



COMPARATIVE EVALUATION OF THE EFFICACY OF TOPICAL AMLEXANOX 5% ORAL PASTE AND TRIAMCINOLONE ACETONIDE 0.1% ORAL PASTE IN THE TREATMENT OF MINOR RECURRENT APHTHOUS STOMATITIS -A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

**Aim:** The aim of this systematic review was to compare the clinical efficacy of topical triamcinolone acetonide 0.1% and amlexanox 5% in minor (RAS) treatment. **Background:** The term “aphthous” is derived from a Greek word “aphthae” that means ulceration. Minor Recurrent aphthous stomatitis (RAS) comprises more than 80 to 90% of aphthous stomatitis cases, most commonly seen in second to fourth decade of life.<sup>[1]</sup> Variety of treatment modalities exist which consists of measures to suppress the symptoms as well as reduction in pain and duration of healing of ulcers. Amlexanox is a topical anti-inflammatory, antiallergic drug. It is presently the sole clinically established product approved by the US Food and Drug Administration for the treatment of minor recurrent aphthous ulcers.<sup>[1]</sup> Triamcinolone Acetonide is a topical corticosteroid drug which has anti-inflammatory & immunosuppressive action used in the treatment of minor RAS.<sup>[2]</sup> **Search Method:** With the available literature from PubMed, Google Scholar and grey literature. **Data Collection & Analysis:** The protocol of this review was primarily based totally on the PRISMA, PRISMA pointers and listing were followed so as to extend the standard and transparency of the search. Recommendations of the Cochrane enchiridion and Systematic Reviews of Interventions were followed. Meta- analysis was done based on Pearson’s value. **Results:** Five studies out of ninety five studies were included showed significantly higher potency of Triamcinolone compared to amlexanox for minor RAS treatment regarding pain, healing, and ulcer size reduction. **Conclusion:** Triamcinolone acetonide 0.1% is more effective than Amlexanox 5% in the treatment of minor RAS. **Clinical Significance:** Efficacy of two topical ointments in management of minor recurrent aphthous stomatitis was assessed to understand, reduction in pain, reduction size and ulcer duration of healing in patients.<sup>[5]</sup> The clinical results of this review provide scientific evidence about the efficacy of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste.

**KEYWORDS:** Amlexanox 5%, Triamcinolone Acetonide 0.1%, recurrent aphthous stomatitis, aphthous ulcer.

BACKGROUND

Recurrent aphthous ulcer is the most prevalent oral mucosal disease in humans, estimated to affect between 5% and 50% of the general population.<sup>[4]</sup> The most common manifestation is characterised by small, shallow, round or oval lesions that are surrounded by a raised erythematous halo and are covered by a grey-white pseudomembrane.<sup>[2,3]</sup> Appropriate management of patients with this condition is largely symptomatic and should focus on reducing ulcer duration, relieving pain and reducing or preventing ulcer recurrence. Of the 3 subtypes of RAS, RAS major (MaRAS), RAS herpetiform, and RAS minor (MiRAS), the foremost common MiRAS accounts for 75%–85%.<sup>[2]</sup> Since definitive etiology is unknown, the diagnosis is

entirely supported on history and clinical features.<sup>[8,9]</sup> The most common symptom of RAS minor is pain while mastication, swallowing or speaking.<sup>5</sup>RAS minor is characterised by reoccurrence and usually heals with symptomatic treatment and the duration ranging from 7-14 days.<sup>[6]</sup>

The comorbid factors powerfully related to minor RAS include trauma, genetic predisposition, allergy, nutritional deficiency, hormones, psychological stress, gastrointestinal disturbances.<sup>[5,6]</sup> There is considerable interference with routine activities and affects quality of life.<sup>[4]</sup> Treatment consists of therapeutic measures which are mainly symptomatic and a very few definitive cure. The therapeutic alternative depends on the severity of the

malady, together with the frequency of ulceration, the number of ulcers, their location and period, and also the level of associated orofacial pain.<sup>5</sup> Variety of treatment modalities exist that include the utilization of nutritional supplements, topical agents, antibiotics, immunomodulators, corticosteroids, and alternative non-categorized pharmacotherapeutic agents with varied degrees of effectiveness.<sup>[6]</sup>

Amlexanox 5% is a topical anti-inflammatory, antiallergic drug. It is presently the sole clinically established product approved by the US Food and Drug Administration for the treatment of aphthous ulcers.<sup>[7]</sup> It inhibits the formation of histamines and leukotriene from mast cells, neutrophils, and mononucleate cells

therefore reducing the inflammatory symptomatology of the RAS.<sup>[11]</sup> It has also been developed as a topical oral paste for the treatment of patients with minor RAS.

