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RESEARCH ARTICLE

EVALUATION OF THE EFFICACY OF TOPICAL AMLEXANOX ORAL PASTE AND REBAMIPIDE TABLETS IN THE MANAGEMENT OF RECURRENT APHTHOUS ULCERS

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ABSTRACT

Recurrent aphthous stomatitis is by far the most common ulcerative lesion encountered by the practicing dentist and various drugs have been tried out in the management of recurrent aphthous stomatitis. Rebamipide tablet and Amlexanox oral paste have shown promise in relieving the patients from this miserable condition, therefore these new drugs have been tried in treating patients with recurrent aphthous stomatitis. The basic aim of this study was to test the efficacy of 5% Amlexanox oral paste and Rebamipide tablets in the treatment of recurrent aphthous stomatitis.

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INTRODUCTION

Recurrent Aphthous Ulceration (RAU) or Recurrent Aphthous stomatitis (RAS), is one of the most common oral ailments encountered in children and adults. According to Akintoye *et al* approximately 20% of the general population is affected by RAS, but incidence varies from 5% to 50% depending on the ethnic and socioeconomic group studied (Sunday *et al*., 2005). The etiology of RAS lesions is unknown, but several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as causative agents. The lesions of RAS are characterized by recurrent ulcerations of the oral mucous membranes that occur either single or in multiple locations and are usually associated with pain. Amlexanox is a novel anti-inflammatory, anti-allergic agent that has been used clinically in Japan in alternate formulations (oral tablet, nasal spray, eye drops) for the treatment of bronchial asthma, allergic rhinitis, and conjunctivitis (Khandwala *et al*., 1997). Rebamipide is a gastric mucoprotective agent that is widely used to treat gastritis and gastric ulcer in Japan, South Korea and China (Matsuda *et al*., 2003). It enhances preservation of existing epithelial cells & replacement of lost tissue through a multi factorial mode of action (Rebagen product monograph by Macleods).

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Procedure: The study was a single blind, randomized, placebo controlled trial. In this study, totally 60 patients were included with the following objectives in mind.

- To ascertain whether 5% Amlexanox oral paste and Rebamipide tablets and can bring a dramatic relief of painful symptoms.
- To ascertain whether 5% Amlexanox oral paste and Rebamipide tablets can accelerate the healing process which can be determined by recording the number of days required for complete healing.
- To determine whether the drugs would prove valuable in preventing recurrences or at least in reducing the frequency significantly.
- To determine whether there are any side effects with 5% Amlexanox oral paste and Rebamipide tablets therapy.

The patients were selected based on the following selection criteria.

Criteria for inclusion

- History of recurrent ulcers in the oral cavity.
- Flat ulcers with yellowish sloughy base and distinct erythematous halo (without tissue tags).

- History of appearance of papule on an erythematous base before ulceration.
- Ulceration present on freely mobile and relatively less keratinized mucosal surface such as labial and buccal mucosa, floor of the mouth, ventral surface of tongue etc.
- Patients ready for the study procedure which was explained to them in the language which they understood and who gave written and informed consent were included in the study.

Criteria for exclusion

- Pregnant ladies and nursing mothers were excluded as the safety of drugs under trial is not established in such conditions.
- Patients with known history of allergy or hypersensitivity to these trial drugs were also excluded.
- Patients who were already being treated with any other drug were not included in this study as the beneficial effects of previous drugs given would alter the response of the patient giving rise to incorrect reading.
- Those patients who refused to be included in this study and did not give informed consent were obviously excluded.

In order to obtain an accurate and unbiased result of the efficacy of the drugs, the patients were randomly divided into 4 groups 1, 2, 3 and 4, with 20 subjects each in the first 2 groups and 10 subjects each in the last 2 groups.

Group 1 - Patients were treated with 5% Amlexanox oral paste applied directly on the lesion four times a day for a period of 7 days initially & was further continued in cases where ulcers had not healed till complete healing was achieved.

Group 2 – **Patients were treated with Rebamipide 100mg ta**blets given three times a day for a period of 7 days initially & was further continued in cases where ulcers had not healed till complete healing was achieved.

Group 3 – Patients were treated with Orabase (placebo) applied directly on the lesion four times a day for a period of 7 days.

Group 4 – Patients were treated with sugar tablets (placebo) given three times a day for a period of 7 days.

