REVIEW

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Efficacy and Safety of Topical Tacrolimus in Comparison with Topical Corticosteroids, Calcineurin Inhibitors, Retinoids and Placebo in Oral Lichen Planus: An Updated Systematic Review and Meta-Analysis

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Abstract

Background: Tacrolimus is a powerful macrolide calcineurin inhibitor that has low adverse effects which lead to a rapid response in the control of signs and symptoms in comparison to that of corticosteroids in Oral Lichen Planus(OLP). There have been increasing number of studies establishing the use of topical tacrolimus in oral lichen planus. Still, there is a need to find evidence of the successful use of tacrolimus in comparison to other drugs used in the treatment of OLP, by means of a systematic review and meta-analysis, so that an informed and accurate approach can be utilized. **Methods:** A comprehensive literature review was performed, including PubMed, the Cochrane Library, published up to and including December 2021. There were no restrictions on date of publication. Articles available in English language were included. Using the Cochrane Collaboration tool, we assessed the risk of bias for randomized controlled trials. A meta-analysis was performed on the relevant studies. **Results:** A total of 11 RCTs evaluating the effects of tacrolimus were included in this study after application of inclusion and exclusion criteria. Seven studies revealed a low bias risk, three presented a moderate risk and one had a high risk of bias. The results revealed no significant difference in clinical resolution and adverse effects between tacrolimus and corticosteroids. The pooled data from our meta-analysis shows that there is not sufficient evidence to prove that Tacrolimus is better in efficacy than other topical corticosteroids. **Conclusion:** According to the current systematic study and meta-analysis, there is not sufficient evidence to prove that Tacrolimus is better in efficacy than other drugs. Uniform trials are required with larger sample sizes and standardized methodology are required for a better analysis.

Keywords: Systematic review- meta-analysis- tacrolimus- calcineurin inhibitors- oral lichen planus

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Introduction

Chronic mucocutaneous disease are known to manifest on oral mucosa causing severe discomfort to an individual thus affecting their quality of life. "Most prevalent of them is oral lichen planus, showing a global incidence of 1.01%" (González-Moles et al., 2021). These lesions are known to be immunologically mediated causing inflammatory degeneration of basal cells.

Lichen planus has been treated over the years with corticosteroids, calcineurin inhibitors, retinoids, antifungal therapy, immunomodulators etc. either systemically or by local application. Despite a diverse treatment regime, corticosteroids are the mainstay of the therapy, which are also known to cause a myriad of adverse effects.

Tacrolimus, a calcineurin inhibitor is being used as a topical agent in management of lichen planus (Rozycki et al., 2002). There have been increasing number of studies establishing the use of topical tacrolimus in oral lichen planus (OLP). Still, there is a need to find evidence of the successful use of tacrolimus in comparison to other drugs used in the treatment of OLP, by means of a systematic review and meta-analysis, so that an informed and accurate approach can be utilized. This systematic review and meta-analysis focussed on the review question- "Is Tacrolimus better in efficacy and safety as compared to other drugs in the treatment of Oral lichen planus."

Materials and Methods

Protocol And Registration

The National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews approved this systematic review for registration

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(registration number: CRD42022304013). The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 standards were followed in creating this study protocol" (Page et al., 2021).

Search Strategy

An in-depth literature search using databases from PubMed, Cochrane, and Google Scholar was done up to December 2021. The articles were selected as per the inclusion and exclusion criteria mentioned in Table 1. Two reviewers (JP and MW) screened the articles independently, and the eligible text as per inclusion criteria were selected for full text reading. In the event of a disagreement, a third reviewer (VS) was consulted before any final judgments on inclusion or exclusion were made.

Data extraction

The following data was collected from the studies: Author name and year of publication, intervention, sample size, sample design, outcome measures (Decrease in lesion size, remission of lesion, decrease in pain, adverse effects), conclusion.

Statistical Analysis

Statistical analysis was undertaken using Review Manager (RevMan) 5.3. The continuous outcome measures related to net clinical score and regression of the size of the lesion were expressed as standardized mean difference (SMD) whereas the dichotomous data related to change in size, complete resolution and recurrence of the lesion as well as occurrence of adverse events were put across as relative risks (RRs) with 95% confidence intervals (CIs). Random effect model placed P value at <0.05. Q test assessed Heterogeneity, for $p < 0.1$, as well as by the I^2 test.

Results

Literature search

Figure 1 displays the PRISMA statement flowchart summarizing the selection procedure. A total of 109 articles were identified after screening on PUBMED and COCHRANE. After removing duplicate entries (71) from the initial count of 109, there were 38 papers left. After title and abstract screening, 35 full-text articles were evaluated for eligibility. Twenty-four articles were removed after