A topical steroid like triamcinolone acetonide 0.1% is said to be effective in cases of aphthous ulcers.<sup>[16]</sup> Triamcinolone falls under the class of corticosteroids specifically a glucocorticoids.<sup>[16,17]</sup> It exhibits anti-inflammatory and immunosuppressant activity via inhibiting the phospholipase A2 enzyme on the cell membrane phospholipid layer, and thereby hinders the breakdown of leukocyte lysosomal membranes and prevents the formation of arachidonic acid.<sup>[17,18]</sup> It exhibits anti-inflammatory and immunosuppressant activity.<sup>[18]</sup>

Character	Type of RAS		
	Minor	Major	Herpetiform
Peak age of onset (decade)	Second	First and second	Third
Number of ulcers	1-5	1-3	5-20 (up to 100)
Size of ulcers (mm)	<10	>10	1-2
Duration	7-14 days	2 weeks-3 months	7-14 days
Heal with scarring	No	Yes	No
Site	Non-keratinized mucosa especially labial/buccal mucosa. Dorsum and lateral borders of the tongue	Keratinized and non-keratinized mucosa, particularly soft palate	Non-keratinized mucosa but particularly floor of the mouth and ventral surface of the tongue

Figure1: Difference between minor, major and herpetiform ulcers.<sup>[1,2]</sup>



Minor Aphthae



Major Aphthae



Herpetiform Ulcer

### Clinical Relevance

Minor RAS, comprises more than 80%-90% of RAS cases. RAS is current in 5%–25% of the population presenting oftentimes between the second to fourth decades of life.<sup>[4,5]</sup> Though reoccurrence is noted in recurrent minor ulcers the healing period is between 7-14 days with symptomatic treatment.<sup>[5,6]</sup>

Systemic therapy is indicated where the pain is intense and topical treatment is unable to relieve symptoms and also in patients with immunosuppression conditions.<sup>[8,9]</sup> The clinical results of this review provide scientific evidence about the efficacy of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste.<sup>[9]</sup>

### Focused Question

Is there any difference in the efficacy of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste in the treatment of minor Recurrent Aphthous Stomatitis (RAS)?

### Outcome Measures

The primary outcome was to compare the effectiveness of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste of the minor RAS thus improving the condition of the patients with minor RAS. The secondary outcome was to compare the efficacy of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste in the management of minor RAS and improve in life quality in the subjects with minor RAS.

### Aim and Objectives of The Study

#### Aim

To comparatively evaluate the efficacy of topical amlexanox 5% oral paste and triamcinolone acetonide 0.1% oral paste in the treatment of minor recurrent aphthous stomatitis (RAS).

#### OBJECTIVES

1. To evaluate the difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% pain assessment in patients with RAS.
2. To evaluate the difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% reduction in size in patients with RAS.

3. To evaluate the difference in Amlexanox 5% and Triamcinolone Acetonide 0.1% duration of healing in RAS.

### Inclusion and Exclusion Criteria

#### Inclusion Criteria

1. Eligibility criteria included human randomized and non-randomised trails and prospective and retrospective cohort studies.
2. All studies done on patients with minor recurrent aphthous ulcer patients aged 18–48 years of either gender.
3. Visual analogy scale (VAS) ranging from 1 to 10 was used to measure pain where 1 indicated no pain and 10 indicated severe pain.
4. Patients having minor aphthous ulcers not more than 48 hours old, not having taken any analgesic, antiseptic or corticosteroid therapy prior to the study.

#### Exclusion criteria

1. Studies in any other language.
2. Studies that have no access to full text.
3. Animal studies.
4. In vitro studies.
5. Case series.
6. Case reports.
7. Studies in unpublished formats.

### Search Strategy

An electronic search without restriction of dates or language was conducted on PubMed, Google scholar from December 2010 till December 2020 articles were selected. A search for unpublished studies (grey literature) was conducted on Grey Literature Report and OpenGrey databases. Searches in the ClinicalTrials.gov database and in the references of the included studies (cross referencing), were also conducted. The data extracted were sorted as quantitative and qualitative and tabulated for ease comparison. Articles that did not meet the inclusion criteria were excluded. MeSH terms, keywords and other free terms related to “RAS [MeSH]”, “Amlexanox 5% [MeSH]”, “Triamcinolone Acetonide 0.1% [MeSH]” .” pain [All fields]”, “aphthous ulcer[All fields]”, “oral ulcer[All fields]” were used with Boolean operators(OR,AND) to combine searches. The same keywords were used for all the search platforms followed the syntax rules of each database.

