with recurrent aphthous stomatitis. Dental materials journal. 2003;22(1):21-9.

[27] Rao PS. Recurrent aphthous stomatitis: a review. Journal of Orofacial sciences. 2010 Sep 1;2(3):60.

[28]Koray M, Ofluoglu D, Senemtasi A, İşsever H, Yaltirik M. The efficacy of hyaluronic acid gel in pain control of recurrent Aphthous stomatitis. Int J Dent Oral Sci. 2016 Jun 13;3:273-5.

[29]Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA. The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. Journal of oral pathology & medicine. 2006 Sep;35(8):461-5.

[30]Compilato DO, Carroccio AN, Calvino FR, Di Fede G, Campisi G. Haematological deficiencies in patients with recurrent aphthosis. Journal of the European Academy of Dermatology and Venereology. 2010 Jun;24(6):667-73.

[31]Koybasi S, Parlak AH, Serin E, Yilmaz F, Serin D. Recurrent aphthous stomatitis: investigation of possible etiologic factors. American journal of otolaryngology. 2006 Jul 1;27(4):229-32.

[32]Donatsky O. Epidemiologic study on recurrent aphthous ulcerations among 512 Danish dental students. Community dentistry and oral epidemiology. 1973 Oct;1(1):37-40.

[33]Field Ea, Brookes V, Tyldesley Wr. Recurrent aphthous ulceration in children—a

review. International journal of paediatric dentistry. 1992 Apr;2(1):1-0.

[34]McCullough MJ, Abdel-Hafeth S, Scully C. Recurrent aphthous stomatitis revisited; clinical features, associations, and new association with infant feeding practices?. Journal of oral pathology & medicine. 2007 Nov;36(10):615-20.