Amlexanox in the treatment of recurrent minor aphthous ulcers
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Abstract
Background: Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most common oral mucosal disease. Aims & Objectives: To evaluate the efficacy of topical anti-inflammatory agent amlexanox, along with topical anesthetic agent Lignocaine gel, 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 5% amlexanox applied four times daily. The control group of 50 patients was given with topical anesthetic paste Lignocaine 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 can reduce the frequency, duration and symptoms associated with the aphthous ulcers with no side-effects attributed to the drug.

Key Words: Recurrent Aphthous Stomatitis; Amlexanox; Lignocaine; Visual Analogue Scale

Introduction
Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most common oral mucosal disease.(1) Hippocrates (460-370BC) was the first to use the term aphthai, he used this term to describe all disorders affecting the mouth.(2) However, the first valid clinical description of RAS is credited to Von Mikulicz and Kummel in 1888.(3) 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.(4)

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 crater form based covered by a grey white pseudo membrane and surrounded by a distinct erythematous halo.(5) Many investigators have classified RAS into three subtypes: minor aphthous ulcers, major aphthous ulcers and herpetic form ulcer.(1)

The purpose of this study is to evaluate the efficacy of amlexanox in promoting ulcer healing, decreasing ulcer number, size, erythema, resolving pain and recurrence associated with RAS when applied topically.

Materials and Methods
A total of 100 patients with minor RAS were volunteered in the study. These patients were randomly selected from the outpatient department of oral medicine and radiology, Al-Badar Rural Dental College, Gulbarga.

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 of:
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, Immune-modulators 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 calibrated 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 5% amlexanox 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 comprises of 50 patients and received topical anesthetic agent Lignocaine gel.

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 to 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 to 36 years (mean 27 years). At the time of presentation, the number of the ulcers in each patient and the sites of the ulcers were recorded 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 in the study group and Lignocaine gel in the 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 number and size of the ulcers on 1st day and 3rd day (Table 1). 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>
<thead>
<tr>
<th></th>
<th>1st DAY</th>
<th>3rd DAY</th>
<th>6th DAY</th>
<th>9th DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ulcers Mean</td>
<td>1.72</td>
<td>1.26</td>
<td>0.92</td>
<td>0.42</td>
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<tr>
<td>SD</td>
<td>1.9498</td>
<td>0.9340</td>
<td>0.744</td>
<td>0.5689</td>
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<tr>
<td>Size of ulcers Mean</td>
<td>4.31</td>
<td>2.64</td>
<td>1.92</td>
<td>0.738</td>
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<tr>
<td>SD</td>
<td>1.5776</td>
<td>1.8157</td>
<td>1.8527</td>
<td>1.3617</td>
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<tr>
<td>Erythema of ulcers Mean</td>
<td>2.92</td>
<td>2.2</td>
<td>1.2</td>
<td>0.44</td>
</tr>
<tr>
<td>SD</td>
<td>0.2713</td>
<td>0.6633</td>
<td>0.7746</td>
<td>0.5713</td>
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<tr>
<td>Pain in VAS Mean</td>
<td>8.34</td>
<td>5.92</td>
<td>3.74</td>
<td>1.98</td>
</tr>
<tr>
<td>SD</td>
<td>2.1129</td>
<td>2.4645</td>
<td>2.5676</td>
<td>2.3021</td>
</tr>
</tbody>
</table>

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.

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.

Comparing the means of the VAS scores, showed significant difference in both the
groups and between two groups. However when overall comparison of the score was made, the study group had lower pain scores then the control group.

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.

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: a history of recurrent ulcers since childhood or adolescence and presence of typical multiple round or ovoid ulcers on examination.

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.

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 foliate, serum vitamin B12 and serum ferritin is suggested by few authors. These investigations are useful only if there are other clinical findings suggestive of nutritional or hematological abnormalities.

Immune deregulation in a genetically susceptible individual is also accepted and reasonably documented cause of RAS. Immuno-pathogenesis of RAS probably involves a cell mediated immune response. Few studies have shown an alteration in the T-cell fractions in individuals of RAS. Role of humoral immunity in RAS too has been suggested by some authors. In a study on Spanish patient the IgG2 subclass was lowered. Hence treatments such as corticosteroids and Immunosuppressive agents like cyclosporine, azathioprine, thalidomide are also used but can produce a number of serious side effects.

5% Amlexanox (Lexanox), a topical anti-inflammatory agent has recently been found to have significant role in management of minor aphthous ulcers. Amlexanox (C16H15N2O4) is a topical anti-inflammatory, anti-allergic drug. Amlexanox potentialy inhibit the formation and release of histamine and leukotrines 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.

In present study patient on amlexanox reported reduced number of ulcers on comparison to pretreatment period and in control group though the number reduced it was not of that significance, indicating greater ulcer free days in study group. Size and erythema also reduce in both the groups. On comparison between the groups the size and erythema was lower in the study group than the control group.

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 similar to the study of Atul Khandwala.(6)

Conclusion

Amlexanox 5% oral paste 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. Hence topical amlexanox could be a treating modality for minor RAS and has tremendous scope for further research in management this intractable condition.

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