The efficacy of topical hyaluronic acid in the management of oral lichen planus

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BACKGROUND: The aim of this study was to evaluate the efficacy of a topical hyaluronic acid (HA) gel preparation (0.2%) in the management of oral lichen planus (OLP).

METHODS: A total of 124 patients with erosive OLP participated in a randomized, placebo-controlled, double-blind trial to evaluate the efficacy of a topical HA preparation. Outcome measures included soreness relief following immediate application, oral function and size of erosive/ulcerative area. Patients were medicated for 28 days and completed a log diary recording oral function and soreness scores.

RESULTS: Application of topical HA produced a significant reduction (P < 0.05) in soreness scores when compared with placebo for up to 4 h post-application. There was no difference between treatment groups (P > 0.05) with respect to oral function. Patients treated with 0.2% HA showed a significant reduction (P < 0.05) in the size of the erosive/ulcerated area after 28 days of treatment when compared with baseline. There was no significant difference in changes in ulcerative areas between treatment groups.

CONCLUSIONS: Topical HA (0.2%) does appear to be of some benefit in the management of erosive lichen planus providing efficacy for up to 4 h after administration. Very frequent applications should be considered to obtain a more significant clinical benefit. Topical HA gel may be a useful addition to the treatment option for OLP.


Keywords: efficacy; oral lichen planus; topical hyaluronic acid

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa. It affects between 0.5% and 4% of the adult population and has a higher prevalence in middle-aged females (1). The pathogenesis of OLP remains uncertain, but it is thought to arise from an immune response to a number of antigens within the oral epithelium. A variety of risks or predisposing risk factors have been identified for OLP, which include periodontal and gingival inflammation arising from deposits of plaque and calculus, hypersensitivity to amalgam and other metals, trauma to oral mucosa and stress (2). There is also evidence that in certain populations, viruses (mainly hepatitis C) may be important in the immunopathogenesis of OLP (3).

Different forms of OLP have been recognized, which relate to clinical appearance. The current classification describes three major forms: reticular/hyperkeratotic, atrophic/erythematous and ulcerative/erosive forms (4).

The symptoms arising from OLP vary markedly and often relate to the specific category. Pain and soreness, which interfere with oral function, are more commonly associated with the ulcerative form (5). Other symptoms related to OLP include soreness on tooth brushing, burning mouth and oral discomfort arising from eating hot, cold or spicy food.

OLP can be associated with considerable morbidity and altered quality of life, especially when patients suffer from ulcerative lesions (6).

A range of treatments have been evaluated in the management of OLP (3). Topical medications seem to be the most widely used; however, a Cochrane review failed to identify a superior agent for the management of this common condition (7). Despite this finding, many reviews of the treatment of OLP suggest that topical steroids are the most widely used (6–11).

Hyaluronic acid (HA) is a linear polymer of glucuronic acid, N-acetylglucosamine disaccharide. The main function of HA appears to be in tissue healing and a variety of mechanisms have been identified (12–14). Clinical studies have also confirmed the potential of topical HA in promoting the healing process. The compound has been evaluated in the healing of leg ulcers (15) and the nasal mucosa after surgery (16). It has also been shown to reduce the incidence of
high-grade radio-epithelitis in patients who have undergone radiotherapy for head and neck, breast or pelvic carcinomas (17).

Recently, we have evaluated the efficacy of a topical hyaluronic gel (0.2%) in the relief of symptoms in patients with recurrent aphthous ulceration (18). In this placebo-controlled, randomized double-blind trial, patients who were treated with 0.2% HA had less ulcers after 5 days of application when compared with the placebo group. This would suggest that 0.2% HA does have some impact on the healing/duration of recurrent aphthous ulceration. Topical HA has not been evaluated in the management of OLP.

The aim of this study was to carry out a randomized, placebo-controlled investigation into the efficacy of a topical hyaluronic gel (0.2%) in the relief of symptoms in patients with OLP, and to evaluate the product in reducing size of ulcerative/erosive areas.

Materials and methods

A total of 124 adults who presented with a new clinical and histopathological diagnosis of OLP participated in the study. Patients were enrolled consecutively and all had atrophic-ulcerative lesions. Patients were excluded from the study if they were taking systemic chemotherapy, immunosuppressant drugs associated with lichenoid reactions or where suffering from malignant disease.

The protocol for the study had received approval from the local Joint Ethics Committee (Ref 2003/16). All patients were enrolled from the Oral Medicine Clinic. Eligible patients had to present with pain/discomfort arising from an erosive area of OLP. If the patients agreed to participate in the study, the consent forms were completed and instruction sheets given with regard to the purpose of the investigation. Once the patients were enrolled, they underwent an oral examination. The size of any ulcer or erosive area was measured with callipers to the nearest mm and the maximum dimension recorded (e.g. the maximum extension of the area).

