Received: 15th October 2013 Accepted: 16th December 2013 Conflict of Interest: None

Original Research

Clinical study to know the efficacy of Amlexanox 5% with other topical Antiseptic, Analgesic and Anesthetic agents in treating minor RAS

D D Darshan[1], C N Vijay Kumar[2], A D Manoj Kumar[3], N S Manikantan[3], Dhanya Balakrishnan[2], M P Uthkal[4]

Contributors:

[1]Assistant Professor, Department of Oral Medicine & Radiology, K V G Dental College & Hospital, Sullia, Karnataka, India; [2]Reader, Department of Conservative Dentistry & Endodontics, K V G Dental College & Hospital, Sullia, Karnataka, India; [3]Reader, Department of Prosthodontics, K V G Dental College & Hospital, Sullia, Karnataka, India; [4]Assistant Professor, Department of Oral Medicine & Radiology, Malabar Dental College and Hospital, Mallappuram, Kerala, India.

Correspondence:

Dr. Darshan DD. Department of Oral Medicine and Radiology, K V G Dental College & Hospital, Sullia, Karnataka, India. Phone: +91 – 9986220538. Email: darshandevang@gmail.com

How to cite the article:

Darshan DD, Kumar CN, Kumar AD, Manikantan NS, Balakrishnan D, Uthkal MP. Clinical study to know the efficacy of Amlexanox 5% with other topical Antiseptic, Analgesic and Anesthetic agents in treating minor RAS. J Int Oral Health 2014;6(1);5-11.

Abstract:

Background: To evaluate the efficacy of topical anti-inflammatory agent (amlexanox 5%), along with topical antiseptic, analgesic, and anesthetic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2%), in promoting ulcer healing, decreasing ulcer size, erythema, pain and recurrence in minor RAS.

Materials & Methods: A randomized control trial was conducted on 100 patients of RAS who fulfilled the inclusion criteria. The number, size, erythema and pain with the ulcer were recorded. Visual analogue scale (VAS) and erythema scale were used to record pain and erythema. 50 patients comprising the study group received anti inflammatory paste (amlexanox 5%) applied four times daily and the control group of 50 patients received topical antiseptic, analgesic, and anesthetic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2%) paste, patients were evaluated after 3rd, 6th, 9th and on 30th, 60th day for recurrence.

Results: The study group had reduction in ulcer number, size; erythema, pain and frequency of ulcers during follow up. The healing period and recurrence of ulceration reduced in both the groups but the study group had significant reduction in 30th and 60th day follow up for recurrence of ulcers.

Conclusion: Amlexanox 5% can reduce the frequency, duration and symptoms associated with the aphthous ulcers with no side-effects attributed to the drug.

Key Words: Amlexanox, recurrent aphthous stomatitis (RAS), visual analogue scale (VAS)

Introduction

Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most common oral mucosal disease known to human beings and has ever since been the subject of considerable clinical and research attention, because of its multiple etiologies and various treatment modalities with no much of cure. The term "aphthae" refers to presence of an otherwise undefined ulcer. Hippocrates (460-370BC) was the first to use the term aphthai, he used this term to describe all disorders affecting the mouth. However, the first valid clinical description of RAS is credited to Von Mikulicz and Kummel (1888). The prevalence of RAS in general population is of the order of 5 to 25%,[1] effecting men and women of all ages, races, and geographic regions.[2]

The disease is characterized by recurrent, painful ulcers that are small, round to ovoid, affecting non-keratinized oral mucosa such as buccal mucosa, lateral and ventral aspects of the tongue, floor of the mouth and soft palatal and oropharyngeal mucosa with a crateriform based covered by a grey white pseudomembrane and surrounded by a distinct erythematous halo.[3]

Many investigators have classified RAS into three subtypes: minor aphthous ulcers, major aphthous ulcers and herpetiform ulcer.[4-9]

Minor RAU is the most common manifestation of the disorder, occurring in 75-80% of patient with RAU. This is characterized by shallow round or oval lesions of < 10 mm in diameter.[4-9]

Major RAU is a more severe from, affecting approximately 10% of patients with RAU. Lesions are generally deeper than those observed in minor RAU, often exceed 10 mm in diameter and generally take several weeks to heal with scar.[4-9]

Herpetiform ulcers are multiple clusters of ulcers and are between 2-3 mm in diameter, approximately 10% of patients presenting with RAU have the herpetiform manifestation.[4-9]

