Comparative efficacy of antiviral agents for prevention and management of herpes labialis: A systematic review and network meta-analysis

Kim Hoe Koe, Sajesh K Veettil, Mari Kannan Maharajan, M Sakil Syeed, Athira Balakrishnan Nair, and Divya Gopinath

School of Postgraduate Studies, International Medical University, Kuala Lumpur 57000, Malaysia

Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, USA

School of Pharmacy, University of Nottingham Malaysia, Semenyih, 43500, Malaysia

Freelancer, Evidence Synthesis

Basic Medical and Dental Sciences Dept, College of Dentistry, Ajman University, P O Box 346, UAE

Centre for Transdisciplinary Research, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India

Abstract

Objective: To compare the relative efficacy and safety of antiviral agents used in the prevention and management of herpes labialis through a network meta-analysis of clinical trials.

Methods: A systematic search was performed in Ovid Medline PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Clinicaltrials.gov for randomized controlled trials (RCTs) reporting a comparison of antiviral agents in the management and prevention of herpes labialis in healthy/immunocompetent adults. The data extracted from the selected RCTs were assessed and a network meta-analysis (NMA) was performed. The interventions were ranked according to the surface under the cumulative ranking (SUCRA).

Results: A total of 52 articles were included for qualitative synthesis and for the quantitative part, 26 articles were analyzed for the primary treatment outcome and 7 studies were analyzed for the primary prevention outcome. The combination therapy of oral valacyclovir and topical clobetasol was the best ranked with a mean reduction in healing time of -3.50 (95% CI -5.22 to -1.78) followed by vidarabine monophosphate of -3.22 (95% CI -4.59 to -1.85). No significant inconsistencies, heterogeneity, and publication bias were reported for TTH outcome analysis. For primary prevention outcomes, only 7 RCTs fulfilled the inclusion criteria, and none of the interventions was shown to be superior to each other. The absence of adverse events was reported by 16 studies, whereas other studies reported mild side effects only.

Conclusion: NMA highlighted that several agents were effective in the management of herpes labialis among which the combination of oral valacyclovir with topical clobetasol therapy was the most effective in reducing the time to heal. However, further studies are required to determine which intervention is the most effective in preventing the recurrence of herpes labialis.

Keywords: Herpes labialis; efficacy; antiviral agents; treatments; prevention; management; systematic review; network meta-analysis

Correspondence

Divya Gopinath, Basic Medical and Dental Sciences Dept, College of Dentistry, Ajman University, P O Box 346, UAE. E-mails: divyagopinath@imu.edu.my; d.gopinath@ajman.ac.ae

Conflict of Interest

The authors declare no conflict of interest.

Source of Funding

This research did not receive any external funding.

1. Introduction

Herpes labialis is an infectious disease caused by herpes simplex virus type 1 (HSV-1) in the orofacial region and is especially common in infants and adolescents. The chances of herpes labialis recurrence are common among individuals, where the infection is generally contagious during times of active replication but can also spread when symptoms are absent. 1, 2 After the initial exposure, the primary infection spreads to sensory nerve cells and establishes latent infections. 1 The primary infection with HSV-1 may be asymptomatic or manifest as erythematous vesicles, which later rupture to form encrusting ulcers. The HSV virus incorporated in the ganglions awaits a stimulus to initiate viral replication. 1–3

The disease progression in recurrent herpes simplex labialis (HSL) typically incorporates multiple stages. The resurgence of labial HSV is typically triggered by many factors, including stress, trauma from surgery/operations, infectious febrile ailments, and certain drugs like corticosteroids. 2, 3 Although several management strategies are available for the treatment of recurrent herpes labialis nucleoside analog inhibitors including acyclovir, valacyclovir, penciclovir, and famciclovir are considered appropriate choices as they overcome some of the constraints of other interventions. 4 However the treatment is only considered effective if started as soon as the appearance of symptoms (within 24-48 hours). At the same time, there is limited data on the usage of antiviral medications for prophylaxis of herpes labialis. 5 The reports from Álvarez et al., (2020) 6 summarised the effectiveness of current antiviral medications and molecules used in treating HSV infections. Even to this day, there were minimal clinical trials which reported direct comparison or assessment of the relative efficacy between available interventions.