Patients were then asked to complete a score of oral function ability. The criteria were as follows:

3 = Severe difficulty in eating, cannot tolerate hot drinks, must use a straw for drinking purposes, can only eat bland food, e.g. soup or homogenized food.
2 = Can eat some solid food, but must avoid hot drinks, crusty bread, flavoured foods and alcoholic drinks.
1 = Can eat most normal foods, but must avoid spicy food or citrus fruits.
0 = Can eat and drink anything.

After the baseline examination, a clinician applied to the erosive area a topical preparation containing 0.2% HA or an identical placebo. The placebo was identical in appearance to the HA gel and contained methylcellulose gel, xylitol and other excipients. Both preparations were in a gel formulation and contained within a translucent 5-ml syringe and allocation was randomized and double-blind. Patients were instructed on how to apply the gel for subsequent applications.

Prior to dosing, patients were asked to record a baseline pain/soreness score arising from the erosive/ulcerated area of their OLP. These scores were completed on a 100-mm visual analogue scale (VAS) whose boundaries were marked ‘no soreness’ and ‘worst possible soreness’. Recordings were made at 5 min, 60 min, 2, 3 and 4 h post-applications. The first three recordings (baseline, 5 and 60 min) were made under supervised conditions. Thereafter, patients were discharged from the clinic with log diaries and sufficient supply of gel for 4–5 times a day application for the next 28 days. Each time they applied the gel, they were asked to record soreness scores at 5 and 60 min after application. In addition, the subjects were asked to record once a day on their ability to eat.

Patients were asked to return to the clinic for review at 15 and 29 days post-baseline. At these visits, log diaries were checked and the ulcerated/erosive lesion measured. On the final visit (day 29), the OLP was again assessed according to the Thongprasom’s method. Patients were asked to comment on the ease of gel application and unwanted effects using a 2-point scale were as follows: 1 = easy to apply and 0 = difficult to apply; 1 = pleasant and painless on application, and 0 = unpleasant and irritant at use.

If during the 29-day investigation, patients resorted to additional treatment to alleviate their discomfort, they were asked to record in the log diaries the type and frequency of alternative medication used.

All clinical observations on the patient OLP and measurements of the ulcerated/erosive area were completed by the same clinician (AN) and the same study nurse was responsible for instructing gel application for all patients (JB).

Statistical analysis

The main outcome measure from this study was relief of soreness between treatment groups based upon repeated VAS recordings. Assuming a standard deviation of 15 mm on the 100-mm VAS, a power calculation based upon a sample size of 60 patients per group and an alpha level of 0.05 would allow the detection of a mean difference between treatments of 10 mm on the VAS with 84% power.

Analysis of variance according to the model of repeated measurements between subjects, integrated by covariate analysis at baseline, was used to assess differences between treatment groups for demographic variables and soreness scores. The Duncan and Tukey-Kramer tests for multiple comparisons of unconfirmed means were used to assess differences in ulcer size (from baseline) between treatment groups. Chi-squared statistics were used to evaluate changes in OLP status, effect of treatment, eating ability, need to use adjunctive treatment and ease of use. A $P$-value < 0.05 was used.

Results

The demographic details of the 124 patients consented to take part in the study are shown in Table 1. Evaluable evidence was provided by 113 patients on
Table 1  Demographic details of patients and other baseline information of those who participated in the study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.2% Hyaluronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Males</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Females</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>58.46</td>
<td>55.3</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mean baseline soreness scores (mm) ± SD</td>
<td>38.5 ± 25</td>
<td>38 ± 20.5</td>
</tr>
<tr>
<td>as recorded on 100-mm VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of ulcerated or erosive area (mm) ± SD</td>
<td>15.5 ± 0.7</td>
<td>16.1 ± 0.7</td>
</tr>
<tr>
<td>Oral lichen planus type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophic</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Desquamative gingivitis</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Erosive</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation; VAS, visual analogue scale.

day 29. Eleven patients were deemed protocol violators as they had not completed satisfactorily their log diaries. There was no significant difference between the two groups regarding their age, sex distribution and clinical features. Table 1 also records the classification of the clinical type of OLP. Again, there was no significant difference (P > 0.05) between treatment groups with respect to the classification of the different types of OLP.

The symptomatic effect on soreness showed a significant reduction (P < 0.05) after 5 min compared with baseline in the 0.2% HA-treated group (Fig. 1). All the other observations maintained the same significant reduction (P < 0.05) with respect to baseline throughout the 4-h observation period. In the placebo group, none of the observations reached a statistically significant reduction.

For the remainder of the 28 days, there was no difference between the treatment groups for reduction in soreness score (P > 0.05, data not shown).

The changes in ulcer size during the observation period are shown in Table 2. Patients treated with 0.2% HA recorded a significant reduction in the size of their ulcerated/erosive area (P < 0.05) on day 29 when compared with baseline. Although there was a reduction in the placebo group, the difference was not statistically significant (P > 0.05). There were no differences between treatment groups at any of the time intervals.

Placebo and 0.2% HA had no effect on the extent and severity of the OLP as described by Thongprasom’s criteria. There were no significant changes from the baseline measures for both treatment groups (P > 0.05).