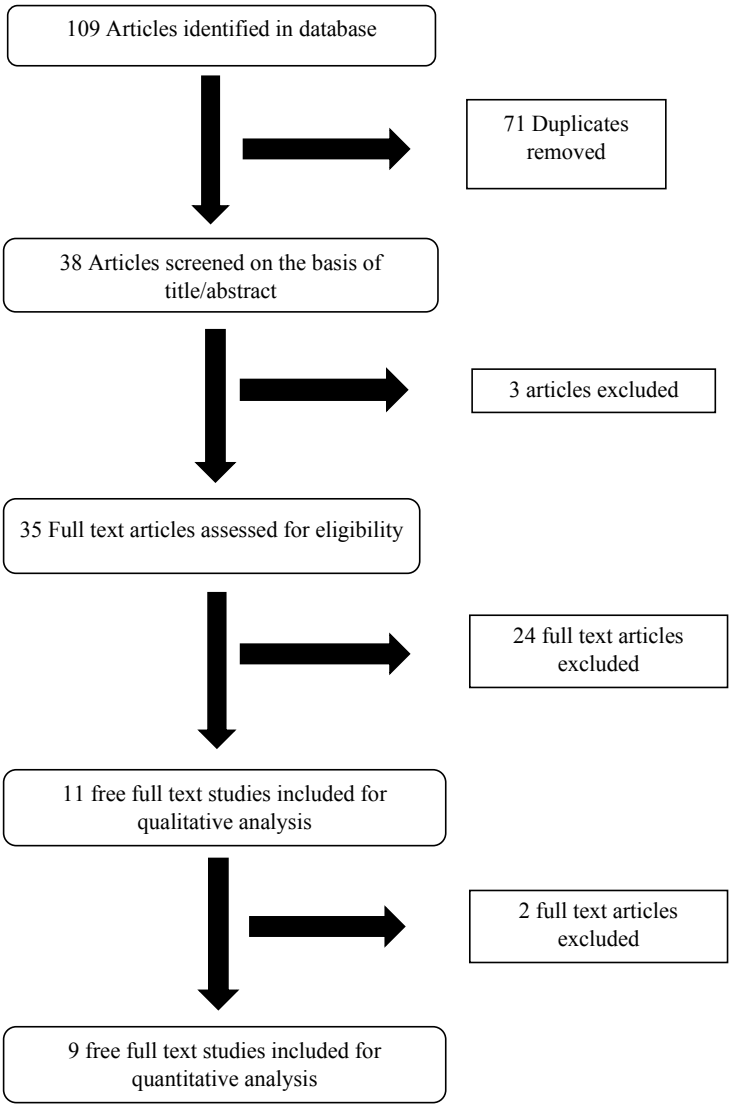

Figure 1. Flowchart of Selection of Studies

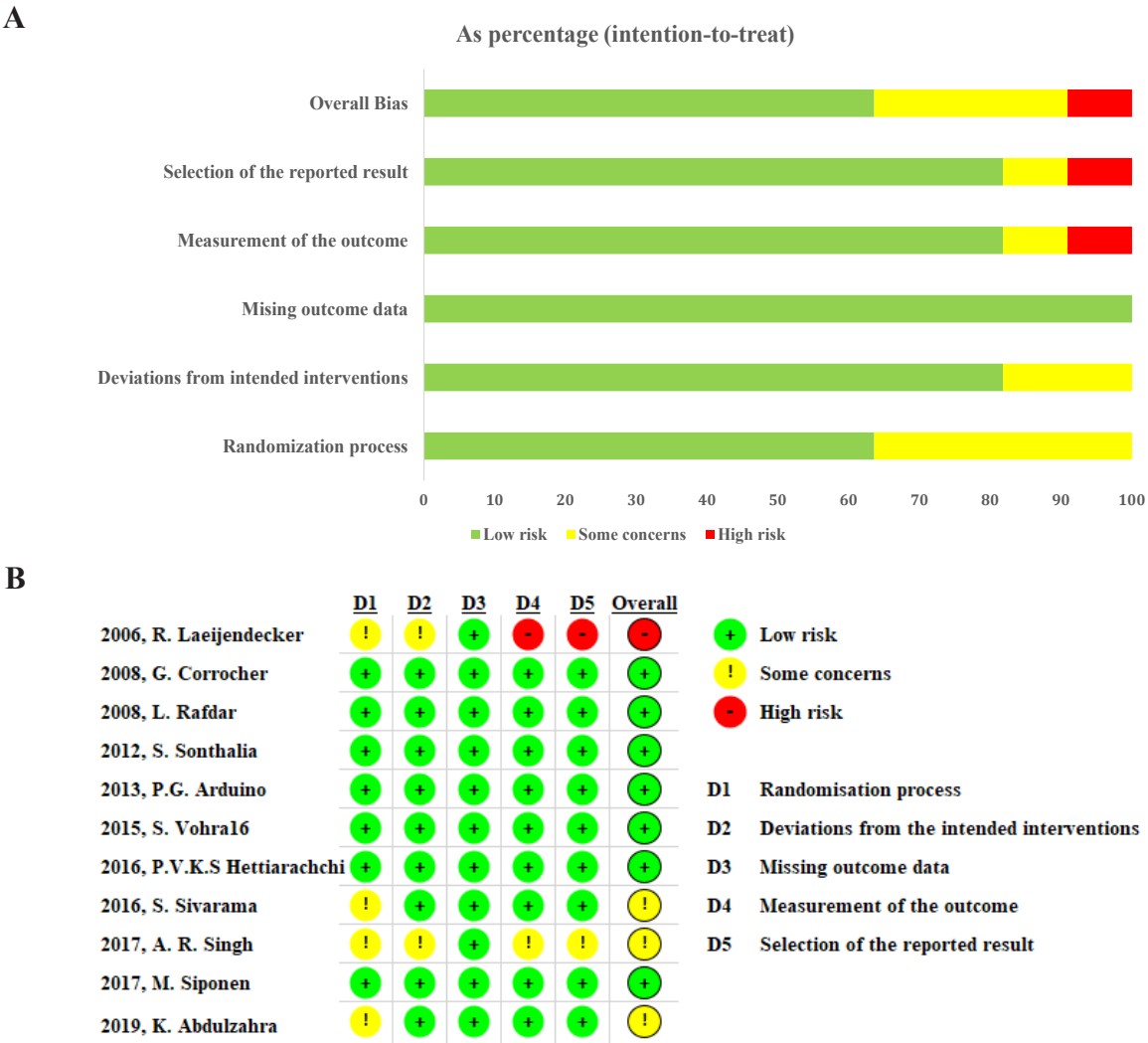

Figure 2. A, Risk of bias graph. B, Risk of bias summary

reading the complete text because they didn't match the requirements for inclusion. Finally, 11 articles were examined in the qualitative analysis, whereas 9 out of 11 articles were analyzed for quantitative synthesis.

Study Characteristics

• The characteristics of 11 studies are listed in Table 2 (Abdulzahra, 2019; Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Radfar et al., 2008; Singh et al., 2017; Siponen et al., 2017; Sivaraman et al., 2016; Sonthalia et al., 2012; Vohra et al., 2016). 10 studies were unicentric trials and 1 was a multi-centre trial (Singh et al., 2017) published between 2006 and 2015. We found 11 relevant randomized trials covering 404 participants. Four studies were conducted in Europe (Arduino et al., 2014; Corrocher et al., 2008; Laeijendecker et al., 2006; Siponen et al., 2017), four in India (Singh et al., 2017; Sivaraman et al., 2016; Sonthalia et al., 2012; Vohra et al., 2016), one each in USA (Radfar et al., 2008), Sri Lanka (Hettiarachchi et al., 2017) and Iraq (Abdulzahra, 2019). Participants in the study included both genders, aged 12 to 60 years. Ethical clearance was obtained in all 11 studies. Informed consent was obtained in 9 studies whereas 2 studies did not provide any information about consent (Abdulzahra, 2019; Radfar et al., 2008). The review comprised a total of 405 participants. Nine studies comprised the meta-analysis.