RAU can also be classified as simple aphthosis or complex aphthosis. The Simple manifestation is characterized by

short – lived episodes involving a few lesions that heal quickly with minimal pain. Conver-sely, complex aphthosis is a more disabling state, char-acterized by numerous and large lesions, continued ulceration and marked pain. Furthermore, lesions may occur in the genital or perianal regions.[10,11]

Despite extensive investigations, studies have failed to find the exact etiology and pathogenesis of this condition. Hereditary, hematinic deficiencies, immune dysregulation, some food, drugs, psychic stress, local trauma, hormonal disturbances, infections, cessation of smoking, poor oral hygiene are proposed factors.[1,3]

Since the etiology is unknown, the diagnosis is entirely based on history and clinical criteria and no laboratory procedures exist to confirm the diagnosis.

Although a variety of treatment modalities have been suggested to eliminate or reduce the duration of recurrences, their clinical value remains unproven and can be controversial, most common treatment involves the use of topical agents to provide symptomatic relief, and these include antibiotics, analgesics, non-steroidal anti-inflammatory drugs, corticosteroids and immunomodulators.[12,13]

The purpose of this study is to evaluate the efficacy of amlexanox 5% in promoting ulcer healing, decreasing ulcer number, size, erythema, resolving pain and recurrence associated with RAS when applied topically. Compared with topical antiseptic, analgesic, and anesthetic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2%

Materials and Methods

A total of 100 patients with minor RAS were volunteered in the study. These patients were randomly selected from different private dental clinic of different parts of Karnataka.

The following criteria were utilized to select patient:

1. Patients giving history of recurrence ulcers in the oral cavity with at least 2 episodes per year and with no signs of any systemic disease.
2. Patients above 12 years with apparently normal immune system.

Exclusion criteria comprised:

1. Patient with any systemic disease causing oral ulcerations like- gastrointestinal disorders (ulcerative colitis, Cohns disease), Bechets disease, Reiter syndrome, hematological diseases, nutritional deficiencies and allergic conditions
2. Patients who are receiving or have received chemotherapeutic drugs. immunomodulators or systemic corticosteroids in the recent 1 year.
3. Patient having other mucosal lesions, with recurrent minor aphthous ulcers
4. Pregnant and lactating mothers.

All patients underwent a routine hematological investigation to rule out any hematological abnormalities. An informed consent was obtained and randomized controlled study was performed. Patient details were recorded on pro-forma designed for this study. A Clinical examination was performed to assess the number, site, size with caliberated periodontal probe, erythema with (erythema scale 0, 1, 2, 3) and Pain using Visual Analogue Scale (VAS) from 1 to 10 (with 10 being the most severe). 50 patients were randomly selected to receive amlexanox 5% oral paste at the first visit presenting with minor aphthous ulcers with instructions to apply four times daily, preferably following oral hygiene procedures, till the ulcer heals they formed the study group. The control group also comprised of 50 patients and received topical antiseptic, analgesic, and anesthetic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2% paste.

The patients were then recalled at 3rd, 6th, 9th, 30th and 60th day, following the onset of treatment. The effectiveness of the treatment in both the groups were assessed on the basis of reduction in number, size, maximum VAS scores, maximum erythema score and the recurrence at 30th and 60th day. Statistical test like student's t-test for comparison of the study and the control group, and paired t-test for comparison of parameters obtained at different time periods with the baseline values within the group itself was used. A p-value of ≤0.05 was taken as statistically significant.

Results

In the study group, out of 50 patients, 41 were male and 9 were females (male: female ratio of 4.5:1) their age range from 14 years -36 years (mean 25 years). Of the 50 patient in comparison group, 32 were males and 18 were females (male: female ratio of 1.7:1) their age range from 18 years - 36 years (mean 27 years).

At the time of presentation, the number of the ulcers in each patient (Table 1) and the sites of the ulcers were recorded (Table 2) in both the groups.

The first day values (baseline value) of all patients were collected i.e. the number of ulcers, size of ulcers, erythema in ulcers (erythema scale 0, 1, 2, 3), and maximum pain recorded on (VAS). Following administration of amlexanox 5% in the study group and topical analgesic, anesthetic and antiseptic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2% in control group, the patients were recalled at intervals of 3rd, 6th, 9th day and 30th and 60th day to check recurrence of new ulcers.

The comparison of the number, size, erythema, maximum pain, during different stages with the first day values were made.

Study group showed significant results, but values were not significant on 1st day and 3rd day in the number. Similarly comparing the control groups also yielded significant difference in number, size, erythema, pain. Except, for the

Table 1: Number of ulcers at the time of presentation in both the groups.