Oral function scores are shown in Table 3. There was no significant difference (P > 0.05) in the distribution of score between treatment groups or changes from baseline.

Few patients required adjunctive treatment (use of topical steroids): on day 15, one patient in the placebo group and three in the 0.2% HA group were resorting to using topical steroids. This number increased to eight and seven in the placebo group and 0.2% HA group, respectively, on day 29. Only a few patients (three in each treatment group) found the gel difficult to use and 15 patients in the placebo group complained on the taste of the gel, compared to eight in the HA 0.2% group. These differences were not statistically significant (P > 0.05).

Table 2  Changes in ulcer or size of erosive area (in mm) during the observation period

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>0.2% Hyaluronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>15.5 ± 0.7</td>
<td>16.1 ± 0.7</td>
</tr>
<tr>
<td>Day 15</td>
<td>12.7 ± 0.76</td>
<td>13.8 ± 0.77</td>
</tr>
<tr>
<td>Day 29</td>
<td>13.5 ± 0.72</td>
<td>13 ± 0.7</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD.

*Significant difference (P < 0.05) from baseline.

Table 3  Distribution of scores arising from oral function questionnaires for the two treatment groups during the 29-day observation period

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>0.2%</th>
<th>Placebo</th>
<th>0.2%</th>
<th>Placebo</th>
<th>0.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA</td>
<td></td>
<td>HA</td>
<td></td>
<td>HA</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult in eating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Can eat some</td>
<td>13</td>
<td>20</td>
<td>10</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Can eat most</td>
<td>14</td>
<td>20</td>
<td>19</td>
<td>22</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Can eat anything</td>
<td>34</td>
<td>21</td>
<td>23</td>
<td>24</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>Not recorded</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

HA, hyaluronic acid.
Discussion
Topical medications are widely used in the management of OLP. Agents that have been employed for this purpose include mainly corticosteroids and calcineurin inhibitors (19). Whilst there is widespread use of these agents, there is only weak evidence for the effectiveness of any of the topical treatments (7). Moreover, tachyphylaxis, defined as a rapidly decreasing response to a physiologically active agent after administration of a number of doses, is not uncommon with the chronic use of the topical steroids (20).

The management of OLP is further complicated with the risk of malignant change (21, 22). Patients with uncomfortable or ulcerative OLP tend to require treatment quite frequently and for extended periods. Immunosuppressants are frequently used for such patients, and theoretically some of these drugs could be implicated in malignant transformation. Particularly tacrolimus (23) has been associated with oral malignant transformation. Thus, there is a clear need to find an alternative therapy for OLP.

In this study, the primary outcome measure was the efficacy of the HA gel in reducing soreness/pain arising from the erosive lesion. Linked to this outcome was the effect of the gel on oral function. The secondary outcome measure was to investigate whether repeated application of the gel had any effect on reducing the size of the ulcerated/erosive area (healing).

Topical HA (0.2%) had a significant immediate effect in reducing the pain/soreness associated with erosive lichen planus but apparently, this action is not long-lasting. In a previous investigation of this product in aphthous ulceration, a similar reduction was reported, and it was attributed to a so-called barrier effect (16). However, there is also evidence that HA has some inherent ‘malgesic’ activity (24).

However, these two diseases have a very different outcome and in a chronic disease as OLP, the duration of a therapeutic effect is an extremely important endpoint and the benefit of HA on oral function was somewhat disappointing considering its early impact on reducing soreness/pain scores. Indeed, there were no differences between treatment groups with the distribution of scores in this category.

This may reflect the diffuse nature of OLP on most of the oral mucosa. Patients were instructed to apply the gel to the erosive/ulcerated lesion, and whilst they may have complied with this, other areas of the mouth would not have necessarily benefited. A mouthwash containing 0.2% HA may be more useful in the management of OLP as this would allow a more diffuse contact with most of the oral mucosa. Alternatively, very frequent applications of HA could be considered given its excellent and fast effect on symptomatology.

Evidence from measuring the size of the erosive/ulcerated area suggests that there are benefits from using 0.2% HA for healing. We found a similar property when the gel was used in the management of aphthous ulceration (18). Ulcer count of day 5 of treatment was significantly less in the 0.2% HA group when compared with the placebo group. Both clinical and animal studies have confirmed the effect of HA on tissue healing (12–17). The action may be mediated by moderation of the inflammatory responses, promoting cell proliferation or promoting re-epithelialization via proliferation of basal keratinocytes.

Evidence from this placebo-controlled, randomized trial does suggest that topical HA (0.2%) does have some benefits in the management of OLP. The magnitude of the benefits is statistically significant in the first 4 h after initial application, but their clinical relevance warrants further evaluation. Comparative studies with other topical agents used in the management of OLP would be useful to ascertain further usefulness of this product in this condition. Because it is easy to use and patients report few unwanted effects, a very frequent application scheme should be best suggested to improve significantly the efficacy of HA. Moreover, HA could be used in addition to other topical drugs like steroids and calcineurin inhibitors.

References


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