• There was a considerable amount of methodological variability amongst the studies. This might be explained by variations in the intervention drug's concentration

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Randomized controlled trials (RCT's) evaluating tacrolimus with other drugs in treatment of oral lichen planus irrespective of drug dosage, drug delivery vehicle, treatment and follow-up period, outcome	Non-randomized controlled trial, cohort, case reports, case series, cross sectional studies, meta-analysis
Full-text articles	Paid articles or those that were unavailable as full-text
Articles in English language	Articles not available in English language

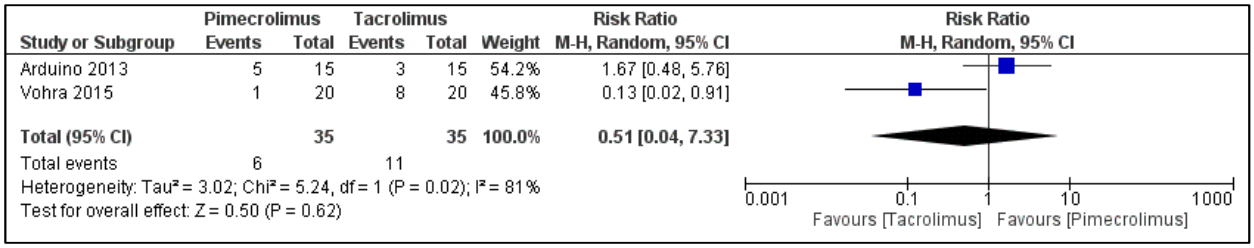

Figure 3. Forest Plot Comparing Tacrolimus with Pimecrolimus for the Occurrence of Adverse Event

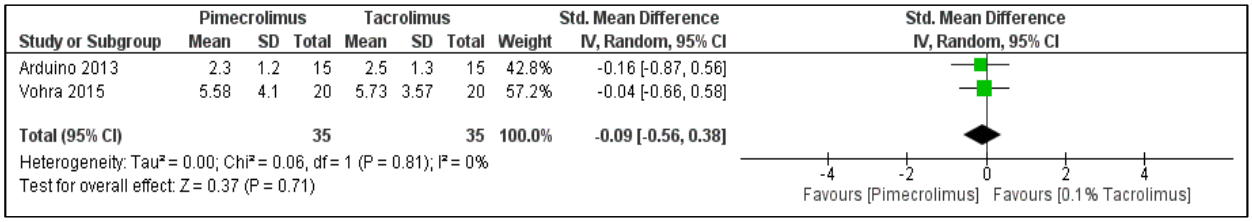

Figure 4. Forest Plot Comparing Tacrolimus with Pimecrolimus for the Net Clinical Score after 8 Weeks of Treatment

(Tacrolimus- 0.1% (Abdulzahra, 2019; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Radfar et al., 2008; Singh et al., 2017; Siponen et al., 2017; Sonthalia et al., 2012; Vohra et al., 2016) , 0.01% (Chainani-Wu et al., 2008) ,0.05% (Arduino et al., 2014)) and comparator drugs (Triamcinolone acetonide- 0.1% (Laeijendecker et al., 2006; Singh et al., 2017; Siponen et al., 2017; Sivaraman et al., 2016), Clobetasol propionate 0.05% (Corrocher et al., 2008; Hettiarachchi et al., 2017; Radfar et al., 2008; Sivaraman et al., 2016; Sonthalia et al., 2012), Pimecrolimus 0.5%8 (Arduino et al., 2014), 1% (Vohra et al., 2016), Isotretinoin gel 0.1% (Abdulzahra, 2019) being used, number of applications of intervention and comparator in a day (4 times/day (Abdulzahra, 2019; Corrocher et al., 2008; Laeijendecker et al., 2006; Sivaraman et al., 2016), 3 times/day (Siponen et al., 2017), 2 times/day (Arduino et al., 2014; Hettiarachchi et al., 2017; Singh et al., 2017; Sonthalia et al., 2012; Vohra et al., 2016) , tapering dose form (Radfar et al., 2008)) and duration of treatment period (12 weeks (Singh et al., 2017), 8 weeks (Arduino et al., 2014; Sonthalia et al., 2012; Vohra et al., 2016), 6 weeks (Abdulzahra, 2019;