Number of ulcers	Study group	Control group
Prodromal phase	1	2
1 ulcer	39	36
2-4 ulcer	6	12
5 or more ulcer	4	0

Table 2: Site distribution of the ulcers in the Study and Control group.

Site of ulcers	Study group	Control group
Labial mucosa and lip	24	22
Buccal mucosa	12	9
Lateral border and dorsum of tongue	10	11
Floor of mouth and ventral aspect of tongue	2	5
Soft palate	2	3

Table 3: Pair wise comparison of the 1st day with 3rd, 6th, 9th days of treatment with amlexanox 5% in study group w.r.t the number of ulcers, size of ulcers, erythema of ulcers, maximum pain in (VAS) of the ulcers. (Mean and (SD) standard deviation of study group with amlexanox 5%).

		1st Day	3rd Day	6th Day	9th Day
Number of ulcers	Mean	1.72	1.26	0.92	0.42
	SD	1.9498	0.9340	0.744	0.5689
Size of ulcers	Mean	4.31	2.644	1.924	0.738
	SD	1.5776	1.8157	1.8527	1.3617
Erythema of ulcers	Mean	2.92	2.2	1.2	0.44
	SD	0.2713	0.6633	0.7746	0.5713
Pain in VAS	Mean	8.34	5.92	3.74	1.98
	SD	2.1129	2.4645	2.5676	2.3021

Table 4: Study group t-value for 3rd, 6th, 9th day compared with 1st day.

	3rd Day	6th Day	9th Day
Number of ulcers	1.50	2.71	4.53
	NS	S	S
Size of ulcers	4.89	6.93	12.12
	S	S	S
Erythema of ulcers	7.11	14.81	27.74
	S	S	S
Pain in VAS	5.27	9.78	9.86
	S	S	S

number and size of the ulcers on 1st day and 3rd day (Table 3, 4, 5, 6). On comparing the number of ulcers between two groups, there was no significant difference between 1st, 3rd, 6th day. Results were significant on 9th day only indicating considerable reduction in number in study group then control group. Though the number also reduced in study group it was not statistically significant (Table 7) (Graph 1).

There was significant reduction in the size of ulcer in both the groups when 3rd, 6th, 9th, day values were compared with the first day values of respective group. On comparing between two groups, there was significant difference on 3rd, 6th and 9th day. Indicating considerable reduction in size of ulcers in study group compared to control group (Table 4 and 6) (Graph 2).

There was also significant reduction in the erythema of ulcer in both the groups when 3rd, 6th, 9th day values when compared with the first day values of respective group. On comparing between the groups significant difference was noted on 6th and 9th day showing good results in the study group than control group (Table 4 and 6) (Graph 3).

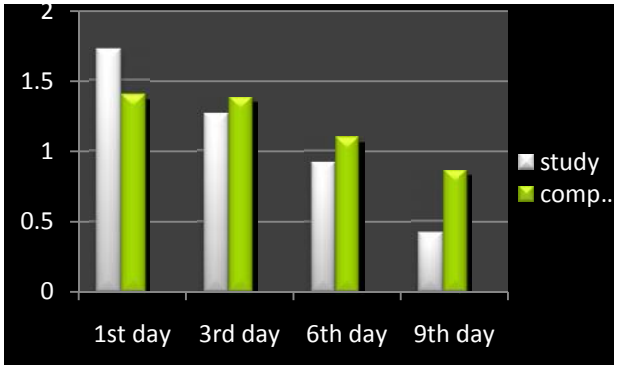
Comparing the means of the VAS scores, showed significant difference in both the groups and between two

Table 5: Pair wise comparison of the 1st day with 3rd, 6th, 9th, days of treatment with topical analgesic, anesthetic and antiseptic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride2% control group w.r.t the number of ulcers, size of ulcers, erythema of ulcers, maximum pain in (VAS) of the ulcers. (Mean and (SD) standard deviation of control group with dentogel).