**Table 1: The search strategy and PICOS tool.**

Search strategy	
Focused question	To evaluate the efficacy of Topical Amlexanox 5% Oral Paste and Triamcinolone Acetonide 0.1% Oral Paste in the treatment of minor Recurrent Aphthous Stomatitis (RAS)
Population	#1. Patients with RAS OR RAS [MeSH] OR Oral ulcer OR Aphthous ulcer OR Pain
Intervention	#2. “Amlexanox 5% [MeSH]”, “Triamcinolone Acetonide 0.1% [MeSH]” .” pain [All fields]”, “aphthous ulcer[All fields]”, “oral ulcer[All fields]”
Comparisons	#3 “Amlexanox 5% [MeSH]”, “Triamcinolone Acetonide 0.1% [MeSH]” .” pain [All fields]”, “aphthous ulcer[All fields]”, “oral ulcer[All fields]” MeSH]” .
Outcomes	#4. effectiveness “Amlexanox 5% [MeSH]”, “Triamcinolone Acetonide 0.1% [MeSH]” OR Efficacy of Amlexanox 5% [MeSH]”, “Triamcinolone Acetonide 0.1% [MeSH]”
Study design	Controlled clinical trials, Randomised controlled trials

Search combination	#1AND #2AND
<b>Database search</b>	
Language	Only English
Electronic database	PubMed, Google scholar
Journals	Journal of Indian Academy of Oral Medicine & Radiology, International Journal of Clinical and Diagnostic Pathology, Journal of pharmacy and Bioallied sciences, International Journal of Contemporary Medical Research, Journal of Advanced Health Sciences and Research
Grey literature	Grey literature report and OpenGrey

**Quality of The Studies**

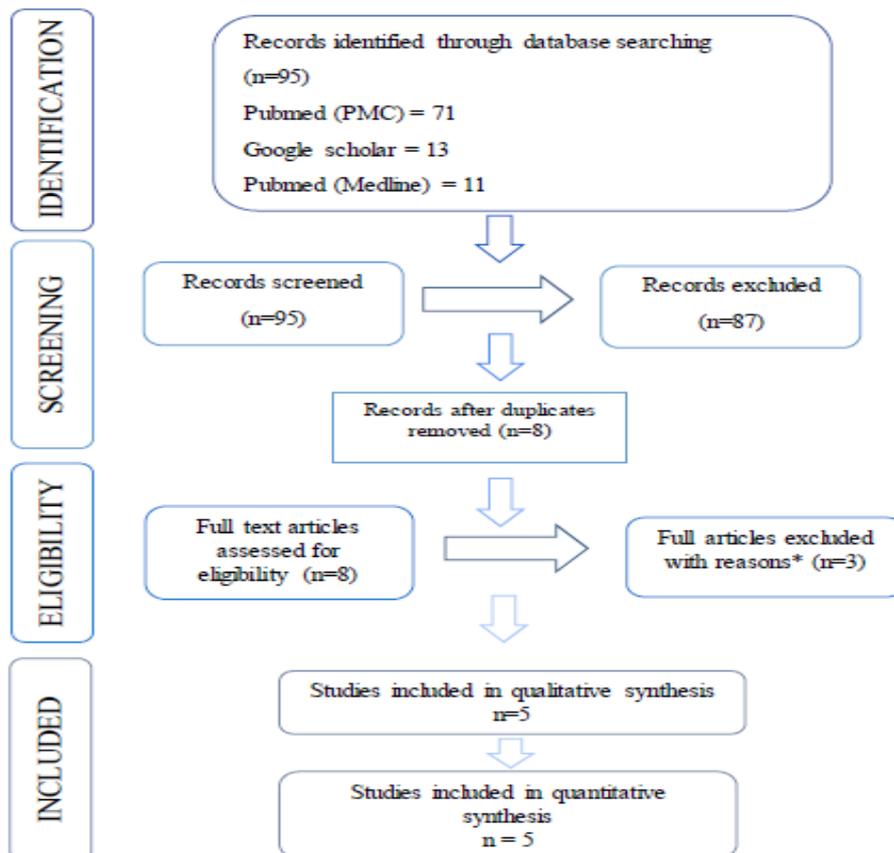
Quality assessment of the selected studies was executed by using the Cochrane Collaboration Tool (<http://ohg-cochrane.org>) for randomised control trails (RCTs) including random sequence generation, allocation concealment, blinding of the participants, incomplete outcome data, selective reporting and other bias. The Newcastle-Ottawascale ([http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)) was applied for non-randomised studies to judge each included study on selection of studies, comparability of cohorts and the ascertainment of either the exposure or outcome of interest.

**Assessments of The Risks of Bias**

Risk of bias and study quality analyses were performed independently by two reviewing/authors. Studies in which one of the criteria did not match were described as having a moderate risk of bias and studies where two or more of the criteria were missing were as having a high potential risk of bias. For the selection categories and result, the studies can get a star/point for each item.

For the comparison study or category two stars/points can be assigned. According to NOS, the maximum score assigned to a study is nine stars/points. Studies rated 6 stars and up are considered as high quality.