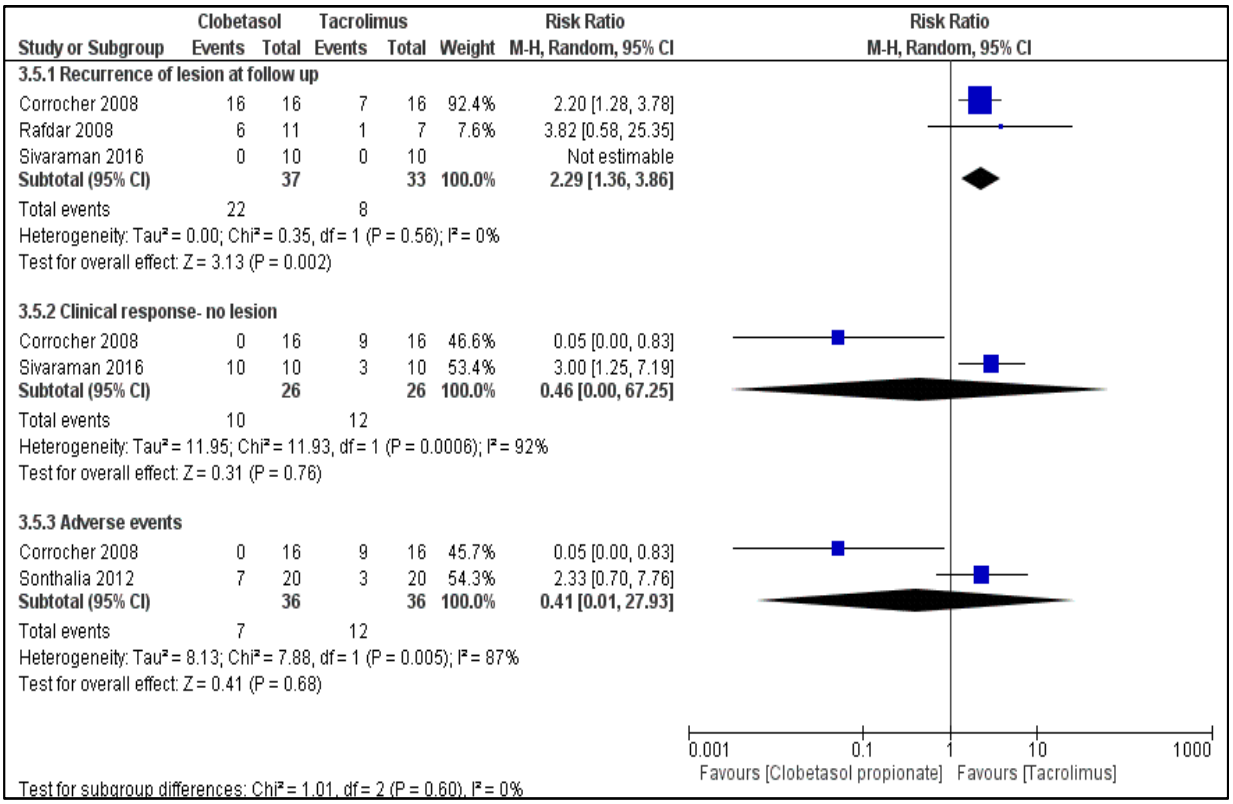

Figure 5. Forest Plot Comparing Tacrolimus with Triamcinolone Acetonide for the Regression of the Size of the Lesion and the Occurrence of Adverse Event

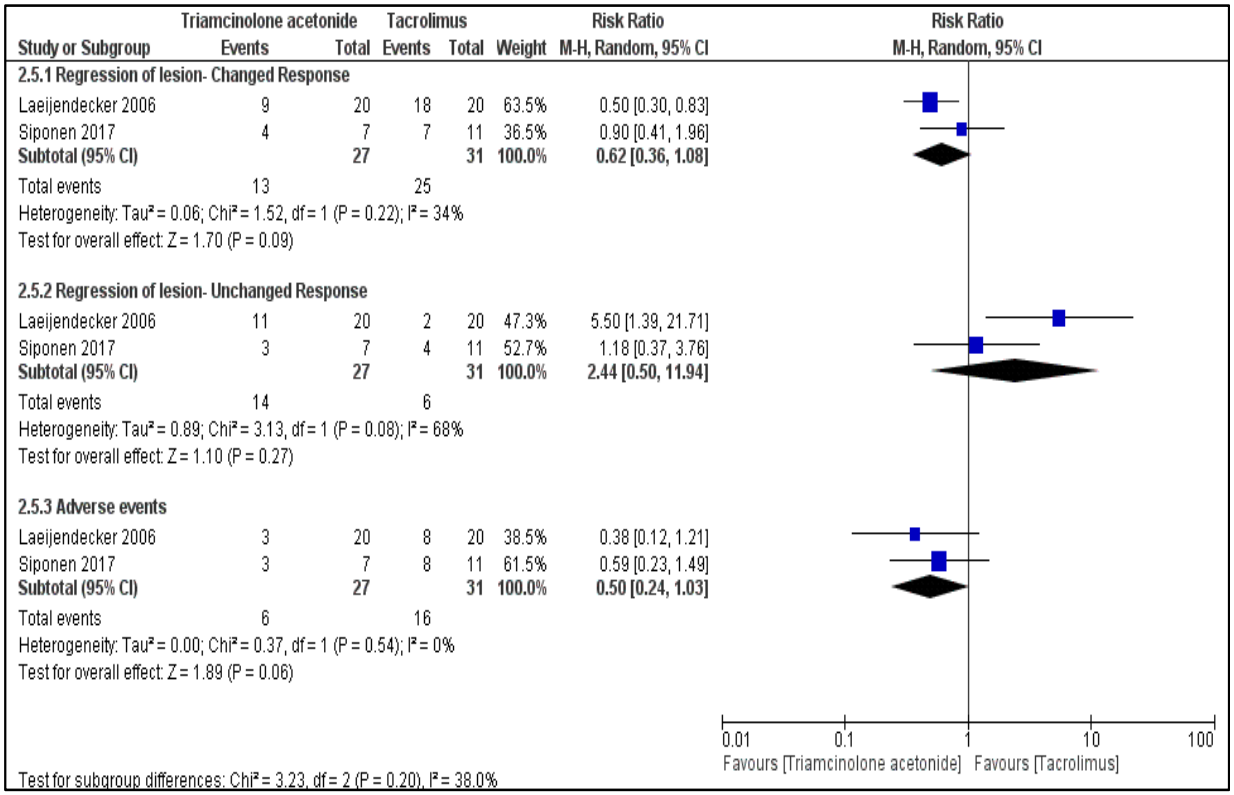

Figure 6. Forest Plot Comparing Tacrolimus with Clobetasol for the Recurrence of the Lesion at Follow up, the Clinical Response Score Showing Complete Resolution of the Lesion and the Occurrence of Adverse Event

Laeijendecker et al., 2006; Radfar et al., 2008; Siponen et al., 2017; Sivaraman et al., 2016), 4 weeks (Corrocher et al., 2008), 3 weeks (Hettiarachchi et al., 2017))

• The post-intervention outcome measures differed between the studies. The decrease or regression in lesion size was assessed as the primary outcome measure by using different scales in the studies. The most commonly used scale was the Thongprassom scale which was used in 3 studies (Abdulzahra, 2019; Arduino et al., 2014; Hettiarachchi et al., 2017) followed by the modified version of Piboonniyom et al. scale in 2 studies (Sonthalia et al., 2012; Vohra et al., 2016). Ordinal score was used in 1 study (Laeijendecker et al., 2006), four point scale was used in 1 study (Corrocher et al., 2008). One study each used the staging given by Farzaneh Agha - Hosseini et al. (Sivaraman et al., 2016), Kaliakatsou et al. (Singh et al., 2017) and modified clinical score by Setterfield et al. (Siponen et al., 2017) One study (Radfar et al., 2008) did not use any score or staging but measured the lesion size in cm^2.

• Pain was evaluated in 7 studies. While 4 studies used the VAS scale (Arduino et al., 2014; Hettiarachchi et al., 2017; Radfar et al., 2008; Siponen et al., 2017), 1 study each used the four point scale (Corrocher et al., 2008) and the pain and burning sensation according to Raj et al (Singh et al., 2017). One study did not clearly specify the scale but the rating used was same as that of VAS scale (Abdulzahra, 2019).

• Number of participants facing adverse effects during the treatment period were evaluated in 7 studies (Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Siponen et al., 2017; Sonthalia et al., 2012; Vohra et al., 2016) while 2 articles mentioned the adverse effects faced but not number of participants/ groups (Radfar et al., 2008; Singh et al., 2017).