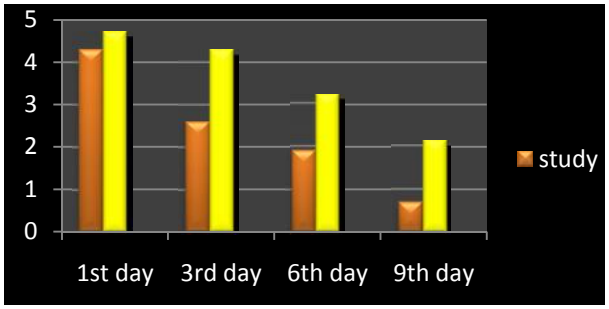
		1st Day	3rd Day	6th Day	9th Day
Number of ulcers	Mean	1.4	1.38	1.1	0.86
	SD	0.8485	0.8693	0.7	0.7486
Size of ulcers	Mean	4.73	4.3	3.222	2.142
	SD	1.8309	1.8762	1.9959	1.9172
Erythema of ulcers	Mean	2.98	2.32	1.74	1.16
	SD	0.14	0.5455	0.6264	0.6437
Pain in VAS	Mean	9.18	7.68	5.94	4.82
	SD	0.9315	1.4204	2.0631	2.2243

Table 6: Control group t-value for 3rd , 6th ,9th day compared with 1st day.

	3rd Day	6th Day	9th Day
Number of ulcers	0.12	1.92	3.38
	NS	NS	S
Size of ulcers	1.16	3.93	6.90
	NS	S	S
Erythema of ulcers	8.29	13.66	19.53
	S	S	S
Pain in VAS	6.24	10.12	12.79
	S	S	S



Graph 1: comparison of the Study and Control group w.r.t mean number of ulcers.



Graph 2: comparison of the Study and Control group w.r.t mean size of ulcers.

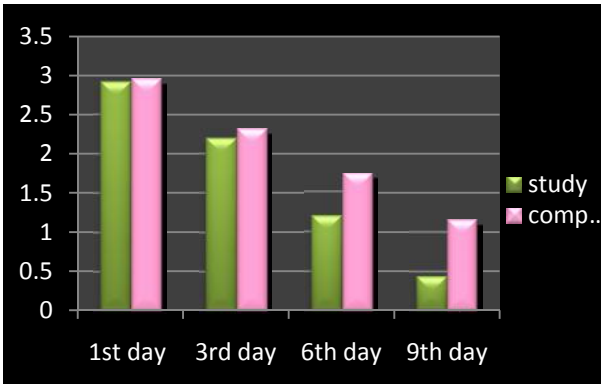
groups. However when overall comparison of the score was made, the study group had lower pain scores then the control group (Table 4 and 6) (Graph 4).

Recurrence was calculated between two groups on 30th and 60th day, study group showed 18% recurrence in 30th day and 14% recurrence in 60th day and control group showed 26% recurrence in 30th day and 28% recurrence in 60th day (Table 8) (Graph 5).

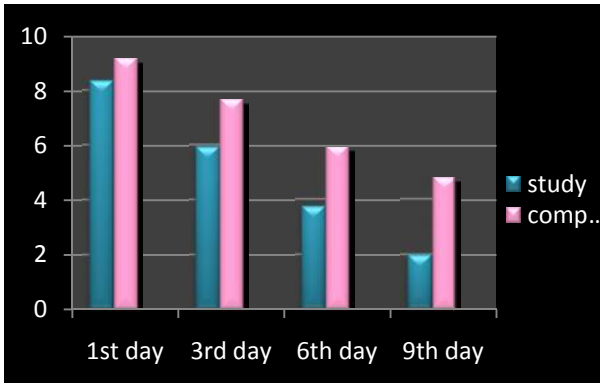
Table 7: t-value between Study group and Control group.				
	1st Day	3rd Day	6th Day	9th Day
Number of ulcers	1.06	0.67	1.25	3.31
	NS	NS	NS	S
Size of ulcers	1.23	4.49	3.37	3.65
	NS	S	S	S
Erythema of ulcers	1.39	0.99	3.83	5.92
	NS	NS	S	S
Pain in VAS	2.57	4.37	4.72	6.27
	S	S	S	S

NS- No significance for p>0.05 S-Significance for p<0.05 Calculated for table value (1.96), < (1.96) no signifince > (1.96) signifince

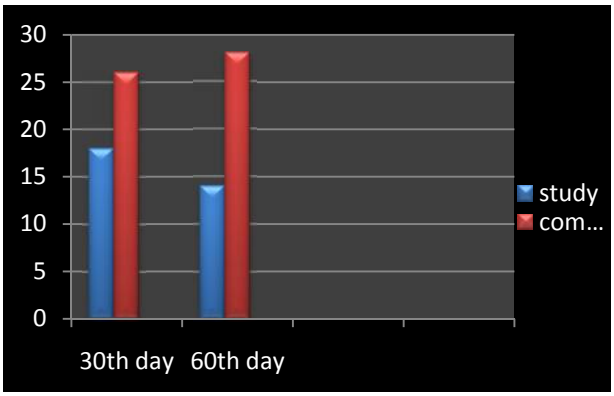
Table 8: % of recurrence between Study group and Control group on 30th and 60th day follow-up				
Recurrence	**30th Day**	**%**	**60th Day**	**%**
Study group	9 patients	18%	7 patients	14%
Control group	13 patients	26%	14 patients	28%



Graph 3: comparison of the Study and Control group w.r.t mean erythema of ulcers.



