ABSTRACT

Background: Recurrent aphthous ulceration, or RAU, is a common oral disorder of uncertain etiopathogenesis for which only symptomatic therapy is available. The goals of therapy include the management of pain and functional impairment by suppressing inflammatory responses, as well as reducing the frequency of recurrences or avoiding the onset of new aphthae.

Aim: The aim of this study was to explore the effectiveness of 5% Amlexanox oral paste in the treatment of recurrent aphthous ulcers, and compare the results with those of polyherbal formulation (HiOra SG gel).

Method: 30 patients with diagnosis of minor recurrent aphthous ulcers were included in this clinical study. The individuals were randomly divided into Group 1 (HiOra SG gel) and Group 2 (5% Amlexanox oral paste). The number, size and pain level of ulcers were measured and recorded on treatment days 0, 4 and 7. Finally, the results were compared using student unpaired t test.

Results: While Amlexanox oral paste significantly reduced ulcer size (p<0.001 for day 4 and day 7) HiOra SG was less beneficial in reducing ulcer size (p=0.014 for day 4 and p<0.001 for day 7). HiOra SG showed greater effectiveness in alleviating ulcer pain (p<0.001 for day 4 and day 7) than 5% Amlexanox (p=0.082 for day 4 and p<0.001 for day 7). However, no significant difference was observed in reducing the number of ulcers between 5% Amlexanox and HiOra SG.

Conclusion: Although, HiOra SG seems to be more promising in resolution of pain associated with RAU, Amlexanox oral paste is as effective and safe in the treatment of these ulcers.

Keywords: aphthous, amlexanox, polyherbal formulation, RAU (Recurrent aphthous ulceration).
cyclic neutropenia. It is unclear whether these presentations are manifestations of the underlying disease or represent a separate oral disorder.

Various factors have been suggested to precipitate outbreaks of recurrent aphthous stomatitis in predisposed persons, including oral trauma, the cessation of smoking (for reasons that are unclear), anxiety or stress, sensitivities to food (e.g., to preservatives and agents such as benzoic acid or cinnamondehyde), and hormonal changes related to the menstrual cycle. However, evidence to support the causative role of these factors is scarce.

Since the etiology is unknown, the diagnosis is entirely based on history and clinical criteria and no laboratory procedures exist to confirm the diagnosis (Ship 1996). Due to the indeterminate etiology of the disease, it is difficult to find a definitive cure and current treatments are aimed towards ameliorating the symptoms.

Treatment for RAU is symptomatic; the goals being to decrease pain, healing time, number and size of the ulcer, and to increase disease-free periods. Current treatment options include topical agents, systemic and topical steroids, corticosteroids, silver-nitrate cauterization, antibiotics (penicillin G and doxycycline), mouth rinses containing active enzymes Carbenoxolone mouthwash, laser treatments and combination therapy. Other therapeutic options available are 5% amlexanox. Other medications (such as levamisole, colchicine, and pentoxifylline azathioprine or other immunosuppressants such as dapsone) have been suggested for the treatment of more refractory cases, but limited data are available to support their effectiveness. Thalidomide seems to have a place in the treatment of resistant aphthous ulceration in patients positive for HIV antibody.

For common forms of recurrent apthous stomatitis, standard topical treatment options that provide symptomatic relief include analgesics, anesthetics, antiseptics, anti-inflammatory agents, steroids, sucralfate, tetracycline suspension, and silver nitrate. Dietary modifications may also support therapeutic measures. In resistant cases of benign aphthosis or aphthosis with systemic involvement, appropriate systemic treatment can be selected from a wide spectrum of immunomodulators that include colchicine, prednisolone, cyclosporine A, interferon-α, tumor necrosis factor-antagonists, anti-metabolites, and alkylating agents.

Amlexanox \((C_{25}H_{31}N_{7}O_{3})\) is a topical anti-inflammatory, anti-allergic drug. It has been developed as a 5% topical oral paste for the treatment of patients with RAS and is currently the only clinically proven product approved by the US FDA for the treatment of aphthous ulcers. HiOra-SG gel is a polyherbal formulation with principal ingredients of Glycyrrhiza glabra, Jasminum grandiflorum, Azadirachta indica, Ocimum basilicum, Boerhaavia diffusa, Syzygium aromaticum and Triphala. The clinical efficacy of this polyherbal formulation in the management of stomatitis has been studied and proved.