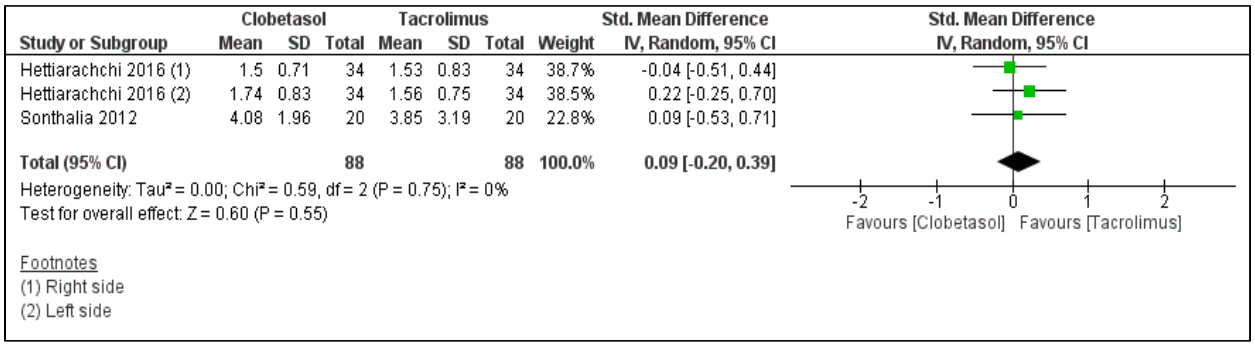

Figure 7. Forest Plot Comparing Tacrolimus with Clobetasol Propionate for the Regression of the Size of the Lesion after 4-5 Weeks of Treatment

Table 2. Selected Studies for Inclusion in Systematic Review

Sr. No.	Year Of Publication	Interventions	No. Of Participants	Type Of Study	Outcomes	Adverse Effects	Conclusion
1	2006, R. Laeijendecker11 - Rotterdam, The Netherlands	Group 1: topical tacrolimus0.1% ointment 4 times daily Group 2: triamcinolone acetonide 0.1% in Hypromellose 20% ointment 4 times daily	40 Group 1: 20 Group 2: 20	prospective randomized study	Primary outcome measure: Assessment of extent and the severity of the lesion No. of participants showing complete healing (Tacrolimus) = 6 No. of participants showing complete healing (Triamcinolone) = 2 No. of participants showing improvement (Tacrolimus) = 12 No. of participants showing improvement (Triamcinolone) = 7 Secondary outcome measure: Side-effects Tacrolimus = 8 Traimcinolone = 3	Both groups: Transient irritation including burning or stinging at the site of application lasting for about 10–30 min.	Topical tacrolimus 0.1% was significantly more effective than triamcinolone acetonide 0.1%
2	2008, G. Corrocher12 - Verona, Italy	1. 2 ml of tacrolimus 0.1% ointment (equivalent to 0.2 mg of tacrolimus), 4 times daily for 4 weeks 2. 2 ml of clobetasol propionate 0.05% ointment (equivalent to 1 mg of clobetasol), 4 times daily for 4 weeks	32 Group 1: 16 Group 2: 16	Randomized, double-blind clinical trial	Primary outcome measure : Reduction in mucosal lesion extension based on four-point scale Median score (Tacrolimus) : 0 (Clobetasol) : 1 Secondary outcome measure: Decrease in pain and burning sensation based on four-point scale Median score of pain (Tacrolimus) : 0 (Clobetasol) : 1 Median score of burning sensation (Tacrolimus) : 0 (Clobetasol) :1 Adverse events: Tacrolimus= 9/16 Clobetasol = 0/16	Tacrolimus group: Initial worsening of burning sensation during the first 2 days of treatment n=9	Topical tacrolimus 0.1% ointment was significantly more effective than topical clobetasol propionate 0.05% ointment
3	2008, L. Rafdar13 - Buffalo, New York; and Oklahoma City, Oklahoma	1. Clobetasol 0.05% 4 times/day for 2 weeks followed by 3times/day for 2 weeks, 2 times/day for 1 week, and 1 time/day for 1 week. 2. Tacrolimus 0.1% ointment 4 times/day for 2 weeks followed by 3 times/day for 2 weeks, 2 times/day for 1 week, and 1 time/day for 1 week	Enrolled in study: 30 Patients: 29 Tacrolimus group = 15 Clobetasol group = 14	Randomized double-blind study	Primary outcome measure: Change in the target lesion size Mean (Tacrolimus) : 0.924 (Clobetasol) : 0.906 Secondary outcome measure: Pain evaluation by visual analog scale (VAS) Mean (Tacrolimus) : 1.32 Mean (Clobetasol) : 1.96	Not specified-burning sensation (n=1) Clobetasol-upset stomach and nausea (n=1)	Clobetasol = Tacrolimus Most of the patients treated in this study expressed a significant improvement in quality of their life in terms of eating well and performing oral hygiene without discomfort.
4	2012, S. Sonthalia14 - Delhi, India	1. clobetasol propionate (0.05%) ointment 2. tacrolimus (0.1%) ointment for eight weeks.	40 Clobetasol group: 20 Tacrolimus group: 20	Randomized, double-blind clinical trial	Primary outcome measure: complete response rate (CRR)- percentage of patients attaining complete response at eight weeks of the study. (Tacrolimus) = 70% (Clobetasol) = 40% Secondary outcome measures : 1.percentage of patients attaining complete or partial response at eight weeks (Tacrolimus) = 95% (Clobetasol) = 70% 2.percentage of patients attaining complete or partial response at 12 weeks. (Tacrolimus) = 95% (Clobetasol) = 90%	Both groups: transient burning sensation following the application of the ointment, which lasted for a few seconds to a few minutes (n=3 in each group) Clobetasol group: Secondary candidal infection (n=4)	Both were found to be efficacious Tacrolimus> Clobetasol in patients who are at risk for developing oral candidiasis