**PRISMA 2009 Flow Diagram**



\*Studies Excluded due to

1. Not fitting in the inclusion criteria=62
2. Study did not estimate the difference between Amlexanox 5% and Triamcinolone acetonide =14
3. Study included no RAS minor cases=6
4. Review article=8

**Figure 2: Flowchart of the search strategy.**

**Table 2: Main characteristics of selected studies-Quantative.**

Authors (year)	Study design	No. of subjects	Age gender	VAS	Frequency	Healing time 5% Amlexanox	Healing time 0.1% Triamcinolone Acetonide	Author's Conclusion
Satish Balwani.et al (2009)	Randomised control trail	60	M=F 20to 40 years	Mild to moderate	<3 episodes	4.10± 1.50 days (range 3-7)	1.08 ± 1.25 days (range 1-4)	The difference was statistically significant ( $P \leq 0.05$ ).Both amlexanox and triamcinolone acetamide are effective and safe in the treatment of aphthous ulcers.
Altaf Hussain Chalkoo.et al(2017)	Randomised control trail	36	M=F 20to 40 years	Mild to moderate	<4 episodes	2.05 ± 1.50 days (range 3-7)	1.11 ± 1.36 days (range 1-4)	There was reduction of pain and ulcer size significantly at subsequent follow up visits at 3rd, 5th and 7th days ( $p < 0.01$ ).No significant difference was noted between Triamcinolone and Amlexanox for their efficacy on pain relieving effect as well as on tingling in the present study.
Dr. Shrivastav.et al (2018)	Randomised control trail	24	M=F 20to 40 years	Mild to moderate	<4 episodes	3.12 ± 1.50 days (range 3-7)	1.24 ± 1.36 days (range 1-4)	Both 5% amlexanox and 0.1% triamcinolone acetamide found to be effective in reducing size, erythema and pain in cases of aphthous ulcers.
Rohit Singh et.al (2019)	Randomised control trails	60	M=F 18to 40 years	Mild to moderate	<4 episodes	4.17 ± 1.80 days (range 4-7)	2.24 ± 1.36 days (range 2-4)	The above clinical trial demonstrates the comparable clinical efficacy of 5% amlexanox oral paste in decreasing erythema, ulcer size, pain, and healing time of recurrent aphthous ulcers (minor) and can be considered as a substitute to topical corticosteroid preparations in these participants, except in pain control.
Kavita Kumari .et al (2020)	Randomised control trails	60	M=F 18to 40 years	Mild to moderate	<4 episodes	5.17 ± 1.80 days (range 5-7)	4.24 ± 1.36 days (range 4-5)	Both the drugs used in this study were effective in reducing pain, size of ulcer, erythema, and improving healing in patients with recurrent aphthous stomatitis. However, the results were better with triamcinolone acetamide as compared with amlexanox indicating its effectiveness in treating RAS.

**Data Synthesis**

**Table 3: Presentation of risk of bias evaluation for included RCTs according to the Cochrane Collaboration’s tool.**

<b>Random sequence generation</b>	+	+	+
Allocation concealment	+	+	?
Blinding of participants and personnel	-	-	-
Incomplete outcome data	?	?	?
Selective reporting	+	+	+
Other bias	?	?	?
	<b>Shrivastav et al. (2018)</b>	<b>Rohit Singh et al. (2019)</b>	<b>Kavita Kumari et al. (2020)</b>

**Table 4: Presentation of risk bias evaluation for included non RCTs according to the Newcastle-Ottawa assessment scale.**

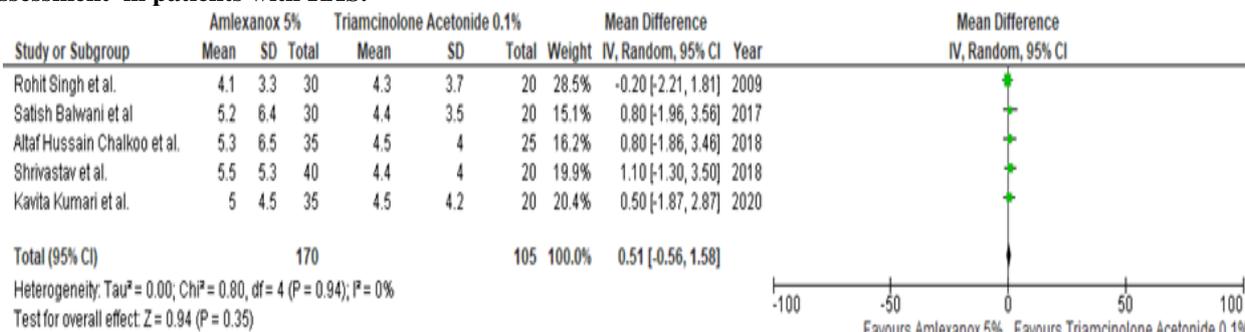
	<b>Selection (max.4 stars)</b>	<b>Comparability (max.2 stars)</b>	<b>Outcome (max.4 stars)</b>
Satish Balwani(2017)	★ ★ ★	★ ★	★ ★
Altaf Hussain Chalkoo1 (2018)	★ ★ ★	★ ★	★ ★ ★