Currently available treatment options for aphthous ulceration are associated with various adverse effects and therefore, there is need for novel therapies that are effective with fewer side effects. The present study was conducted to evaluate and compare the clinical efficacy and safety of 5% Amlexanox and HiOra SG in the management of aphthous ulceration.

**AIMS AND OBJECTIVES**

The present study was carried out to evaluate the clinical efficacy of polyherbal formulation (HiOra SG gel) in comparison with 5% Amlexanox (Lexanox) in the management of aphthous ulceration.

**MATERIALS AND METHOD**

This study was conducted on 30 patients with minor aphthous ulcers who visited the Department of Oral Medicine, Diagnosis and Radiology, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar.

**Inclusion criteria**

- Patients with a history of recurrent aphthous ulcers
- Patients with one to three ulcers of less than 48 hours duration
- Patients with known drug hypersensitivities
- Patient who had applied any topical corticosteroid, topical antimicrobial drug or any other topical medication to the area of treatment within two weeks before day 1 of the study
- Patients who had taken non steroidal anti inflammatory agents or systemic steroids before day 1 of the study
- Patients with ulcerative colitis, Crohn's disease, Behcet's syndrome or anaemia
- Patients undergoing orthodontic therapy
- Patients who had undergone dental surgery of any type within two weeks before the study
- Pregnant and breast feeding female patients.

The patients were randomly divided into 2 groups - Group 1 patients were treated with polyherbal formulation (HiOra SG gel, Himalaya Pharmaceutical Ltd). Group 2 patients were treated with 5% Amlexanox oral paste (Lexanox, Macleods Pharmaceutical Ltd). Patients were instructed to apply the ointment to the ulcer 4 times a day (after meals and before bedtime) for 6 days (day 1 to day 7). The baseline parameters regarding number, size of the ulcer and pain associated were taken and recorded on the day of the first visit. The ulcer's
size was measured by using a calibrated dental probe with millimeter markings on treatment days 0, 4 and 7. When subjects presented with multiple ulcers, evaluation for all ulcers were averaged.

To evaluate pain, a visual analog scale (VAS) consisting of a 10-cm horizontal line between poles connoting no pain (origin) to unbearable pain was used. Subjects were told to mark the line with a vertical line at the point that best represented the present pain level of the ulcer. For analysis of subjects with healed ulcers, all treated ulcers had to have healed completely for the subject to be counted as healed. Statistical analysis was done to compare two treatment groups using Students unpaired t-test.

RESULTS

By the blinded randomization procedures, Group 1 and Group 2 were similar as per the demography including age, sex, medical history, known allergies and baseline values of ulcer history, number, size and pain. The mean time between initiation and when subjects said they had first noticed symptoms was about 24 hours for both treatment groups.

Table 1 shows mean number of ulcers at different days of the study for each treatment group. The mean number of ulcers for both treatment groups was similar at the start of study (2.13) . By treatment day 4 reduction in number of ulcers was almost similar whether treated with either HiOra SG or Amlexanox (2.00). The percentage change in number of the ulcers at the end of the treatment was more in Group 2 (24.44 %±28.08) than Group 1 (9.89 %± 17.67). The reduction in number of ulcers between day 0 and day 7 was statistically significant for those treated with 5% Amlexanox (p<0.01). However there was no statistically significant difference in the healing of ulcers between the groups from day 0 to day 7 (p>0.05).

Measurements of mean maximum ulcer size recorded (table 2) was almost similar for both treatment groups (10.07 mm2 for group1 and 9.27 mm2 for group 2) on day 0. At the Day 4 visit, the effectiveness index of the Amlexanox group was greater than that of the HiOra SG group (p < 0.001). However, ulcer size between the Group 1 and Group 2 was not significantly different on the Day 4 (p = 0.076). At the Day 7 visit, compared with those of the Group 1, the Amlexanox group maintained a significantly greater effectiveness index (p < 0.001). The overall mean reduction in ulcer size at the end of treatment was 18.15% for patients treated with HiOra SG and 61.93% for Amlexanox group. Regardless of the treatment group, results showed a statistically significant improvement in the lesion sizes overall (p < 0.001).

