Clinical efficacy of allicin – A novel alternative therapeutic agent in the management of minor recurrent aphthous stomatitis

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Abstract

**Background:** Recurrent aphthous ulceration is one of the most common inflammatory, ulcerative oral mucosal conditions. Most of the currently available treatments aim at symptomatic relief, thereby improving the quality of life.

**Aims and Objectives:** To evaluate the efficacy of allicin in mouthrinse and systemic form in the management of minor recurrent aphthous stomatitis (RAS).

**Materials and Methods:** A total of 42 patients with minor RAS were randomly divided into Group A (allicin mouth rinse-21) and Group B (allicin capsules-21). The baseline parameters of the ulcer, i.e., size, pain, and erythema were recorded on the day 1, day 4, and day 7, respectively. The recurrence rate of the ulcer was evaluated for 6 months at monthly intervals.

**Results:** In both groups, the marked improvement was observed in the parameters during the follow-up visits. Both forms of allicin were proved to be effective but no statistically significant difference was observed. Recurrence was observed in both the groups.

**Conclusion:** Both forms of allicin were found to be equally effective in the management of minor RAS with a good safety record. Both were not found to be effective in preventing the recurrence.

Introduction

Recurrent aphthous stomatitis (RAS) is a very common and poorly understood painful oral mucosal inflammatory ulcerative condition that affects the quality of life. Due to its diverse etiology and a wide range of treatment modalities, it has gained considerable amount of clinical and research attention. Potential trigger factors include genetics, trauma, tobacco, drugs, nutritional deficiency, gluten sensitive enteropathy/ celiac diseases, inflammatory bowel disease, sodium lauryl sulfate-containing toothpaste, hormonal changes, stress, food hypersensitivity, viral and bacterial infections, and immunologic factors. Depending on the socio-economic or ethnic group studied its incidence can vary from 5% to 50%. Clinically, it has three different presentations, minor, major, and herpetiform ulcers of which minor aphthae accounts for about 75-85% of all cases. A wide range of treatments ranging from topical agents to systemic medications, physical modalities, natural remedies, home remedies and homeopathic remedies have been tried, the goal being to decrease symptoms, reduce the ulcer number and size and to increase disease-free periods.

Not much research has been carried on the effect of ayurvedic medications on RAS. Garlic has long been known for centuries as an effective herbal medicine against a large number of ailments. Allicin is a major component of garlic with anti-inflammatory, anti-microbial, anti-oxidation, and immunomodulation properties which could be beneficial in reducing symptoms, promote ulcer healing and prevent the recurrence of recurrent aphthous ulcers.

The present study aimed at evaluating the efficacy of allicin mouth rinse and allicin capsules in reducing the size, pain and erythema of the ulcers and preventing its recurrence.

Materials and Methods

**Source of data**

The present study was conducted among the outpatients attending the Department of Oral Medicine and Radiology, Oxford Dental College Hospital and Research Center, Bengaluru. The study duration was from 2014 January to 2015 July.
Selection criteria

Inclusion criteria
1. Men and women aged 18-50 years who can follow a doctors’ advice
2. Presenting with single or multiple minor aphthous ulcers of <48 h duration
3. Ulcers must be in locations easily accessible for evaluation and treatment, such as the buccal mucosa, labial mucosa, floor of the mouth, or tongue. [7]

Exclusion criteria
1. History of allergies to allicin
2. Pregnancy and lactation
3. Taking systemic/topical non-steroidal anti-inflammatory drugs, immune modulatory agents, antibiotics within 2 weeks before study entry
4. Patients with bleeding disorders
5. Patients on corticosteroid therapy
6. Ulcers as a manifestation of systemic diseases. [9]

Patient selection

Patients with a history of minor RAS diagnosed based on major criteria, [8] who visited the OPD at the Oxford Dental College during the period 2014-2015 were enrolled into the study. All patients were selected according to the specific inclusion and exclusion criteria. [7] The research proposal was reviewed and approved by the Ethical Committee of the Oxford Dental College and Hospital, RGUHS University. The whole study process was described to the patients before and informed consent was taken. A detailed medical and dental history was obtained to rule out any other systemic or local conditions causing oral ulcerations. A complete blood count was done for each patient to rule out nutritional deficiency.

About 42 minor RAS patients were randomly divided into Group A (21-mouth rinse group) and Group B (21-Systemic group). In Group A, subjects were instructed to gargle with 5 ml of allicin mouth rinse (5 mg allicin/5 ml, dispensed by M/s Cash Pharmacy, Bengaluru) 4 times a day (after meals and before bedtime) for 7 days. For Group B, allicin 250 mg capsules were given (Himalaya Lasuna Capsules, product available in market, 1 capsule per day at bedtime for 2 months).