Graph 4: comparison of the Study and Control group w.r.t maximum VAS scores to measure pain.



Graph 5: comparison of the Study and Control group w.r.t mean recurrence of ulcers. Showing a tremendous reduction in the recurrence of ulcers in the study group when compared to control group.

Discussion

Recurrent aphthous stomatitis is one of the most common oral ailments. The patient of RAS presents with painful, recurring ulcers of the oral cavity. Diagnosis of RAS rests on features like: a history of recurrent ulcers since childhood or adolescence and presence of typical multiple round or ovoid ulcers on examination.[3]

Although most cases of RAS are idiopathic, a careful history taking and physical examination is essential to rule out any secondary cause. A number of systemic conditions can give rise to oral ulcerations resembling RAS. They are Crohns disease, Ulcerative Colitis, Gluten-Sensitive Enteropathy, Behcets syndrome, Reiters syndrome, Sweets

syndrome, cyclic neutropenia, nutritional deficiencies, and drugs like Nicorandril.[14]

If the history and clinical examination are characteristic of RAS, routine laboratory testing is not necessary in most individuals. A complete blood count and measurements of levels of red-cell, folate, serum vitamin B_{12} and serum ferritin is suggested by few authors.[15,16] These investigations are useful only if there are other clinical findings suggestive of nutritional or haematological abnormalities.

Immune dysregulation in a genitically susceptible individual is also accepted and reasonably documented cause of RAS. Immunopathogenesis of RAS probably involves a cell mediated immune response. Few studies have shown an alteration in the T-cell fractions in individuals of RAS.[17,18] Role of humoral immunity in RAS too has been suggested by some authors. In a study on Spanish patient the IgG_2 subclass was lowered.[19] Hence treatments such as corticosteroids and Immunosuppressive agents like cyclosporine, azathioprine, thalidomide are also used but can produce a number of serious side effects.[1]

Amlexanox 5% (Lexanox), a topical anti-inflammatory agent has recently been found to have significant role in management of minor aphthous ulcers.[13] Amlexanox ($C_{16}H_{14}N_2O_4$) is a topical anti-inflammatory, anti-allergic drug. Amlexanox potentialy inhibit the formation and release of histamine and luekotrines from mast cells, neutrophils, and mononuclear cells. Histamine and leukotrines are vasoactive inflammatory mediators which can only increase the permeability of vessels and therefore cause swelling of the involved tissues, but also contribute to inflammation by affecting the functions of other leukocytes in the involved area.[20,21]

In present study patient on amlexanox 5% reported reduced number of ulcers on comparison to pre treatment period and in control group, though the number reduced was not of that significance indicating greater ulcer free days in study group. Size and erythema also reduce in both the groups. On comparision between the groups the size and erythema was lower in the study group than the control group. This reduction was not significant on the 1 day of ulcer size and 1st, 3rd day of erythema which showed near approximation with previous studies done by Jie Liu et al and Greer et al.[20,22]

Signs and symptoms in both the groups had reduced which was noted by reduction in the VAS scores throughout treatment and post-treatment period. This indicates that both drugs could bring about reduction in the pain. However, on comparing between two groups, the patients on amlexanox 5% had a significant lower VAS values than the control group. Which showed approximation with previous studies done by Atul Khandwala et al.[12,13]

Calculating recurrence, study group showed 18% recurrence in 30th day and 14% recurrence in 60th day follow-up and control group showed 26% recurrence in 30th day and 28% recurrence in 60th day follow-up showing tremendous reduction in recurrence of ulcers in the study group then control group.

No adverse effects were reported in the present study. Corroborating with the study of Atul Khandwala wher in no adverse reactions were reported.[23]

Conclusion

Anti-inflammatory oral paste (Amlexanox 5%) when used topically can bring considerable improvement in signs and symptoms associated with RAS. This study has shown reduction in number, size, erythema, pain associated with ulcers and also the reduction in recurrence of ulceration with no side-effects attributed to the drug. When compared with topical antiseptic, analgesic, and anesthetic agent (benzalkonium chloride 0.01%, choline salicylate 8.7% and lidocaine hydrochloride 2% paste.

