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JH Lee, JY Jung, D Bang

Abstract

Background Hyaluronic acid (HA) is a primary component of the extracellular matrix, and the efficacy of HA on oral ulcers is rarely reported.
Objective To observe the efficacy and safety of the topical application of 0.2% HA gel on recurrent oral ulcers and to compare its effects in patients with recurrent aphthous ulcers (RAU) and the oral ulcers of Behçet's disease (BD)
Materials and methods Thirty-three outpatients with recurrent oral ulcers were included in the study (17 patients: BD, 16 patients: RAU). The patients used topical 0.2% HA gel twice daily for 2 weeks. The subjective parameters of patients [number of ulcers, healing period, visual analogue scale (VAS) for pain] were investigated and objective assessments (number of ulcers, maximal area of ulcer and inflammatory signs) were inspected by a physician.
Results A subjective reduction in the number of ulcers was observed in 72.7% of the patients. A decrease in the ulcer healing period was observed in 72.7% of the patients; 75.8% experienced improvement in VAS for pain. Objective inspection of the ulcers showed a reduction of numbers in 57.6% of the patients, and 78.8% of the ulcers showed a decrease in area. Among the inflammatory signs, swelling and local heat were significantly improved after treatment. No significant differences were found between the BD group and RAU group in subjective and objective parameters, except for inflammatory signs. No sideeffects were observed.
Conclusions The topical application of 0.2% HA gel seems to be an effective and safe therapy in patients with recurrent oral ulcers; the study supports the use of HA in BD with oral ulcers.

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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

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Keywords
Behçet's disease, hyaluronic acid, recurrent aphthous ulcers, recurrent oral ulcers

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Conclusions The topical application of 0.2% HA gel seems to be an effective and safe therapy in patients with recurrent oral ulcers; the study supports the use of HA in BD with oral ulcers.

Introduction

The recurrent aphthous ulcer (RAU) is the most common form of recurrent oral ulcers. RAU is characterized by recurring painful ulcers of the mouth that are round or ovoid and have inflammatory halos. Individual aphthous ulcers may be classified morphologically as minor, major or herpetiform ulcers. Minor aphthous ulcers comprise 80% of all aphthous ulcers, measure < 5 to 10 mm, are usually located on the buccal and labial mucosa and heal spontaneously in 7 to 10 days without scarring. Ten per cent of all lesions are major aphthous ulcers, which are larger than 10 mm and are deeper. They may heal over weeks to months and often result in scarring. The remaining 10% of aphthous ulcers are herpetiform ulcers, which are smaller (1–3 mm), grouped or coalescent ulcers that may be present on the keratinized mucosa of the dorsal tongue and palate and heal spontaneously over 1 to 4 weeks. Herpes simplex virus is not, by definition, found in these lesions.[1]

RAU can be further classified based on clinical disease severity as simple and complex aphthous ulcers. Simple

aphthous ulcers represent the common presentation of a few lesions, which heal in 1 to 2 weeks and recur infrequently. Complex aphthous ulcers, on the other hand, represent a complicated clinical picture of severe disease, numerous, large or deep lesions, new lesions developing as older lesions heal, marked pain or disability, and occasionally, associated genital or perianal lesions.[1,2] Oral or genital aphthous ulcers are a required feature for the diagnosis of Behçet's disease (BD) and often are the initial presenting sign. These aphthous ulcers are similar to those seen in patients with complex aphthous ulcers. The most common sites of oral ulceration are the buccal mucosa, gums, tongue, lips and pharynx. Oral ulcers in BD are typically painful, 1 to 3 cm in diameter, shallow or deep and have a yellow fibrinous base. Patients may have single or multiple ulcers lasting between 1 and 4 weeks. Ulcers may be herpetiform, with pinpoint lesions occurring in coalescing clusters.[3]

Hyaluronic acid (HA) is a naturally occurring polymer within the skin and has been studied since its discovery in 1934. It can consist of between 200 and 10 000 disaccharide units with a molecular weight in normal tissues exceeding 10^6. Chemically, it belongs to the glycosaminoglycans, which have repeating disaccharide units of uronic acids and hexosamines. It can be found in many tissues and body fluids of mammals, with the highest concentrations in connective tissue and skin.[4]

HA has been widely used in ophthalmology, rheumatology and dermatology because of its anti-inflammatory and anti-edematous effects.[5–8] Its clinical applications in dermatology now encompass use not only as a biomaterial for bioengineering purposes or a temporary dermal filler in aesthetic dermatology, but also for the stimulation of wound healing and as a drug vehicle in topical formulations.[9] Only a few studies of the effects of HA in oral disease were found.[10–13] Recently, the effect of topical 0.2% HA gel on RAU was reported.[13]

The objectives of this prospective study were to observe the efficacy and safety of the topical application of 0.2% HA gel on recurrent oral ulcers and to compare its effects in patients with RAU and the oral ulcers of BD.