For both Group A and Group B, the baseline parameters were taken and recorded on the day of the first visit. Reduction in ulcer size, pain and erythema were evaluated on the morning of day 4 and day 7 and recurrence rate of the ulcer were evaluated for 6 months at monthly intervals. Periodic telephonic follow-ups were made to ensure administration of capsules. In patients with single or multiple ulcers, the ulcer that has occurred most recently and in an area easily accessible was chosen for evaluation. Subjects were instructed that if any allergic reactions occur they should discontinue usage of medication and inform the investigator immediately.

To evaluate pain, a visual analog scale (VAS) consisting of a 10-cm horizontal line between poles connoting “without pain” to “maximal 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. To determine the size of the ulcers, a calibrated William’s periodontal probe with millimeter markings was used to measure the ulcer size at the maximum diameter of the ulcer. The degree of erythema was evaluated on a 4 point scale ranging from 0 to 3 based on the methods of Greer et al. with some modifications. [9]

There were two dropouts from each group. The patients did not come for follow-up on the 4th day as they were relieved of pain and discomfort after using medication. At the end of study period, we had 19 patients in each group.

The evaluation of recurrence in both the groups was done by monthly follow ups either by clinical examination or by telephonic follow-up.

Statistical analysis

Descriptive statistics was used to determine the frequency, number and percentage for each parameter of ulcer. Data were analyzed using the SPSS version 22. Student unpaired t-test was used to compare differences between the VAS scores for pain, erythema and ulcer size between the two groups, with P values set at 0.05 and 95% confidence interval. The recurrence rate of ulcers between both the groups was compared using Z test for proportions with P value set at 0.05.

Results

Base line characteristics of study participants

In the study sample of 38 patients, 23 (60.5%) were males and 15 (39.5%) were females. Out of 38 RAS patients, a maximum number of patients 22 (57.9%) belonged to 21-30 years of age group, followed by 7 (18.4%) in 15-20 years of age, 6 (15.8%) in 31-40 years and the least of 3 (7.9%) in 41-50 years. In the study sample, 25 (65.8%) patients presented with single ulcers and 13 (34.2%) patients presented with multiple ulcers [Table 1].

Analysis of healing of ulcer

The mean ulcer size at baseline for the patients of Group A was 4.47 ± 2.01 and that of Group B was 4.21 ± 1.62 and matched well at the study entry (P = 0.65). After using allicin mouth rinse, and allicin capsules patients were recalled on the 4th and 7th day. The mean ulcer size on day 4 for Group A was 2.26 ± 2.31 and that of Group B was 1.42 ± 1.61. On day 7, the mean ulcer size of Group A and Group B were 0.74 ± 1.52 and 0.11 ± 0.32, respectively. From day 1, the results revealed a significant reduction of ulcer size in both Group A and Group B on day 4 (2.21 ± 1.93 and 2.79 ± 1.13, respectively) and day 7 (3.74 ± 2.26 and 4.11 ± 1.60, respectively). On day 7, marked improvement in ulcer size was observed from the 4th day in both Group A and Group B (1.53 ± 1.65 and 1.32 ± 1.53, respectively). No statistically significant difference between Group A and Group B was observed between the 1st and 4th day (P = 0.26), 1st and 7th day (P = 0.56), and 4th and 7th day (P = 0.68) [Table 2].
**Table 1:** Baseline characteristics of study participants (n=38)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Males</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15-20</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>22 (57.9)</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>6 (15.8)</td>
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<tr>
<td></td>
<td>41-50</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Number of ulcers</td>
<td>Single</td>
<td>25 (65.8)</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>13 (34.2)</td>
</tr>
<tr>
<td>Size of ulcers</td>
<td>Day 1 (mean±SD)</td>
<td>4.34±1.8</td>
</tr>
<tr>
<td></td>
<td>Day 1 (mean±SD)</td>
<td>6.5±1.9</td>
</tr>
<tr>
<td>Erythema</td>
<td>Day 1 (mean±SD)</td>
<td>1.71±0.5</td>
</tr>
</tbody>
</table>

SD: Standard deviation

**Analysis of pain score**

The mean pain score at baseline for the patients of Group A was 6.74 ± 1.70 and that of Group B was 6.26 ± 2.28 and matched well at the study entry (P = 0.47). The mean pain scores on day 4 for Group A and Group B were 0.63 ± 1.01 and 0.89 ± 1.41, respectively. On day 7 the pain score for both the groups were zero. These data depicts a marked reduction in pain in both Group A and Group B between 1st and 4th day (6.11 ± 1.63 and 5.37 ± 1.98), 1st and 7th day (6.74 ± 1.70 and 6.26 ± 2.28) and 4th and 7th day (0.63 ± 1.01 and 0.89 ± 1.41). No statistically significant difference in pain reduction between Group A and Group B was observed between 1st and 4th day (P = 0.21), 1st and 7th day (P = 0.47) and 4th and 7th day (P = 0.51) [Table 3].