**Meta-Analysis**

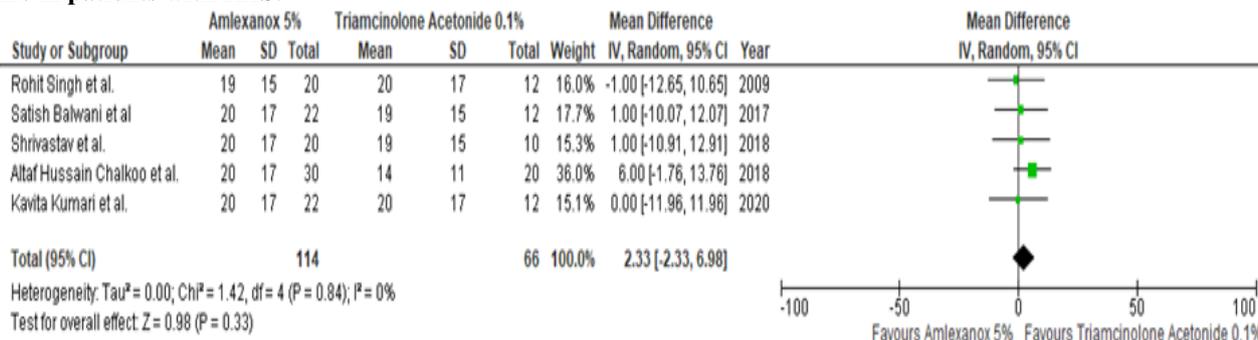
Five studies were included in meta-analysis.<sup>[1,2,3,4,5]</sup> The pain assessment was compared difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% in patients with minor recurrent aphthous ulcer. The Pearson’s value was 0.35 in table 5. Difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% in

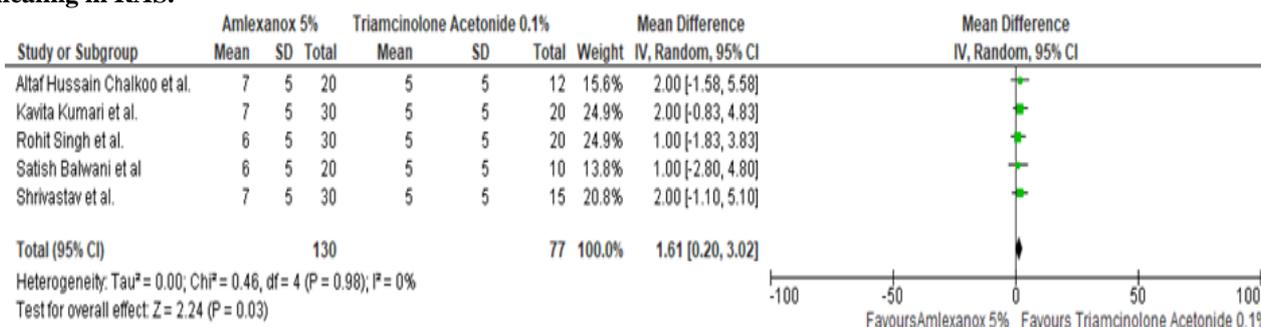
size reduction in patients with minor recurrent aphthous stomatitis was noted as the Pearson’s value 0.33 in table 6. Based on difference in Amlexanox 5% and Triamcinolone Acetonide 0.1% duration of healing in minor recurrent aphthous stomatitis Pearson’s value of 0.03 was noted in table 7.

**Table 5: Forest plot on difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% for pain assessment in patients with RAS.**



**Table 6: Forest plot on difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% for reduction in size in patients with RAS.**



**Table 7: Forest plot based on difference in Amlexanox 5% and Triamcinolone Acetonide 0.1% for duration in healing in RAS.**

## DISCUSSION

Apthous ulcers are most common recurrent ulcers in oral mucosa characterised by repeated painful, single, or multiple well-demarcated ulceration with peripheral red halo.<sup>[20,22]</sup> RAS (recurrent aphthous stomatitis) mainly of 3 types minor, major and herpetiform. forms, in this article we have included studies with minor RAS. There are various treatment modalities for RAS starting from home remedies to advanced modalities like Laser Therapy.<sup>[33]</sup> However, there is no curative medical aid to forestall the return of ulcers, and all available treatment modalities will solely scale back the frequency or severity of the lesions the first treatment goal for RAS is to scale back inflammation and length of ulceration.<sup>[40,41]</sup> The goal of treatment is to decrease pain, healing time, ulcer size, erythema and prevent recurrence. In this Systematic Review we have compared the efficacy of topical amlexanox 5% oral paste and triamcinolone acetonide 0.1% oral paste in the treatment of minor recurrent aphthous stomatitis. The factors which were considered in this study were, pain assessment, reduction in size and duration of healing time.