Materials and methods

Patients

Our study was an open prospective study done on an outpatient basis. Informed consent was obtained, and the protocol was approved by the ethical review board. The 33 patients who participated in the study were outpatients of the BD Specialty Clinic at the Severance Hospital of Yonsei University, and had recurrent oral ulcers (female, 28; male, 5; mean age ± SD, 39.8 ± 15.1 years; range, 15–68 years). The criteria for inclusion were a clear history of recurrent oral ulcers occurring at least twice a year, and at least one ulcer present at the initial visit. Patients were excluded if they had an active eye disease or any underlying haematological disorder or organ involvement requiring systemic therapy, or had received recent systemic therapy for at least 12 weeks or topical therapy for at least 4 weeks prior to the study. We divided the patients into two groups according to the criteria of the International Study Group for BD: a BD disease group (17 patients) and a RAU group (16 patients).

Treatment

The patients used 0.2% HA gel (Gengigel®) twice a day for 2 weeks. Side-effects were monitored during the study. No patients were given any concurrent disease-specific or immunosuppressive topical or systemic drugs during the study period.

Evaluation

All results were obtained by the same investigator and were based on a combination of the data recorded by the physician at the clinic visit and the data reported by the patients on the occurrence of oral ulcers. Subjective parameters from patients, consisting of the number of ulcers, healing period and level of pain were evaluated at baseline and after 2 weeks. The level of pain was assessed with the Visual Analogue Scale (VAS). The VAS is a scale from 1 to 10, with 1 representing no pain and 10 representing the worst possible pain. In addition, the overall response at the end of the treatment period was graded by the patients as follows: improvement, no effect and deterioration.

The objective assessment consisted of the number and maximal area of ulcers, and inflammatory signs (swelling, redness, local heat) at baseline and after 2 weeks. The parameter of inflammatory signs was scored on a scale of 0 to 3 (0, negative; 1, mild; 2, moderate; and 3, severe).

Statistical analysis

Subjective parameters and objective parameters were compared at baseline and at 2 weeks after the treatment in all recurrent oral ulcer patients using the paired *t*-test. In each group, within-group changes at baseline and at 2 weeks after the treatment were checked using the Wilcoxon signed-rank test. Differences between the two groups were compared using the Mann–Whitney *U*-test. Differences in improvement ratings of each parameter between groups were tested using the Fisher's exact test. A significance level of 0.05 was used for all analyses.

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Table 1 Subjective assessment of number of ulcers, healing period and VAS by patient

	BD group		RAU group		Total	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Number of ulcers						
Baseline	2.5	± 2.7	2.9	± 2.2	2.7	± 2.5
Week 2	1.4	± 1.7	1.2	± 1.8	1.3	± 1.7
Week 2-Baseline	− 1.1	± 1.6	− 1.7	± 1.3	− 1.4	± 1.5
Intra-group *P*-value	0.05947		0.001740*		< 0.0001*	
Inter-group *P*-value	0.1688					
Healing period (days)						
Baseline	15.5	± 13.4	13.4	± 6.4	14.5	± 10.5
Week 2	7.4	± 5.6	6.3	± 7.1	6.8	± 6.3
Week 2-Baseline	− 8.1	± 13.0	− 7.2	± 8.0	− 7.7	± 10.7
Intra-group *P*-value	0.003382*		0.003954*		0.0003*	
Inter-group *P*-value	1.0000					
VAS						
Baseline	5.1	± 2.7	3.7	± 2.5	4.4	± 2.6
Week 2	2.6	± 2.6	1.3	± 2.0	2.0	± 2.4
Week 2-Baseline	− 2.4	± 2.3	− 2.4	± 2.3	− 2.4	± 2.3
Intra-group *P*-value	0.01721*		0.003196*		< 0.0001*	
Inter-group *P*-value	0.7846					

*, statistically significant.