**Analysis of erythema score**

The mean erythema score at baseline for Group A was 1.79 ± 0.54 and that of Group B was 1.63 ± 0.50 and matched well at the study entry (P = 0.35). The mean erythema scores on day 4 for Group A and Group B were 0.68 ± 0.48 and 0.42 ± 0.51, respectively. On day 7, the mean erythema score of Group A was 0.16 ± 0.38 and that of Group B was zero. These data shows a marked reduction in erythema in both Group A and Group B between 1st and 4th day (1.11 ± 0.57 and 1.21 ± 0.42), 1st and 7th day (1.63 ± 0.50 for both groups) and 4th and 7th day (0.53 ± 0.51 and 0.42 ± 0.51). Both groups showed an equal reduction in erythema from day 1 to day 7. No statistically significant difference in erythema reduction between Group A and Group B was observed between 1st and 4th day (P = 0.51), 1st and 7th day (P = 1.00) and 4th and 7th day (P = 0.52) [Table 4].

**Recurrence rate of the ulcers**

Both Group A and Group B were followed up for a period of 6-month and checked for recurrence of ulcers. The number of ulcers during every episode was recorded every month. Recurrence of ulcers was significantly reduced up to 1st month but recurrence rate started increasing up to the 5th month. Decrease in recurrence was observed in the 6th month [Table 5].

**Table 2:** Assessment and comparison of mean ulcer size between study groups at different time periods

<table>
<thead>
<tr>
<th>Time period</th>
<th>Group</th>
<th>Mean (mm)</th>
<th>SD</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer size on day 1</td>
<td>Group A</td>
<td>4.47</td>
<td>2.01</td>
<td>0.444</td>
<td>0.65</td>
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<tr>
<td>Ulcer size on day 4</td>
<td>Group A</td>
<td>2.26</td>
<td>2.31</td>
<td>1.305</td>
<td>0.20</td>
</tr>
<tr>
<td>Ulcer size on day 7</td>
<td>Group A</td>
<td>0.74</td>
<td>1.52</td>
<td>1.771</td>
<td>0.08</td>
</tr>
<tr>
<td>Ulcer size between day 1 and 4</td>
<td>Group A</td>
<td>2.21</td>
<td>1.93</td>
<td>−1.127</td>
<td>0.26</td>
</tr>
<tr>
<td>Ulcer size between day 1 and 7</td>
<td>Group A</td>
<td>3.74</td>
<td>2.26</td>
<td>−0.581</td>
<td>0.56</td>
</tr>
<tr>
<td>Ulcer size between day 4 and 7</td>
<td>Group A</td>
<td>1.53</td>
<td>1.65</td>
<td>0.408</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Group A: Mouth rinse group, Group B: Systemic group. SD: Standard deviation

**Discussion**

Numerous treatment modalities are available for RAS, the goal being to decrease symptoms, reduce the ulcer number and size and to increase disease-free periods. The success of these treatment modalities is challenging because of multifactorial etiology and cyclic nature of the disease.[1,5] Topical therapy provides symptomatic relief in most patients with occasional episodes of minor RAS, but it alone does not prevent the development of new lesions in patients who experience regular exacerbation of the condition.[1,6] Systemic therapy is warranted in such cases.

Several topical medications, like analgesic sprays, gels, antibiotic pastes, antiseptic mouthwashes, etc., are commonly prescribed, but these carries the risk of inhibition of laryngeal reflexes if used in the posterior regions of the oral cavity, hypersensitive reactions, augmentation of resistant organisms, secondary opportunistic infection, staining of teeth, etc. Potent topical corticosteroids when used for long period hold the risk of systemic absorption and associated adverse effects and can also predispose the individual to oral candidiasis.[11]

Systemic therapy is warranted in such cases. The treatment strategy depends on several factors like severity of the condition, the rate of recurrence, patient’s medical history, patient’s compliance, etc. The best treatment is the one that prevents the recurrence of the ulcers with least side effects, and the beneficial effects of the drug should always be weighed against its probable adverse effects.[1,12]

These days, due to their decreased adverse effects herbal medicines are acquiring more interest.[13] Antibacterial, antifungal, anti-inflammatory, antioxidant and immunomodulatory properties of many medicinal herbs have been used for reducing pain and healing time of oral aphthous
The present study aimed at evaluating the efficacy of allicin mouth rinse and allicin capsules in reducing the ulcer parameters and preventing its recurrence. Out of 38 patients, Group A was instructed to use allicin mouth rinse 4 times a day for 7 days. Since prolonged contact of the medication with the ulcerated mucosa appears to significantly increase the effectiveness of the treatment, patients were instructed to hold it in the mouth for 1-2 min. To ensure maximum effect patients were instructed to avoid eating or drinking for at least one hour following use. In a similar study conducted by Jiang et al. allicin adhesive tablets were used but these adhesive tablets were limited to being applied to sites that were accessible to patients. In our study, allicin mouth rinse was used so that it can be beneficial for ulcers located in inaccessible areas like posterior part of tongue and palate. Group B was asked to take allicin 250 mg capsule, 1 capsule per day at bedtime for 2 months after food. Bed time was chosen as intake of medicines at bedtime is recommended in ailments affecting head and neck in “Ashtanga hrudaya sutrasthana,” ancient ayurvedic textbook by Vagbhata. 250 mg capsule was advised because to our knowledge this study is the first of its kind and it is always better to start with a lower dosage of the drug to avoid untoward effects.