Subjects were randomly assigned to experimental groups (Amlexanox and Rebamipide) or control groups (placebo) for the study. Patients in both the control groups (i.e. 3 and 4) were given no other medication to ensure control for adequate comparisons. Each patient was instructed to keep a daily record of the presence and the site of new ulcers if any, severity of pain, and side effects of the drugs, if experienced. The patients were instructed to discontinue the drugs if any acute flare up occurred and to report to the operator immediately. All the patients were asked to report for reassessment every third, fifth, seventh and ninth day after the intake or application of the drugs unless the ulcers healed prior to that; in such cases they were told to report the day the ulcer healed. At each visit the oral cavity was reassessed especially in relation to the size of the ulcer (measured with the help of Williams graduated probe) and the associated pain according to the pain score. The day on which healing of all the ulcers took place was noted thereby noting the number of days it took for completed healing, also taking into account the number of days the ulcers were present prior to initial visit. Side effects if any were also noted. All patients were instructed to report to the operator, at monthly intervals or earlier if they noticed a recurrence. When patients turned up with a recurrence, the operator recorded the interval between the two episodes after the drug intake or application. A thorough evaluation of the lesions at second or subsequent episodes was once again done, using the same parameters as the primary visit. The patients were given the same drug for intake or application and the same dose as before with the same instructions, ensuring that they once again fell in the same group. The data obtained from the study (case history and clinical exam) was carefully tabulated in the form of a master chart. Master chart was then critically evaluated and objective conclusions were drawn after submitting the data to statistical analysis using Statistical Analysis Package For Social Science's Software. Statistical analysis of data was done and independent t test was applied for determining the statistical significance of the data.

RESULTS

Table 2 shows that in all the four groups there is a continuous and uniform improvement in the average ulcer size. Table 3 shows the actual number of recurrences in the various groups which occurred during the treatment and follow up period. 6 patients in Group 1 had a recurrence, 1 patient in Group 2 had a recurrence, none of the patients had a recurrence in Group 3 whereas 1 patient in Group 4 had a recurrence.

DISCUSSION

Ulcer pain: Considering the obscure nature of the etiology of RAS, a wide range of treatment modalities exist. Essentially, the therapy for RAS is palliative rather than curative. Amongst the vast array of options two drugs Amlexanox and Rebamipide can prove to be promising modalities for affording effective palliation in RAS primarily because of their anti inflammatory and anti allergic properties. It is seen from the findings that in all the four groups there is a continuous and uniform improvement in the average pain score but statistically there is no significant difference in the improvement of pain in the four study groups. It is also seen that minimum average pain score was recorded in Group 2 for a longer duration during follow-up however this could be also related to the lower average pain score on the first day. Khandwala *et al*, Liu *et al*, Meng *et al* in their studies showed that, a significantly greater percentage of subjects on 5% amlexanox had complete resolution of pain as compared to the placebo group consistent with our study(Khandwala *et al*., 1997; Liu *et al*., 2006; Meng *et al*., 2009). Similarly, administration of rebamipide, gives rise to definite improvement and the beneficial effects of the drug (rebamipide) cannot be denied. But, even the second modality i.e. oral administration of rebamipide failed to show any statistically significant difference in comparison to the placebo group, as far as relief from pain was concerned. Matsuda *et al* stated that out of the 35 patients in his study, the rebamipide group showed a higher efficacy rate than the placebo group in terms of aphthae count and pain.

Table 1. Shows mean pain score of patients in 4 groups

Groups	Mean Pain Scores of Patients in 4 Groups							
	Pain 1	Pain 3	Pain 5	Pain 7	Pain 9	Pain 11	Pain 13	Pain 15
Group 1 (Amlexanox)	5.3	3	1.85	0.8	0.45	0.1	0	0
Group 2 (Rebamipide)	3.55	1.85	0.95	0.5	0.4	0.25	0.15	0.1
Group 3 (Orabase)	5.2	3.2	1.4	0.7	0.2	0.1	0	0
Group 4 (Sugar tablets)	3.8	2.6	1.5	0.8	0.3	0.2	0	0

Table 2. Mean Ulcer Size of Patients in 4 Groups

Groups	Mean Ulcer Size of Patients in 4 Groups												
	Ulcer 1	Ulcer 3	Ulcer 5	Ulcer 7	Ulcer 9	Ulcer 11	Ulcer 13	Ulcer 15	Ulcer 17	Ulcer 19	Ulcer 21	Ulcer 23	Ulcer 25
Group 1 (Amlexanox)	4.5	3.1	2.4	1.4	0.7	0.3	0.1	0.05	0	0	0	0	0
Group 2 (Rebamipide)	3.1	2.3	1.4	0.7	0.5	0.3	0.3	0.2	0.1	0.1	0.05	0.05	0
Group 3 (Orabase)	3	2.8	2.2	1.4	0.8	0.4	0.3	0.2	0.2	0.1	0.1	0.1	0.1
Group 4 (Sugar tablets)	3.6	3	2	1.3	0.5	0.5	0.3	0	0	0	0	0	0