Results

Both groups were similar regarding sex, age and number of patients.

(1) Subjective assessments

The subjective parameters for the patients consisted of the number of ulcers, healing period and VAS of pain for both groups, and the statistical results are summarized in Tables 1 and 2. The overall subjective parameters significantly improved between pre-treatment and post-treatment. A reduction in the average number of ulcers per week was observed in 72.7% of the patients (2.7 ± 2.5–1.3 ± 1.7). A decrease in the ulcer healing period was observed in 72.7% of the patients after treatment (6.8 ± 6.3 days) compared with the baseline (14.5 ± 10.5 days). Of all the patients, 75.8% experienced improvement in VAS for pain. The decreased values in VAS for pain was 4.4 ± 2.6 to 2 ± 2.4.

In the BD group, the healing period (15.5 ± 13.4 days to 13.4 ± 6.4 days) and VAS for pain (5.1 ± 2.7 to 3.7 ± 2.5) were statistically significantly decreased. Although the number of ulcers decreased after treatment in the BD group, the result had no statistical difference (2.5 ± 2.7 to 1.4 ± 1.7). In the RAU group, the number of ulcers, healing period and VAS of pain were statistically significantly decreased (2.9 ± 2.2 to 1.2 ± 1.8, 13.4 ± 6.4 days to 6.3 ± 7.1 days, 7.4 ± 3.0 to 4.3 ± 4.5), respectively. However, no significant differences were found between the BD group and RAU group in subjective parameters.

(2) Objective assessments

The objective assessments of the number and maximal area of ulcers were significantly improved between pre-treatment and post-treatment, as shown in Tables 3 and 4. A reduction in number was also observed in 57.6% of the patients (2.6 ± 2.4 to 1.6 ± 2.0), and 78.8% of the patients showed a decrease in the ulcer area (24.7 ± 31.9 mm^2 to 8.2 ± 11.2 mm^2). The number and maximal size of the ulcers were statistically significantly decreased between pre-treatment and post-treatment in the RAU group (2.9 ± 2.2 to 1.5 ± 2.4, 16.2 ± 20.5 mm^2 to 6.1 ± 7.5 mm^2). In the BD group, only the reduction in maximal size of the ulcers was statistically significant (32.8 ± 38.8 mm^2 to 10.2 ± 13.7 mm^2). However, no significant differences were found between the two groups in number and maximal area of ulcers

For the inflammatory signs parameters, the majority of patients had a mild score for swelling (60.6%), redness (78.8%) and local heat (57.6%) at baseline. After 2 weeks of treatment, the portion of patients who had no signs was increased in terms of swelling (45.5%), redness (33.3%)

Table 2 Subjective assessment of overall response of ulceration by patient

	BD group		RAU group		Total	
	n	**%**	***n***	**%**	***n***	**%**
Number of ulcers						
Improvement	11	64.7	13	81.2	24	72.7
No effect	4	23.5	3	18.8	7	21.2
Deterioration	2	11.8	0	0.0	2	6.1
Inter-group *P*-value	0.5171					
Healing period (days)						
Improvement	13	76.5	11	68.7	24	72.7
No effect	3	17.6	5	31.3	8	24.2
Deterioration	1	5.9	0	0.0	1	3.0
Inter-group *P*-value	0.5582					
VAS						
Improvement	12	70.6	13	81.2	25	75.8
No effect	4	23.5	3	18.8	7	21.2
Deterioration	1	5.9	0	0.0	1	3.0
Inter-group *P*-value	1.0000					

Table 3 Objective assessment of number and maximal size of ulcer by physician

	BD group (*n* = 17)		RAU group (*n* = 16)		Total (*n* = 33)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Number of ulcers						
Baseline	2.4	± 2.7	2.9	± 2.2	2.6	± 2.4
Week 2	1.7	± 1.6	1.5	± 2.4	1.6	± 2.0
Week 2-Baseline	− 0.7	± 1.5	− 1.4	± 1.3	− 1.0	± 1.4
Intra-group *P*-value	0.3944		0.004079*		0.0002*	
Inter-group *P*-value	0.6316					
Maximal size of ulcer (mm^2)						
Baseline	32.8	± 38.8	16.2	± 20.5	24.7	± 31.9
Week 2	10.2	± 13.7	6.1	± 7.5	8.2	± 11.2
Week 2-Baseline	− 22.5	± 35.6	− 10.1	± 18.3	− 16.5	± 28.8
Intra-group *P*-value	0.01242*		0.03616*		0.002*	
Inter-group *P*-value	0.4064					

*, statistically significant.

and local heat (72.7%). The inflammatory signs of swelling and local heat were significantly improved after treatment. The inflammatory sign of redness was improved, but not statistically significantly. Comparing the two groups, swelling and local heat were statistically significantly improved in the RAU group, but the inflammatory signs were not statistically significantly improved in the BD group (data not shown).