In the present study, patients treated with both allicin mouth rinse (Group A) and systemic allicin (Group B) showed marked improvement in ulcer size, pain, and erythema in the successive follow-up visits. On the comparison between the groups, there was no significant difference between Group A and Group B in reducing the size of the ulcer, pain, and erythema in any of the follow-up visits.

Wound healing involves a cascade of events such as inflammation, cell proliferation, matrix deposition and tissue remodeling and involves several factors such as inflammatory cell count, angiogenesis assessment, re-epithelialization, fibroblast, or collagen fiber density. Re-epithelialization occurs through the process of migration, proliferation and differentiation of keratinocytes. Topical allicin was found to be effective in accelerating re-epithelialization of oral ulcer healing process in animal models. Allicin has the ability to penetrate the phospholipid membrane and epithelial discontinuity during ulceration helps easy penetration of allicin into the wound area and release of its various bioactive constituents. This could be the reason for the acceleration of wound healing with allicin mouthrinse in our study. According to the literature, the bioavailability of allyl thiosulfonates was found to be >95% which could have contributed to accelerated healing with systemic allicin. Allicin also increases elastic property of blood vessels and capillary perfusion, thus increasing the blood supply to the area.

Another reason for the effectiveness of allicin mouthrinse and systemic allicin in this clinical trial could be the antimicrobial activity of allicin which reduces bacterial colonization and...
prevents wound infection and exaggerated response. Other probable reasons are the antioxidant and immunomodulatory activity of allicin which was proved in several animal and in vitro studies.

Allicin can decrease the production of inflammatory mediators like tumor necrosis factor alpha, interleukin-1 (IL-1) alpha, IL-2, IL-6, IL-8, IL-12 and interferon gamma by peripheral blood mononuclear cells in dose-dependent manner by downregulating mRNA levels and also stimulate the production of IL-10 and downregulate intercellular adhesion molecule which regulates cellular inflammatory responses. Up-regulation of glutathione production by allicin in vascular endothelial cells down-regulates the levels of pro-inflammatory cytokines and all these helps decrease the excessive inflammatory process associated with RAS and hastens healing. These could be the reason for the accelerated pain relief with allicin mouth rinse and systemic allicin in our study.

Our study proved that both allicin mouth rinse and systemic allicin are equally effective in hastening the healing of ulcers in minor RAS with good safety record within 7 days of this clinical study which would otherwise take 10-14 days in the natural course of the disease without any treatment. There was no significant difference in the effectiveness of allicin mouth rinse and systemic allicin even though the capsules were of high dose compared to mouth rinse and administered for 2 months. This may be due to under dosage of the drug or poor patient compliance. Patients in both Group A and Group B were followed up for a period of 6 months and checked for recurrence of ulcers. Recurrence of ulcers was significantly reduced up to 1st month but recurrence rate started increasing from 2nd month up to the 5th month. Decrease in recurrence was observed in the 6th month. This may be due to poor patient compliance, under dosage of the drug, insufficient duration of systemic therapy or other etiologies may not have been targeted. It has been suggested that responses to garlic may vary with people and thus garlic may be more beneficial for some specific groups. Long-term and large trials on different groups of people are needed to evaluate this. To our knowledge, this study is the first of its kind where allicin mouth rinse and systemic allicin have been tried to determine its effectiveness in the management and recurrence of RAS.

Conclusion

Due to the increasing incidence of unpleasant side effects and resistance to synthetic pharmaceuticals, until a definitive treatment for RAS surfaces, allicin mouthrinse and allicin capsules can be used to manage pain and treat RAS without any major side effects. One should always take into concern both the efficacy and possible side effects of medication when choosing treatment. Since both modes of administration are found to be equally effective in healing of ulcers and no effect is seen in preventing the recurrence, allicin mouth rinse can be considered than systemic allicin to avoid long treatment period and to increase patient compliance. However, there exists a tremendous scope for further research for the use of allicin in the management of RAS. Different dosage regimens have to be tried to check its efficacy. Further studies are needed to understand the various mechanisms of action of allicin as well as its efficacy and safety and make use of its maximum beneficial effect in near future.

References