Table 2. Continued

Sr. No.	Year Of Publication	Interventions	No. Of Participants	Type Of Study	Outcomes	Adverse Effects	Conclusion
5	2013, P.G. Arduino15 - Turin. Italy	Group 1: pimecrolimus 0.5% cream mixed with a hydroxyethyl cellulose adhesive gel Group 2: tacrolimus 0.05% ointment in the same adhesive medium	30 Group 1: 15 Group 2: 15	randomized, double-blind controlled trial	Primary outcome measure: Decrease in lesion size (Tacrolimus)= 2.5 (Pimecrolimus)=2.3 Secondary outcome measure: Decrease in pain (VAS) (Tacrolimus)= 1.8 (Pimecrolimus) = 1.9	Pimecrolimus group: Xerostomia (n=2), episodes of gastroesophageal reflux (2), recurrence of two lesions of herpes labialis (1) Total n= 5 Tacrolimus group: mucosal burning sensation during the first days of the therapy (n=2) and one reported a transient sialorrhoea. Total n= 3	Both are effective in treating OLP Pimecrolimus is more effective in providing long-term resolution of signs and symptoms.
6	2015, S. Vohra16 - Delhi, India	Group A= tacrolimus 0.1% ointment Group B= pimecrolimus 1% cream	40 Group A: 20 Group B: 20	prospective randomized, investigator blinded controlled trial	primary outcome measure: decline in NCS (net clinical score) Mean score (Tacrolimus)= 5.73 (Pimecrolimus)= 5.58 Secondary outcome measure: change in serum IL-6 levels after treatment Mean (Tacrolimus)= 11.40 (Pimecrolimus)= 10.39 Change in IL-8 level after treatment: Mean (Tacrolimus)= 11.75 (Pimecrolimus)= 11.61	Tacrolimus group: Transient burning sensation (n=6), dysgeusia (n=2); Total n= 8 Pimecrolimus group: Transient burning sensation (n= 1)	Both were found to be efficacious
7	2016, P.V.K.S Hettiarachchi17 - Peradeniya, Sri Lanka	1. clobetasol propionate (0.05%) cream 2. tacrolimus (0.1%) cream	68 Group 1: 34 Group 2: 34	randomized, comparative, double-blind study	Primary outcome measure: Decrease in lesion size (Thongprassom classification) for left and right side separately Mean (Tacrolimus) Right side =1.88 Left side=1.94 Mean (Clobetasol) Right side = 1.79 Left side = 1.79 Secondary outcome measure: Decrease in pain (VAS scale) for left and right side separately Mean (Tacrolimus) Right side = 0.71 Left side = 0.76 Average = 0.735 Mean (Clobetasol) Right side = 0.79 Left side = 0.74 Average =0.765	No adverse effects identified in both groups	Topical tacrolimus 0.1% was significantly more effective than topical clobetasol propionate 0.05%
8	2016, S. Sivaraman18 - Pondicherry, India	Group 1- Triamcinolone acetonide 0.1 % Group 2- clobetasol propionate 0.05% Group 3- tacrolimus 0.03%	30 Group 1: 10 Group 2: 10 Group 3: 10	Prospective randomized , triple-blind clinical trial	Primary outcome measure: Lesion size based on staging by Farzaneh Agha-Hosseini et al Mean (Clobetasol) = 9.0 (Triamcinolone acetonide) = 12.0 Mean (Tacrolimus)= 12.8 (Triamcinolone acetonide) = 8.2 Mean (Tacrolimus) = 14.0 (Clobetasol propionate) = 7.0	Not mentioned in article	clobetasol propionate 0.05% ointment has higher efficacy when compared to triamcinolone acetonide 0.1% ointment and tacrolimus ointment 0.03% Triamcinolone 0.1% > tacrolimus 0.03%

Table 2. Continued

Sr. No.	Year Of Publication	Interventions	No. Of Participants	Type Of Study	Outcomes	Adverse Effects	Conclusion
9	2017, A. R. Singh19 - Allahabad, India	1. 0.1 % triamcinolone acetonide buccal paste 2. Oral dapsone 100 mg twice daily + iron and folic acid tablets 3. Topical tacrolimus 0.1 %, twice daily 4. Topical retinoid, twice daily	40 Group 1: 10 Group 2: 10 Group 3: 10 Group 4: 10	open label, parallel and comparative randomized study	Primary outcome measure: Signs according to Kaliakatsou et al Mean (Oral dapsone)=0.1 (Topical retinoid)= 0.7 (Topical tacrolimus) = 0.6 (Topical steroid) = 0.4 Secondary outcome measure: Symptoms according to Raj et al and Mean (Oral dapsone)= 0.4 (Topical retinoid)= 1.0 (Topical tacrolimus) = 0.7 (Topical steroid) = 0.7	Topical agents: Mild tingling in the oral cavity in patients (n= not specified)	1.Oral dapsone > all 2. Topical triamcinolone acetonide= topical tacrolimus= topical retinoid
10	2017, M. Siponen20 - Oulu, Finland	Group 1: 0.1% Tacrolimus ointment Group 2: 0.1 % Triamcinolone Acetonide paste Group 3: Placebo	27 Group 1: 11 Group 2: 7 Group 3: 9	Multi-center, double-blind (first 3-6 weeks), placebo-controlled parallel pilot RCT	Primary outcome measure: change in clinical score (CS) from baseline to week 3 Mean decrease (Tacrolimus) = 10.5 Mean decrease (Triamcinolone) = 10.3 Mean increase (Placebo) = 0.22 Secondary outcome measure: 1) the changes in CS from baseline to week 6 (and 9 if relevant) and to 6 months; Mean CS (Tacrolimus) = decreased from baseline Mean CS (Triamcinolone) = increased, but remained below the baseline 2) the changes in visual analogue scale (VAS) scores measured at visits and at home from baseline to weeks 3 and 6 (and 9 if relevant), and to 6 months; At week 3, Mean VAS (Tacrolimus) was equal to mean VAS of (Triamcinolone). Mean VAS (Placebo) = remained same as baseline 3) the changes in VAS scores measured at home from start of follow-up to weeks 1-8, 9-16 and 17-24. Mean VAS (Tacrolimus) remained the same as start of follow-up Mean VAS (Triamcinolone) increased as compared to start of follow-up.	Tac group: burning sensation, increased sensitivity of the oral mucosa to hot, cold and spicy food or drink, altered taste sensation, unpleasant sensation in the mouth, sensation of dryness, and hoarseness. Systemic adverse effects such as nausea, headache and nightmare (n=73%) Tri group: Smarting sensation in the mouth and tenderness in the gingiva (n=43%) Placebo group: burning and sensitivity to hot food or drink, soreness of the gingiva, and increased salivary flow after applying the paste (n=33%)	1. Tacrolimus= Triamcinolone acetonide 2. Tacrolimus> Placebo 3. Triamcinolone acetonide> Placebo
11	2019, K. Abdulzahra21 - Najaf, Iraq	Group A: Tacrolimus gel 0.1% Group B: Isotretinoin 0.1% gel	28 Group A: 14 Group B: 14	Double blind, randomized controlled trial	Primary outcome measure: change in lesion size based on Thongprassom et al criteria Mean (Tacrolimus) = 1.64 (Isotretinoin) = 2.42 Secondary outcome measure: Pain according to numerical scale Mean (Tacrolimus) = 0.92 (Isotretinoin) = 2.07	Not mentioned in article	Tacrolimus 0.1% is better than Isotretinoin 0.1% gel

• Qualitative analysis was conducted for all 11 articles while only 9 articles satisfied the requirements for inclusion in the meta-analysis (Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Radfar et al., 2008; Siponen et al., 2017; Sivaraman et al., 2016; Sonthalia et al., 2012; Vohra et al., 2016). The 2 articles excluded did not have similar comparator groups or analytical method of evaluating lesion size (Abdulzahra, 2019; Singh et al., 2017).