Table 3 shows the mean pain scores for each treatment group and the estimated treatment difference. Mean maximum pain scores recorded were similar for both treatment groups at beginning of the study (7.67 for Group 1 and 7.53 for Group 2). In Group 1 there was a reduction of pain score from 7.67 to 4.87 and 1.67 at the end of second and third visit respectively. Group 2 however, showed a lesser improvement with pain score of 7.33 at day 4 and 6.67 at day 7. The HiOra SG group had a statistically significant improvement in the pain scores (36.47% vs 2.40%, p < 0.001) at second visit, as well as a significantly higher improvement rate (78.41% vs 10.98%, p < 0.001) on day 7 when compared with that of the Amlexanox group.

### Table 1 - Comparison of Group 1 (HiOra SG) and Group 2 (Amlexanox 5%) regarding number of ulcers at different time intervals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Group 1 (n = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 2 (n = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 1 vs 2 p value</th>
<th>Unpaired p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ulcers</td>
<td>Day 0</td>
<td>2.13 ± 1.19</td>
<td></td>
<td>2.13 ± 0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 4</td>
<td>2.00 ± 1.13</td>
<td>0.014*</td>
<td>2.00 ± 0.76</td>
<td>0.014*</td>
<td>1.00**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>1.80 ± 0.78</td>
<td>0.055**</td>
<td>1.47 ± 0.64</td>
<td>0.007**</td>
<td>0.209**</td>
<td></td>
</tr>
<tr>
<td>%change at day 4</td>
<td>5.00 ± 14.02</td>
<td>0.007**</td>
<td></td>
<td>3.99 ± 10.38</td>
<td>0.007**</td>
<td>0.807**</td>
<td></td>
</tr>
<tr>
<td>%change at day 7</td>
<td>9.89 ± 17.67</td>
<td>0.000***</td>
<td></td>
<td>24.44 ± 28.08</td>
<td>0.000***</td>
<td>0.100**</td>
<td></td>
</tr>
</tbody>
</table>

NS: p>0.05; Not significant; ** p< 0.01 significant at 1% significance level

### Table 2 - Comparison of size of ulcers between two groups at different time intervals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Group 1 (n = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 2 (n = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 1 vs 2 p value</th>
<th>Unpaired p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of ulcer</td>
<td>Day 0</td>
<td>10.07± 3.37</td>
<td></td>
<td>9.27± 2.76</td>
<td></td>
<td></td>
<td>0.483</td>
</tr>
<tr>
<td></td>
<td>Day 4</td>
<td>9.47± 3.39</td>
<td>0.014*</td>
<td>7.40± 2.69</td>
<td>0.000***</td>
<td>0.076**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>8.27± 2.98</td>
<td>0.000***</td>
<td>3.60± 1.50</td>
<td>0.000***</td>
<td>0.000***</td>
<td></td>
</tr>
<tr>
<td>%change at day 4</td>
<td>6.15± 8.53</td>
<td></td>
<td></td>
<td>21.22± 6.51</td>
<td>0.000***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%change at day 7</td>
<td>18.15± 8.86</td>
<td>0.007**</td>
<td></td>
<td>61.93± 8.28</td>
<td>0.000***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS: p>0.05; Not significant; * p< 0.05 significant at 5% significance level; *** p< 0.001; highly significant

### Table 3 - Comparison of pain score between two groups at different time intervals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Group 1 (n = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 2 (N = 15)</th>
<th>Intra Group Paired p value</th>
<th>Group 1 vs 2 P value</th>
<th>Unpaired p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td>Day 0</td>
<td>7.67± 0.90</td>
<td></td>
<td>7.53± 0.92</td>
<td></td>
<td></td>
<td>0.091**</td>
</tr>
<tr>
<td></td>
<td>Day 4</td>
<td>4.87± 0.99</td>
<td>0.000***</td>
<td>7.33± 0.82</td>
<td>0.062**</td>
<td>0.000***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>1.67± 0.73</td>
<td>0.000***</td>
<td>6.87± 0.82</td>
<td>0.000***</td>
<td>0.000***</td>
<td></td>
</tr>
<tr>
<td>%change at day 4</td>
<td>36.47± 11.00</td>
<td>0.000***</td>
<td></td>
<td>2.40± 4.99</td>
<td>0.000***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%change at day 7</td>
<td>78.41± 8.33</td>
<td>0.000***</td>
<td></td>
<td>10.98± 10.24</td>
<td>0.000***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS: p>0.05; Not significant; *** p< 0.001; highly significant
DISCUSSION