Traditional meta-analysis is limited to evaluating trials having no more than 2 interventions for the same disease. However, network meta-analysis (NMA) permits the evidence synthesis of trials with distinct treatment arms to be synthesized thoroughly and compared with direct or indirect evidence. In terms of ranking the best antiviral to use, the latest NMA by Aribi Al-Zoobaee et al., (2020) demonstrated a

comprehensive review of available antiviral treatments, however, it focussed on immunocompromised cancer patients only. 7

Considering the currently available antiviral medications as therapeutic options to treat herpes labialis, and the uncertainty about the comparative effectiveness based on their efficacy, the present study was undertaken to better define the relative efficacy and safety profiles of the currently available antiviral agents for the treatment of herpes labialis. Hence, we reviewed the literature systematically and conducted an NMA to examine the relative efficacy and safety profiles of the currently available antiviral agents. The report aims to provide relevant information to dentists, dermatol-

ogists, other health care professionals, and policymakers to decide upon their treatment after evaluating the potential benefits and harms associated with the antiviral agents for the treatment of herpes labialis.

2. Materials And Methods

The protocol for this NMA was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with registration number RCRD42021247974. This systematic review and NMA follow the attributes outlined in the Cochrane Handbook for Systematic Reviews of Interventions 8 with full reporting performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement which includes NMAs. 9

2.1. Data Sources and Search Strategy

A literature search for relevant RCTs on the prevention and management of herpes labialis/cold sores was performed and drawn from the following sources

Ovid Medline

PubMed

Cochrane Central Register of Controlled Trials (CENTRAL)

Scopus

ClinicalTrials.gov

Further references from selected journals/articles and references from previous systematic reviews or relevant metaanalyses (via Cochrane Database of Systematic Reviews) were searched to ensure that important articles were not missed. For the search strategy, each database was exhaustively explored using search terms that encompassed all resources and materials relevant to herpes labialis/cold sores and the various prevention and management approaches currently available. The tables displaying the search terms used in the databases are provided in the supplementary material (Supplementary Tables S1 to S5)

2.2. Eligibility Criteria

For the selection of studies, all identified articles were based on the following eligibility/selection criteria using the Population, Intervention, Comparison, Outcome, Studies (PICOS) framework.

2.2.1. Inclusion criteria

Participants (P): Healthy/immunocompetent adults with herpes labialis (new and recurrent)

Interventions(I): Antiviral interventions

Comparators(C): Placebo or any interventions with antiviral properties

Outcomes (O): i) Primary treatment outcome – timeto-healing (TTH) ii) Primary prevention outcome – no evidence/appearance of lesions or recurrence of attacks iii) Secondary outcomes – duration of episodes, pain, recovery, encrustation times, global efficacy assessment scores or total symptom scores

Studies (S): Randomized controlled trials (RCTs)

2.2.2. Exclusion criteria Quasi-experimental and non-randomized controlled/clinical trials

Protocols, reviews or letters

Observational and cross-sectional studies

Case reports

Studies reporting only other herpes simplex virus infections (HSV-2, genital infections, herpes encephalitis or herpes keratitis) without reference to herpes labialis, Immunocompromised patients (having cancer, diabetes, HIV or resistance to antivirals)

Missing required results for analysis (no mean values and standard deviations)