Risk of Bias and Quality

• The Cochrane Risk of Bias Tool was used to evaluate the quality of all 11 RCTs. Seven studies revealed a low bias risk (Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Radfar et al., 2008; Siponen et al., 2017; Sonthalia et al., 2012; Vohra et al., 2016), three presented a moderate risk (Abdulzahra, 2019; Singh et al., 2017; Sivaraman et al., 2016) and one had a high risk of bias (Laeijendecker et al., 2006). Only 3 out of 11 studies declared receiving funding for the research (Corrocher et al., 2008; Radfar et al., 2008; Siponen et al., 2017).

•Refer to Figure 2 a and 2 b.

Synthesis Of Results

Nine articles (Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Radfar et al., 2008; Siponen et al., 2017; Sivaraman et al., 2016; Sonthalia et al., 2012; Vohra et al., 2016) in total met the requirements for inclusion in the quantitative analysis. Eight meta-analyses, one of which included a subgroup analysis, were then carried out to evaluate the clinical success and adverse events of Tacrolimus compared with Pimecrolimus, Clobetasol propionate and Triamcinolone acetonide irrespective of their concentrations.

The meta-analysis (Figure 3) assessing the risk of occurrence of adverse events between Tacrolimus and Pimecrolimus groups was conducted using random effect model and Mantel Haenszel method of Risk ratio. The risk of occurrence of adverse events was 0.51 folds higher in Tacrolimus as compared to Pimecrolimus but significant difference was not observed in the risk ratio among the two groups. (RR: 0.51 95% CI = 0.04-7.33, p = 0.62, I^2=81%).

The meta-analysis (Figure 4) assessing the mean net clinical score after 8 weeks of treatment comparing Tacrolimus with Pimecrolimus was conducted utilising the random effect model. The standardized mean difference showed an insignificant difference in the net clinical score after 8 weeks of treatment among patients of both the group (SMD, -0.09, 95% CI = -0.56- 0.38, p=0.71, I^2=0%).

The meta-analysis (Figure 5) assessing the regression of the size of the lesion and the risk of occurrence of adverse events between Tacrolimus and Triamcinolone acetonide groups was completed utilising a random effect model for subgroup analysis and Mantel Haenszel method of Risk ratio. No discernible difference in the risk ratio was found between the groups in the regression of the size of the lesion- change response (RR: 0.62 95% CI = 0.36-1.08, p = 0.09, I^2=34%) and unchanged response (RR: 2.44 95% CI = 0.50-11.94, p = 0.27, I^2=68%), both favoring the Tacrolimus group. The risk of occurrence of adverse events was 0.50 folds higher in Tacrolimus as compared to Triamcinolone acetonide but no significant difference was observed in the risk ratio among the two groups. (RR: 0.50 95% CI = 0.24-1.03, p = 0.06, I^2=0%).

The meta-analysis (Figure 6) comparing Tacrolimus and Clobetasol groups for the occurrence of adverse events, clinical response score demonstrating complete resolution of the lesion, and recurrence of the lesion at follow-up was conducted as a subgroups analysis using the random effect model and Mantel-Haenszel method of Risk ratio. The recurrence of the lesion at follow-up was 2.29 folds higher in Clobetasol propionate group. At follow-up, a significant difference in risk ratio for lesion recurrence was seen across the groups. (RR: 2.29 95% CI = 1.36-3.86, p = 0.002, I^2=0%) favouring the Tacrolimus group.

Although the Tacrolimus group had a 0.46-fold greater rate of complete remission of lesion with a clinical score of 0, there was no significant difference in the risk ratio between the two groups. (RR: 0.46 95% CI = 0.00-67.25, p = 0.76, I^2=92%). Additionally, Tacrolimus had a 0.41-fold higher risk of adverse events than Clobetasol propionate, although there was no significant difference in the risk ratio between the two groups. (RR: 0.41 95% CI = 0.01-27.93, p = 0.68, I^2=87%).

The meta-analysis (Figure 7) assessing the regression of the size of the lesion after 4-5 weeks of treatment comparing Tacrolimus with Clobetasol propionate was conducted using random effect model. The study conducted by Hettiarachchi et al, assessed the regression in the size of the lesion for right and left side separately, so for the purpose of analysis the single study was considered twice. The standardized mean difference showed an insignificant difference in regression of the size of the lesion after 4-5 weeks of treatment among patients of both the group (SMD, 0.09, 95% CI = -0.20-0.39, p=0.55, I^2=0%).

Discussion

OLP is a chronic disease of the oral cavity that may or may not be symptomatic and rarely undergoes spontaneous remission (Alrashdan et al., 2016). Though many treatment modalities have been used in the past, it does not have a definitive cure. Multiple treatment modalities have been employed in the past for treatment of OLP but not sufficient data is available to suggest that a specific treatment modality is most effective. This systematic review was done based on randomized clinical trials only following a rigorous search & in-depth analysis of the treatment outcomes in relation to topical Tacrolimus & other agents in managing OLP. According to the Oxford Centre for Evidence-based Medicine's levels of evidence standards, this systematic review and meta-analysis of clinical trials provides level 1 evidence for assessing the effectiveness of Tacrolimus in comparison to other medications in the treatment of OLP (Oxford Centre for Evidence-Based Medicine- Levels of evidence, 2009). Eleven studies from multiple countries that were published between 2006 and 2015 were included in the review. All 11 articles were randomized control trials. Participants in the study included both genders, aged 12 to 60. A total

of 9 studies (Arduino et al., 2014; Corrocher et al., 2008; Hettiarachchi et al., 2017; Laeijendecker et al., 2006; Radfar et al., 2008; Siponen et al., 2017; Sivaraman et al., 2016; Sonthalia et al., 2012; Vohra et al., 2016) met the requirements for inclusion in the quantitative analysis. The results of this systematic review and meta-analysis can therefore be applied to a large group of people.