Hence topical amlexanox could be a treating modality for minor RAS and has tremendous scope for further research in management this intractable condition.

References

1. Ship JA, Arbor A. Recurrent Aphthous Stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:141-7.
2. Mason J. Concepts in dental public health. Philadelphia: Lippincott Williams & Wilkins; 2005.
3. Scully C. Clinical practice. Aphthous ulcerations. N Engl J Med 2006;355:165-72.
4. Ship II. Epidemiologic aspects of recurrent aphthous ulcerations. Oral Surg Oral Med Oral Pathol 1972;33(3):400-6.
5. Cooke BE. Recurrent oral ulceration. Br J Dermatol 1969;81(2)159-61.
6. Lehner T. Autoimmunity in oral diseases, with special reference to Recurrent oral ulceration. Proc R Soc Med 1968;61(5):515-24.

7. Rennie JS, Reade PC, Hay KD, Scully C. Recurrent Aphthous Stomatitis. Br Dent J 1985;159(11):361-7.
8. Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. Dent Clin North Am 2005;49(1):31-47,VII-VIII.
9. Greenberg MS, Pinto A. Etiology and management of recurrent aphthous stomatitis. Curr Infect Dis Rep 2003;5(3):194-8.
10. Rogers III RS. Recurrent Aphthous Stomatitis: clinical characteristics and associated systemic disorders. Semin Cutan Med Surg 1997;16(4):278-83.
11. Jorizzo JL, Taylor RS, Schmalstieg FC, Solomon AR Jr, Daniels JC, Rudloff HE, Cavallo T. Complex aphthosis: A forme frusta of behcets syndrome? J Am Acad Dermatol 1985;13(1):80-4.
12. 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 Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83(2):222-30.
13. Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al, (Editors). Harrison's principles of internal medicine, 17th ed. New York: McGraw Hill; 2008.
14. Jurge S, Kuffer R, Scully C, Porter SR. Recurrent Aphthous Stomatitis. Oral Dis 2006;12:1-21.
15. Nolan A, Lamey P-J, Milligan KA, Forsyth A. Recurrent aphthous ulcerations and food sensitivity. J Oral Pathol Med 1991;20:473-5.
16. Koybasi S, Parlak AH, Serin E, Yilmaz F, Serin D. Recurrent aphthous stomatitis: investigatigation of possible etiologic factors. Am J Otolaryngol Head Neck Med Surg 2006;27:229-32.
17. Savage NW, Mahanonda R, Seymour GJ, Bryson GJ, Collins RJ. The proportion of suppressor- inducer T-lymphocytes is reduced in recurrent aphthous stomatitis. J Oral Pathol 1988;17:293-7.
18. Landesberg R, Fallon M, Insel R. Alterations of T helper/induced and T suppressor/induced cells in patient with Recurrent Aphthous ulcers. Oral Surg Oral Med Oral Pathol 1990;69:205-8.
19. Vicente M, Soria A, Mosquera A, Perez J, Lamas A, Castellano T, Ramos A. Immunoglobulin G subclass measurements in recurrent Aphthous Stomatitis. J Oral Pathol Med 1996;25:538-40.
20. Liu J, Zeng X, Chen Q, Cai Y, Chen F, Wang Y, Zhou H, Lin M, Shi J, Wang Z, Zhang Y. An evaluation on the efficacy and safety of amlexanox oral adhesive tablets in the treatment of minor recurrent aphthous ulceration in a Chinese cohort: a randomized, double –blind, vehicle-controlled multicenter clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:475-81.
21. Saijo T, Kuriki H, Ashida Y, Makino H, Maki Y. Mechanism of action of amlexanox (AA-673), an oral active antillergic agent. Int Arch Allergy Appl Immunol 1985;78(1):43-50.
22. Greer RO Jr, Lindenmuth JE, Juarez T, Khandwala A. A Double-Blind Study of Topically Applied 5% Amlexanox in the Treatment of Aphthous Ulcers. J Oral Maxillofac Surg 1993;51:243-8.
23. Khandwala A, Van Inwegen RG, Charney MR, Alfano MC.5% Amlexanox oral paste, a new treatment for recurrent minor apthous ulcers: II. Pharmacokinetics and demonstration of clinical safety. Oral Surg Oral Med Oral Pathol Oral Endod 1997;83:231-8.