The rate of decrease in ulceration size depends on the onset of treatment.<sup>[16]</sup> Peri-ulcer erythematous ulcer halo was a predominant feature at baseline in all participants that were considered in the study. This distinction in pain perceived was found to be statistically significant. The average age of the participants enclosed in the study by Shrivastava et al.<sup>[6]</sup> was 27.5 years in comparison with a spread of 25–48 years in the literature. A complete of forty participants completed the trial, of that twenty two were males and eighteen were females with a male-to-female quantitative relation of 1.1:0.9. One study from India suggests a male predilection with a quantitative relation of 4.5:1.<sup>[14]</sup>

In accordance to Kavita Kumari et al<sup>[2]</sup>, authors found that triamcinolone acetonide 0.1% and amlexanox 5% drugs were effective in reducing pain, size of ulcer, erythema, and improving healing in patients with recurrent aphthous stomatitis. There were better results with triamcinolone acetonide 0.1% as comparison of amlexanox 5%. In a recent study improvement until the sixth day in the average pain score at baseline was five, as recorded by a VAS scale at the time of

presentation.<sup>[46]</sup> There was more or less forty five percent reduction in pain on the third day in each groups by the fifth day, control participants showed ninety percent reduction in pain, whereas experimental participants showed a seventy percent reduction in pain.<sup>[44]</sup> Rohit Singh et al demonstrated the comparable clinical efficacy of 5% amlexanox oral paste in decreasing erythema, ulcer size, pain, and healing time of recurrent aphthous ulcers (minor) and can be considered as a substitute to topical corticosteroid preparations in these participants, except in pain control.<sup>[4]</sup>

Five studies were included in meta-analysis.<sup>[1,2,3,4,5]</sup> The pain assessment was compared and the difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% in patients with minor recurrent aphthous ulcer. The Pearson's value was 0.35 in table 5. Difference between Amlexanox 5% and Triamcinolone Acetonide 0.1% in size reduction in patients with minor recurrent aphthous stomatitis was noted as the Pearson's value 0.33 in table 6. Based on difference in Amlexanox 5% and Triamcinolone Acetonide 0.1% duration of healing in minor recurrent aphthous stomatitis Pearson's value of 0.03 was noted in table 7.

To summarize, triamcinolone acetonide 0.1% as compared to amlexanox 5% is more effective in healing of RAS ulcer and helps achieve optimal patient outcomes. Triamcinolone acetonide could be used as an effective drug delivery system for the treatment of recurrent aphthous stomatitis.

## Strengths and Limitations

This systematic review presents several strengths, such as a previous record of protocol, unrestricted search in the literature (including grey literature) selecting the best available evidence, searching process of studies data extraction and risk analysis bias performed.

Nonetheless some limitations may be related to this systematic review the comparative ratio between the two drugs is low, and requirement of gold standard drug is still needed. The study articles considered in this study are only randomised control trail, need for other variants of studies is required for border prospective of the

effectiveness of the drug. The number of articles in this study were limited.

## CONCLUSION

The comparable clinical effectiveness of triamcinolone acetonide and amlexanox oral paste in decreasing erythema, ulcer size, pain, and healing time of aphthous ulcer is noted in this study.<sup>[33]</sup> Follow-up for recurrence of ulcers and hindrance of more episodes might be explored with more studies, with a study article that has bigger sample size with a stress on the advance in quality of life. Both the medication employed in this study were effective in reducing pain, size of ulceration, erythema, and improving healing in patients.<sup>[1,2,3,4,5]</sup> However, the results were higher with triamcinolone acetonide as compared with amlexanox indicating its effectiveness in treating RAS.<sup>[1,2,3,4,5]</sup> Statistically Triamcinolone showed significantly higher potency compared to Amlexanox for RAS treatment, regarding pain, erythema and ulcer size reduction.