In a detailed evaluation of the comparator drugs used vs. Tacrolimus of the above selected studies, various standards were used to evaluate the effectiveness of the medications. including lesion size, pain & adverse effects. In this systematic review, decrease or resolution in lesion size was observed as the primary efficacy outcome. Lesion size was assessed in all the trials, albeit the method of assessment (grading/scale/score) varied. Decrease in signs and symptoms, recurrence of lesion were considered as secondary outcome efficacy. The most commonly used scale for evaluation of signs and symptoms was the VAS scale. Adverse effects observed determined the safety of the drug used. Additionally, there was methodological variation in terms of the research location, study environment, sample size, number and experience of investigators performing procedures and diagnosis, concentration of intervention and comparator drug as well as the treatment duration. A meta-analysis utilising a random-effects model was used to account for this heterogeneity. Based on the clinical success rate, a meta-analysis of the data from 9 trials that met the inclusion criteria was conducted.

Most of the studies evaluated clinical resolution based on Thongprassom classification, which is one of the oldest scoring system developed (Abdulzahra, 2019; Arduino et al., 2014; Hettiarachchi et al., 2017). The most commonly used form and usage of Tacrolimus in these studies was 0.1% 4 times/daily. The most commonly used comparator drug was Clobetasol propionate 0.05% ointment 4 times/day. Treatment duration of these studies varied from 3-12 weeks but most common treatment duration was 6 and 8 weeks. Though the most commonly prescribed treatment duration is 2 weeks, but longer treatment periods have been advised for attempting complete remission of lesion and symptoms (Edwards et al., 2002). Tacrolimus showed almost equal efficacy as compared to other drugs based on the qualitative analysis.

The majority of studies employ the visual analogue scale (VAS) scale as the secondary outcome measure to assess pain (Arduino et al., 2014; Hettiarachchi et al., 2017; Radfar et al., 2008; Siponen et al., 2017). This is an extensively used scale which has been demonstrated to have good validity in the past (Chainani-Wu et al., 2008). On qualitative analysis of the data, it was found that Tacrolimus proved to be a better treatment modality in decreasing symptoms i.e., pain if not as efficacious as compared to other drugs.

The adverse effects were relatively higher in the Tacrolimus groups than other drugs, though most of the adverse effects seen were mild and temporary. Only 1 study reported of systemic adverse effects due to Tacrolimus (Siponen et al., 2017). In March 2005, the FDA released a public health advice concerning the possibility of developing cancer from using tacrolimus, and a 'black box' warning followed. This research was based on case studies in a small number of patients and animal studies (Wooltorton, 2005). Hence, Tacrolimus should be used cautiously for a shorter duration of time because the potential adverse effects of long-term use of Tacrolimus are not completely known.

Regression in lesion size

On comparison of Tacrolimus with Pimecrolimus and Tacrolimus with Clobetasol propionate, it was noted that both groups showed an insignificant difference. Narrow confidence intervals were noted in the forest plot. There was no heterogeneity noted between the groups (Figure 4 and 7).

In comparison of Tacrolimus with Triamcinolone acetonide, wide confidence intervals (CIs) were seen in the forest plot analysis, which may have contributed to the heterogeneity shown by I^2 estimates., i.e., 34%, for regression of size of the lesion-change response and 68% for unchanged response, with non-significant difference favouring the Tacrolimus group. (Figure 5) The wide confidence interval can be attributed to small size of sample and the actuality that only two studies were included in this analysis.

Complete resolution of lesion

In comparison of Tacrolimus with Clobetasol propionate for complete resolution of lesion size, Tacrolimus was more favourable however I^2 was observed to be 92% showing high heterogeneity. The studies did not show any significant difference in both groups. (Figure 6) The high heterogeneity could be due to the different dosages of the drugs.

Adverse effects

On comparison of adverse effects seen on comparing Tacrolimus with Pimecrolimus, an observation was made that patients treated with Tacrolimus were more prone to develop adverse effects than those with Pimecrolimus with a high heterogeneity of 81%. However, it was insignificant. The wide CIs observed could be due to the small sample size as well as difference in the dosages of drugs used, thus contributing to high heterogeneity seen in this analysis (Figure 3).

Similar results were noted on comparing Tacrolimus with Triamcinolone acetonide and Clobetasol propionate, where Tacrolimus had higher adverse effects but no significant difference was observed in both the forest plots (Figure 5 and 6).

Recurrence of lesion at follow-up

Clobetasol propionate group showed more recurrence at follow-up than Tacrolimus group with no heterogeneity noted. This difference was significant (p=0.002) (Figure 6).

The pooled data from our meta-analysis shows that there is not sufficient evidence to prove that Tacrolimus is better in efficacy than other topical corticosteroids. Our study's findings are consistent with earlier systematic reviews and meta-analyses (Guo et al., 2015; Sridharan et al., 2021; Su et al., 2022).

Nevertheless, the present review has its limitations. The

different concentrations and dosages of the intervention and comparator drugs, choice of delivery vehicle, number of applications, clinical scores used, duration of treatment, follow-up and the smaller sample size used could have inadvertently caused the potential heterogeneities across these studies. Thus, it is suggested that a uniform method of analysis of signs and symptoms be formulated for all future studies.

That being said, Tacrolimus can be prescribed with cautiousness only in patients with recalcitrant lesions or at risk of developing candidiasis, as it is a known complication of corticosteroid therapy, after confirming diagnosis based on histology (Sonthalia et al., 2012).

According to the current systematic study and meta-analysis, there is not sufficient evidence to prove that Tacrolimus is better in efficacy than other drugs. Uniform trials with larger sample sizes and standardized methodology are required, so that better analysis can be performed.

Author Contribution Statement

JP: Conceptualization; Data curation and analysis; Investigation (1st investigator); Methodology; Software; Writing-original draft; Writing-review & editing. MW: Conceptualization; Data curation and analysis; Investigation (2nd investigator); Methodology; Software; Writing-original draft; Writing-review & editing. KB: Statistical analysis, Writing-original draft; Writing-review & editing. VS: Investigation (3rd investigator); Methodology; Writing-original draft. RM: Writing-review & editing. SS: Writing-review & editing. All authors reviewed and accepted the final version of the manuscript

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Ethics approval

This study does not need ethics approval as it is a meta-analysis.

Data Availability Statement

This manuscript used data previously published by other authors and all data are presented into the manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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