In all patients, the medication was well tolerated, and no patients were withdrawn from the study because of adverse events.

Discussion

HA is an extracellular constituent of connective tissue. Recently, the significance of HA has increased because of its role in the growth, development, and repair of tissues. The concentration of HA is increased during embryological development[14,15] and wound healing.[16] HA can also bind proteoglycans, which function in cell adhesion and migration. In the early stage of morphogenesis, cell growth, proliferation and migration predominate, and concentrations of HA characteristically rise.[17] The demonstration of the

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Table 4 Objective assessment of overall response of ulceration by physician

	BD group		RAU group		Total	
	n	**%**	***n***	**%**	***n***	**%**
Number of ulcers						
Improvement	7	41.2	12	75.0	19	57.6
No effect	8	47.0	4	25.0	12	36.4
Deterioration	2	11.8	0	0.0	2	6.1
Inter-group *P*-value	0.1036					
Maximal size of ulcer (mm^2)						
Improvement	13	76.4	13	81.2	26	78.8
No effect	2	11.8	1	6.3	3	9.1
Deterioration	2	11.8	2	12.5	4	12.1
Inter-group *P*-value	1.0000					

HA-rich foetal wound matrix has provided a new approach to the understanding of scarless foetal wound healing.[18] The increased concentrations of HA can modulate foetal wound healing by orchestrating healing through regeneration rather than by scarring.[16]

The use of HA in the treatment of inflammatory processes is established in orthopedics, rheumatology, and ophthalmology. Significant improvements in clinical parameters could also be found in the treatment of osteoarthritis of the knee,[5] rheumatoid arthritis,[6] radiodermatitis[7] and cataract surgery.[8] In oral disease, clinical trials were conducted to study the effect of the topical application of HA-containing gel in the treatment of plaque-induced gingivitis.[10–12] Recently, the effect of topical 0.2% HA on RAU was reported. In this report, topical 0.2% HA application immediately reduced discomfort and also reduced ulcer duration. The occurrence of new ulcers was lower when patients are treated with this preparation.[13]

In our study, we investigated the subjective and objective effects of HA in BD patients and non-BD patients with recurrent oral ulcers. The subjective and objective effects were similar, and the treatment with HA was strikingly effective. HA gel therapy significantly decreased the number of ulcers, healing period, VAS of pain, ulcer activity score and maximal area of the ulcers. These results suggest that HA may act purely as a barrier, or have a protective effect against stimuli arising in the oral environment, to promote the healing of oral ulcers. The inflammatory signs of swelling and local heat were significantly improved after treatment. The anti-inflammatory effect may be due to the action of exogenous HA as a scavenger to drain prostaglandins, metalloproteinases and other bio-active molecules.[19] The anti-edematous effect may also be related to the osmotic activity.[12] HA is a hygroscopic macromolecule and highly osmotic. In the skin and perhaps on the oral mucosa, this property is likely to be relevant in controlling tissue hydration during periods of change, such as the inflammatory process or response to tissue injury.[13] Although the results of this study suggest that topical application of 0.2% HA gel is an effective therapy in patients with recurrent oral ulcers, further study to directly compare its efficacy with topical steroid application is required.

BD is a chronic, relapsing, systemic vasculitis of unknown aetiology. BD is characterized by recurrent oral ulcers, genital ulcers and uveitis. BD is considered to be a multisystemic inflammatory disease with vascular, articular, gastrointestinal, urogenital, pulmonary and neurologic involvement.[20] Oral ulcers represent the onset feature of the disease in the majority of patients (47–86%) and are recurrent and painful. They are identical to RAU in appearance, but they tend to be more frequent and occur in crops. The majority of experience in the treatment of oral ulcers in BD comes from the studies performed in patients with RAU. In our study, no significant differences were noted between the BD group and the RAU group in most parameters (except in number of ulcers, and redness among inflammatory signs). We think that the number of ulcers may be associated with the disease activity of BD, and that topical agents cannot prevent the development of ulcers. However, topical HA has an effect on decreasing healing time and size of developed oral ulcers in BD. Therefore, a therapeutic remedy used with RAU, HA, can be applied to the oral ulcers of BD.