The principal ingredients of HiOra-SG gel are Glycyrrhiza glabra (ulcer healing and anti allergic effect on IgE, antimicrobial activity), Jasminum grandiflorum (wound healing activity, antimicrobial activity), Azadirachta indica (antimicrobial activity), Ocimum basilicum (antimicrobial activity), Boerhaavia diffusa (immunomodulatory activity, anti inflammatory and wound healing), Syzygium aromaticum (analgesic and mild anesthetic effects on sensory nerve endings) and Triphala (antimicrobial, astringent and ulcer healing activity). Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-(1) benzopyrano-(2,3-b)-pyridine-carboxylic acid, also denoted as CHX 3673. The beneficial effects of 5 % Amlexanox oral paste in accelerating the healing of aphthous ulcers has been demonstrated in well controlled clinical studies. Although Amlexanox has been shown in preclinical studies to have both antiallergic and anti inflammatory properties, the mechanism by which 5 % Amlexanox accelerates the healing of aphthous ulcers is unknown.

Sukumaran et al in a randomized placebo controlled study to evaluate the efficacy of polyherbal formulation (HiOra SG) in stomatitis noted that while significant reduction in number of ulcers is seen at the end of three weeks, only mild reduction is present at the end of first week. In the present study, 5 % Amlexanox oral paste accelerated the healing of ulcers at the end of the treatment, but the initial results were similar to HiOra SG. There have been a number of studies of the efficacy of 5% Amlexanox in the management of recurrent aphthous ulceration. These studies have demonstrated that 5% Amlexanox accelerates ulcer healing. However, it was noted that the magnitude of benefit was significantly variable between subjects and that 5% Amlexanox paste might be of further benefit if treatment is commenced during the prodromal stage of ulceration. A randomized trial compared the use of Amlexanox during the prodromal phase of ulcer symptoms with its use once an ulcer was evident. The likelihood of having an ulcer by day 3 was significantly lower in the early use group (35 percent) than in the late-use group (97 percent).

Greer et al. in their study have shown that patients treated with 5% Amlexanox had a 76 % reduction in ulcer size than a vehicle (40%). 5% Amlexanox oral paste was evaluated in four vehicle-controlled, randomized, double-blinded, multi-center clinical studies involving 1335 subjects. These studies provide evidence that in comparison to no treatment or vehicle, the subject treated with 5% Amlexanox showed reduction in ulcer size in a highly significant manner starting from first evaluation day after treatment administration.4 In the aforementioned study, similar results suggesting greater decrease in ulcer size in Amlexanox group than HiOra SG group were noted. Delayed healing with HiOra SG could be because of lack of adhesive ingredient in its composition which compromises its protective effect.

In one small placebo-controlled, double blind trial, patients receiving Amlexanox had a significantly greater reduction in ulcer size on day 5 than did patients receiving placebo (median reduction, 76 % vs. 40 %) and their ulcers were more likely to be rated by the investigators as having improved, although changes in pain ratings did not differ significantly between the two groups.8 In the present study also, HiOra SG showed greater effectiveness in pain resolution. The pain relieving capacity of HiOra can be attributed to the synergistic action (analgesic, anaesthetic and astringent) of its ingredients.

The only type of adverse events reported by some studies on treatment with Amlexanox was local transient stinging at the application site. In our study however, none of the patients reported any adverse effects with the use of HiOra or Amlexanox.

CONCLUSION

The results of this study suggest that HiOra SG gel is more beneficial than Amlexanox in resolution of pain associated with aphthous ulceration. The beneficial effect of HiOra SG gel could be attributed to the synergistic action of its potent herbs. However, 5% Amlexanox shows greater efficacy in ulcer improvement overall. Further studies to directly compare the efficacy of 5% Amlexanox with other treatment options in case of frank ulceration, and in the prevention of ulcer development if the treatment is commenced at the prodromal stage, is required.

REFERENCES

6. Murray B, Biagioni PA and Lamey PJ. The efficacy of Amlexanox OraDiscTM on the prevention of recurrent