## REFERENCES

- Shrivastava K, Naidu G, Deshpande A, Handa H, Raghuvanshi V, Gupta M. Comparative evaluation of the efficacy of topical amlexanox 5% oral paste and triamcinolone acetonide 0.1% oral paste in the treatment of Recurrent Aphthous Stomatitis (RAS). *J Indian Acad Oral Med Radiol*, 2018; 30: 235-40.
- Kavita, Kumari et al. "Assessment of Efficacy of 5% Topical Amlexanox and 0.1% Topical Triamcinolone Acetonide in Management of Recurrent Aphthous Stomatitis." *Journal of pharmacy & bioallied sciences*, 2020; 12(1): S444-S447.
- Altaf Hussain Chalkoo, Bashir Ahmad Wani, Prenika Sharma, Tauseefa Jan. An evaluation of the efficacy of amlexanox and triamcinolone topical paste in the treatment of recurrent aphthous stomatitis. *International Journal of Contemporary Medical Research*, 2018; 5(9): I20-I22.
- Dr. Rohit Singh, Dr. Supriya Singh, Dr. Aaysha Tabinda Nabi, Dr. Irfanul Huda, Dr. Kumar Anand and Dr. Samar Ali Fara. Comparative evaluation of efficacy of topical 5% amlexanox oral paste and 0.1% triamcinolone acetonide oral paste in the treatment of oral ulcers. *International Journal of Clinical and Diagnostic Pathology*, 2019; 2(2): 338-340.
- Nasry SA, El Shenawy HM, Mostafa D, Ammar NM. Different modalities for treatment of recurrent aphthous stomatitis. A Randomized clinical trial. *J Clin Exp Dent*, 2016 Dec 1; 8(5): e517-e522. doi: 10.4317/jced.52877. PMID: 27957263; PMCID: PMC5149084.
- Rodriguez M, Rubio JA, Sanchez R. Effectiveness of two oral pastes for the treatment of recurrent aphthous stomatitis. *Oral Dis*, 2007; 13: 490-4. 9.
- Katti G, Darshan DD. Amlexanox in the treatment of recurrent minor aphthous ulcers. *Int. J Dent Clin*, 2011; 3.23.6
- Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent*, 2014; 6: e168-74.
- Montgomery-Cranny JA, Wallace A, Rogers HJ, Hughes SC, Hegarty AM, Zaitoun H. Management of recurrent aphthous stomatitis in children. *Oral Med*, 2015; 42: 564-72.
- Ofluoglu D, Ergun S, Warnakulasuriya S, Namdar-Pekiner F, Tanyeri H. An evaluation of the efficacy of a topical gel with triester glycerol oxide (TGO) in the treatment of minor recurrent aphthous stomatitis in a Turkish cohort: a randomized, double-blind, placebo-controlled clinical trial. *Med Oral Patol Oral Cir Bucal*, 2017; 22: e159-66.
- Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. *Dent Clin North Am*, 2014; 58: 281-97.
- Aggarwal H, Singh MP, Nahar P, Mathur H, Gv S. Efficacy of low-level laser therapy in treatment of recurrent aphthous ulcers: a sham controlled, split mouth follow up study. *J Clin Diagn Res*, 2014; 8: 218-21.
- Gomes CC, Gomez RS, Zina LG, Amaral FR. Recurrent aphthous stomatitis and helicobacter pylori. *Med Oral Patol Oral Cir Bucal*, 2016; 21: e187-91.
- Edgar NR, Saleh D, Miller RA. Recurrent aphthous stomatitis: a review. *J Clin Aesthet Dermatol*, 2017; 10: 26-36.
- Rivera C. Essentials of recurrent aphthous stomatitis. *Biomed Rep*, 2019; 11: 47-50.
- Abbasi F, Raoof M, Khatami R, Shadman N, Borjian-Borojjeni F, Nazari F. Effectiveness of amlexanox and adcortyl for the treatment of recurrent aphthous ulcers. *J Clin Exp Dent*, 2016; 8: e368-72.
- Chalkoo AH, Wani BA, Sharma P, Jan T. An evaluation of the efficacy of amlexanox and triamcinolone topical paste in the treatment of recurrent aphthous stomatitis. *Int J Contemp Med Res*, 2018; 5: I20-2.
- Belenguer-Guallar I, Jiménez-Soriano Y, ClaramuntLozano A. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent*, 2014; 6: e168-74 2.
- Jurge S, Kuffer R, Scully C, Porter SR. Mucosal disease series. Number VI. Recurrent aphthous stomatitis. *Oral Dis*, 2006; 12: 1-21.
- Aggarwal H, Singh MP, Nahar P, Mathur H, Gv S. Efficacy of lowlevel laser therapy in treatment of recurrent aphthous ulcers - a sham controlled, split mouth follow up study. *J Clin Diagn Res*, 2014; 8: 218- 21.
- Liang MW, Neoh CY. Oral aphthosis:management gaps and recent advances. *Ann Acad Med Singapore*, 2012; 41: 463-70.
- Abbasi F, Raoof M, Khatami R, Shadman N, BorjianBorojjeni F, Nazari F. Effectiveness of Amlexanox and Adcortyl for the treatment of