Because HA can be found in many tissues and body fluids, with the highest concentrations in connective tissue and skin, it is possible that HA will have a similar effect in genital ulcers. Further study is needed to evaluate the effect of HA on genital ulcers.

In conclusion, topical application of 0.2% HA gel seems to be an effective and safe therapy, especially for reducing the number, healing period, pain, and area of ulcers, as

well as inflammatory signs in recurrent oral ulcer patients. These results suggest that HA can be used in BD patients with oral ulcers.

References

1 Rogers RS III. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg* 1997; **16**: 278–283.

2 Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc* 2003; **134**: 200–207.

3 Jorizzo JL, Taylor RS, Schmalstieg FC. Complex aphthosis; A forme fruste of Behçet's syndrome? *J Am Acad Dermatol* 1985; **13**: 80–84.

4 Toole BP. Hyaluronan and its binding proteins, the hyaladherins. *Current Opinion Cell Biol* 1990; **2**: 839–844.

5 Adams ME, Atkinson MH, Lussier AJ *et al*. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter comparing hylan G-F 20 alone, hylan G-F 20 with non-steroid inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage* 1995; **3**: 213–225.

6 Matsuno H, Yudoh K, Kondo M, Goto M, Kimura T. Biochemical effect of intra-articular injections of high molecular weight hyaluronate in rheumatoid arthritis patients. *Inflammation Res* 1999; **48**: 154–159.

7 Liguori V, Guillemin C, Pesce GF *et al*. Double blind, randomised clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. *Radiotherapy Oncol* 1997; **42**: 155–161.

8 Caporossi A, Baiocchi S, Sforzi C, Frezzotti R. Healon GV versus Healon in demanding cataract surgery. *J Cataract Refractive Surg* 1995; **21**: 710–713.

9 Weindl G, Schaller M, Schäfer-Korting M, Korting HC. Hyaluronic acid in treatment and prevention of skin diseases: molecular biological, pharmaceutical and clinical aspects. *Skin Pharmacol Physiol* 2004; **17**: 207–213.

10 Vangelisti R, Pagnacco O, Erra C. Hyaluronic acid in the topical treatment of gingival inflammations: preliminary clinical trial. *Attualita Terapeutica Internazionale* 1997; **15**: 2–3.

11 Pagnacco A, Vangelisti R, Erra C *et al*. Double-blind clinical trial vs placebo of a new sodium-hyaluronate based gingival gel. *Attualita Terapeutica Internazionale* 1997; **15**: 4–7.

12 Jentsch H, Pomowski R, Kundt G, Gocke R. Treatment of gingivitis with hyaluronan. *J Clin Periodontol* 2003; **30**: 159–164.

13 Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA. The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. *J Oral Pathol Med* 2006; **35**: 461–465.

14 Toole BP, Gross J. The extracellular matrix of the regenerating new limb: synthesis and removal of hyaluronate prior to differentiation. *Devl Biol* 1971; **25**: 57–77.

15 Kujawa MJ, Pechak DG, Fiszmann MY *et al*. Hyaluronic acid bonded to cell culture surface inhibits the program of myogenesis. *Devl Biol* 1986; **113**: 10–16.

16 Longaker MT, Adzick NS. The biology of fetal wound healing: a review. *Plast Reconstr Surg* 1991; **87**: 788–798.

17 Laurent TC, Fraser JRE. Hyaluronan. *FASEB J* 1992; **6**: 2397–2404.

18 De Palma RL, Krummel TM, Durham LA 3rd *et al*. Characterization and quantitation of wound matrix in the fetal rabbit. *Matrix* 1989; **9**: 224–231.

19 Laurent TC, Laurent UB, Fraser JRE. Functions of hyaloronan. *Ann Rheumatic Dis* 1995; **54**: 429–432.

20 Yazici H. Behçet's syndrome: an update. *Curr Rheumatol Rep* 2003; **5**: 195–199.