Table 3. Shows Recurrence in four groups

Pts.	Group 1 (Amlexanox)	Group 2 (Rebamipide)	Group 3 (Orabase)	Group 4 (Sugar tablets)
1	-	-	-	-
2	-	-	-	-
3	-	-	-	-
4	-	-	-	-
5	-	-	-	-
6	-	-	-	1
7	-	-	-	-
8	3	-	-	-
9	-	-	-	-
10	-	-	-	-
11	1	-		
12	1	-		
13	1	-		
14	-	1		
15	-	-		
16	-	-		
17	-	-		
18	2	-		
19	3	-		
20	-	-		
Total	6	1	0	1

But, this study was carried out in patients with Behcets syndrome (Matsuda, 2003). When comparison was made between Group 1 (amlexanox) and Group 2 (rebamipide), Group 1 showed relief from pain in 30% of the patients, whereas Group 2 showed improvement in 70% of the patients on the 5th day. Therefore it is worth noting that in this study, oral administration of rebamipide proved to be more beneficial compared to local application of amlexanox in providing relief from pain. But, it failed to show any statistically significant difference in comparison to amlexanox.

Ulcer size: The size of the ulcer can be used as important criteria for judging the efficacy of drugs under trial. It is observed in this study that local application of amlexanox and oral administration of rebamipide are effective in reducing the ulcer size. Rebamipide appears to be superior in promoting rapid healing compared to amlexanox. However, the difference between the efficacy of two drugs in achieving complete healing is not statistically significant ($p<0.05$). Group 1 patients (amlexanox) and Group 2 patients (rebamipide) showed appreciably rapid healing by 7th day when compared to their respective placebo groups. In other words both the drugs under trial appear to promote faster healing of the aphthous ulcers and appear to be more beneficial than the placebo group.

When compared between Group 1 and 2, the efficacy appears to be almost similar as average number of days taken for healing in Group 1 is 8.53 and for Group 2 is 8.2. Khandwala *et al*, Liu *et al*, Meng *et al*, showed that application of 5% Amlexanox topical paste was shown to statistically accelerate complete ulcer healing compared with placebo group, consistent with our study (Khandwala *et al*., 1997; Liu *et al*., 2006; Meng *et al*., 2009).

Recurrence: Amlexanox has only local action. Possibly because of the localized and limited action more recurrences were recorded in the patients who received amlexanox. The second drug i.e. rebamipide on the other hand has shown greater potential in preventing the frequency of RAS. This may be because of systemic administration that the effect may be more long lasting. Parvathi *et al* said that, the overall results showed mean number of episodes whose values were not statistically significant, similar to our study (Parvathi Devi *et al*., 2014).

Adverse effects: In our study it was observed that there was no adverse event noted in any of the patients included in all the four groups. Khandwala *et al* said that an overall excellent safety profile for 5% Amlexanox paste is supported by the following: (1) very low reported incidence of side effects in

subjects treated for aphthous ulcers; (2) very low reported incidence of side effects and no systemic effects on clinical chemistries in subjects treated four times a day for 28 days with 5% Amlexanox paste; (3) prior clinical use with higher doses of Amlexanox for the treatment of asthma; and (4) animal safety studies (Khandwala *et al*., 1997).

Conclusions

- Topical application of amlexanox is effective in providing relief from pain and in the early stages, it is better than the placebo in this study.
- Oral administration of rebamipide is more effective in controlling pain associated with RAS when compared to placebo in this study.
- Administration of rebamipide is more effective in controlling the pain as compared to application of amlexanox in this study.
- Group 1 (amlexanox) patients showed moderate improvement as compared to no improvement in reduction of ulcer size in the placebo group in the early stage of trial in this study.
- Rebamipide was found to be more effective in reducing the ulcer size as compared to the placebo in this study.
- In this study administration of rebamipide provided faster healing (reduction in ulcer size) as compared to the topical application of amlexanox.
- Rebamipide and amlexanox were ineffective in preventing recurrence all together. In this study patients treated with rebamipide reported with decreased number of recurrences as compared to the patients treated with amlexanox.
- None of the patients included in this study presented any adverse reaction to the drugs prescribed.

Recommendations

Both the drugs used in this trial are almost equally effective in providing relief from pain and promoting rapid healing of the ulcers in RAS. However as amlexanox is a shade better in providing faster relief and rebamipide provides relief which is longer lasting. It is recommended that both the drugs can be simultaneously prescribed to the patients to derive the maximum beneficial action.

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