- recurrent aphthous ulcers. *J Clin Exp Dent*, 2016; 8: e368-72.
23. Jiang XW, Zhang Y, Zhang H, Lu K, Yang SK, Sun GL. Doubleblind, randomized, controlled clinical trial of the effects of diosmectite and basic fibroblast growth factor paste on the treatment of minor recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol*, 2013; 116: 570-5.
  24. Abbasi F, Raof M, Khatami R, Shadman N, BorjianBorojeni F, Nazari F. Effectiveness of Amlexanox and Adcortyl for the treatment of recurrent aphthous ulcers. *J Clin Exp Dent*, 2016; 8: e368-72.
  25. Akintoye S, Greenberg MS. Recurrent Aphthous Stomatitis. *Dent Clin North Am*, 2014; 58: 281-97.
  26. Ofluoglu D, Ergun S, Warnakulasuriya S, NamdarPekiner F, Tanyeri H. An evaluation of the efficacy of a topical gel with Triester Glycerol Oxide (tgo) in the treatment of minor recurrent aphthous stomatitis in a Yurkish cohort: A randomized, double-blind, placebocontrolled clinical trial. *Med Oral Patol Oral Cir Bucal*, 2017; 22: e159-66.
  27. Akintoye S, Greenberg MS. Recurrent Aphthous Stomatitis. *DentClin North Am*, 2014; 58: 281-97.
  28. Ofluoglu D, Ergun S, Warnakulasuriya S, NamdarPekiner F, Tanyeri H. An evaluation of the efficacy of a topical gel with Triester Glycerol Oxide (tgo) in the treatment of minor recurrent aphthous stomatitis in a Yurkish cohort: A randomized, double-blind, placebocontrolled clinical trial. *Med Oral Patol Oral Cir Bucal*, 2017; 22: e159-66.
  29. M Rodri'guez, JA Rubio, R Sanchez:Effectiveness of two oral pastes for the treatment of recurrent aphthous stomatitis; *Oral Diseases*, 2007; 13: 490-494.
  30. Liu J, Zeng X, Chen Q, Cai Y, Chen F, Wang Y, et al. An evaluation on the efficacy and safety of amlexanox oral adhesive tablets in the treatment of recurrent minor aphthous ulceration in a Chinese cohort: a randomized, double-blind, vehicle-controlled, unparallel multicenter clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2006; 102: 475-81.
  31. Khandwala A, Van Inwegen RG, Alfano MC. 5% Amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 1997; 83: 222-30.
  32. Murray B, McGuinness N, Biagioni P, Hyland P, Lamey PJ. A comparative study of the efficacy of Aphtheal in the management of recurrent minor aphthous ulceration. *J Oral Pathol Med*, 2005; 34: 413-9.
  33. Bell J. Amlexanox for the treatment of recurrent aphthous ulcers. *Clin Drug Investig*, 2005; 25: 555-66.
  34. Hasan, S., Perween, N., Saeed, S. *et al.* Evaluation of 5% Amlexenox Oral Paste and Rebamipide Tablets in Treatment of Recurrent Aphthous Stomatitis and Comparison with Dologel CT. *Indian J Otolaryngol Head Neck Surg* (2020).
  35. Bero Nzhad Mustafa Ali Fakhree Alzubaidee Comparative Evaluation of The Efficacy of Topical Hyaluronic Acid ( 0.2%) and Topical Triamcinolone Acetonide( 0.1%) in The Treatment of Recurrent Aphthous Stomatitis Vol. 19 No. 2 (2020): Diyala Journal of Medicine the volume 19, Issue 2.
  36. Kour, M., Dwivedi, A. A comparative randomized clinical trial to assess the effectiveness of the diode lasers in both contact and non-contact mode and 0.1% triamcinolone acetamide mouth paste in treatment of oral ulcers—an in vivo study. *Laser Dent Sci*, 2020; 4: 33-42.
  37. Vincent SD, Lilly GE. Clinical, historic, and therapeutic features of aphthous stomatitis: literature review and open clinical trial employing steroids. *Oral Surg Oral Med Oral Pathol*, 1992; 74: 79-86.
  38. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: A consensus approach. *J Am Dent Assoc*, 2003; 134: 200-7.
  39. Shashy RG, Ridley MB. Aphthous ulcers: A difficult clinical entity. *An J Otolaryngol*, 2000; 21: 389-93.
  40. Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. *Dent Clin North Am*, 2005; 49: 31-47.
  41. Mimura MA, Hirota SK, Sugaya NN, Sanches JA Jr, Migliari MA. Systemic treatment in severe cases of recurrent aphthous stomatitis – Anopen trial. *Clinics*, 2009; 64: 193-8.
  42. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. *Am J Health Syst Pharm*, 2001; 58: 41-50.
  43. Scully C, Porter S. Oral mucosal disease: Recurrent aphthous stomatitis. *Br J Oral Maxillofac Surg*, 2008; 46: 198-206.
  44. Rennie JS, Reade PC, Hay KD, Scully C. Recurrent aphthous stomatitis – Review. *Br Dent J*, 1985; 159: 361-7.
  45. Zain RB. Classification, epidemiology and etiology of oral recurrent aphthous ulceration/stomatitis. *Ann Dent Univ Malaya*, 1999; 6: 34-7.
  46. Khandwala A, Van Inwegen RG, Alfano MC. 5% Amlexanox oral paste,a new treatment for recurrent minor aphthous ulcers. *Oral Surg Med Oral Pathol Oral Radiol Endod*, 1997; 83: 222-30.
  47. Murray B, McGuinness N, Biagioni P, Hyland P, Lamey PJ. A comparative study of the efficacy of Aphtheal™ in the management of recurrent minor aphthous ulceration *J Oral Pathol Med*, 2005; 34: 413-9.
  48. Murray B, McGuinness N, Biagioni P, Hyland P, Lamey PJ. The efficacy of amelxanox OraDisc™ on the prevention of recurrent minor aphthous ulceration. *J Oral Pathol Med*, 2006; 35: 117-22.

49. Rodriguez, M Rubio JA, Sanchez R. Effectiveness of two oral pastes for the treatment of recurrent aphthous stomatitis. *Oral Dis*, 2007; 13: 490-4
50. Katti G, Darshan DD. Amlexanox in the treatment of recurrent minor aphthous ulcers. *Int J Dent Clin*, 2011; 3: 23-6.