2.3. Data Extraction

Data extraction using Microsoft Excel has been done with three main categories: (i) Study Characteristics (authors, year published, intervention comparisons, randomization, blinding, efficacy and assessment methods); (ii) Intervention (sample sizes, treatment arms, frequencies, duration and followups); (iii) Outcome (primary outcome arms, secondary outcome arms and adverse events). To account for missing mean values or standard deviations(if studies have sufficient data like median and interquartile range), we used either an online estimator 10 or the formulas for converting median into mean: $\chi \approx (a + 2m + b)/4$, and range into variance: $S = (ba)/4 = R/4$, where χ = mean, a = smallest value, b = largest value, m = median, S = variance, and R = range. 10

2.4. Risk of Bias Assessment

The risk of bias in eligible studies was determined using the revised Cochrane risk of bias tool for randomized trials (RoB 2). The assessment included 5 main domains affecting randomization processes, deviations of intended interventions, missing outcomes, measurement methods and selection of reported results, and also 1 overall bias domain. 11

2.5. Data Synthesis and Statistical Analysis

All the data extracted were synthesized using the intentionto-treat principle for the primary analysis. The heterogeneity of those trials was assessed with consideration to I 2 statistic, where if I 2 estimate ≥50%, the evidence demonstrated heterogeneity of substantial levels. 12

In combining direct and indirect evidence from various studies, a frequentist approach involving random-effects NMA had applied based on a consistency model to assimilate the evidence collected.

13–15 When network inconsistency assumption (P >.05) was present, the global inconsistency test was used to evaluate this conflict by incorporating design-by-treatment into the inconsistency model. 14 Inconsistency was also tested one at a time using Separating Indirect from Direct Evidence (SIDE) and Loop-specific approach. 15–17 The probability of each treatment being considered the best (minimum rate of oral herpes labialis) and safest (minimum rate of adverse events) were estimated. Additionally, rankograms with the corresponding ranking of antiviral agents were constructed and the surface area under cumulative ranking (SU- CRA) scores were also calculated. 18, 19 The publication bias was evaluated using the comparison-adjusted funnel plot. All statistical analysis and graph plotting were generated using Stata version 15.0 (StataCorp, College Station, TX).

3. Results

3.1. Literature Search and Study Selection

We identified a total of 1041 studies across all the databases described and these were outlined in the PRISMA flow diagram in Fig. 1. Among these articles, 779 were removed in the initial search, yielding 262 records to be screened. In the screening phase, a further 173 studies were duplicated records, where the remaining 89 full-text articles were downloaded and assessed for their eligibility.

After excluding studies that were found to be cross-over RCTs, contained only abstracts, short commentaries, review summaries or letters, an unspecified number of patients in treatment groups, absence of comparators (only compared different doses of same intervention) and demonstrated obscure results (indistinct data like medians and percentages), the final number included for qualitative synthesis was 52 articles. For quantitative analysis, 26 articles were analyzed for the primary treatment outcome and 7 studies were analyzed for the primary prevention outcome.

3.2. General Study Characteristics

The general characteristics of the 52 eligible studies for qualitative analysis are shown in Supplementary Table 6. The studies included those published from 1977 to 2021 and included a total of 19669 randomized patients, of which 6769 subjects were excluded from post-analysis to finalize 12900 patients in all sample sizes.21- Most of the trials were conducted globally, with most studies from the USA (19), followed by Germany (6), Canada (4), China (3), 2 each from Iran, New Zealand, and Slovakia, and 1 each from Czech Republic, Iceland, Switzerland, Denmark, Israel, Australia, and the Netherlands. The remaining trials encompassed partnerships between countries, with the USA and Canada conducting four trials together and an additional 1 incorporated Australia. Two trials comprised a combined total of 12 countries across 3 continents. 20, 21 There were 23 single-center studies and 29 multi-center studies, mostly conducted at hospitals, clinics, and care centers with schools and departments of oral medicine, dermatology, dermatoepidemiology, research and development. One of the trials involved community pharmacies 22 while 2 trials were conducted at the ski resort. 23, 24 Apart from 2 articles that had 2 identical randomized trials running in parallel, but with independent results 25, 26, all were distinctively randomized controlled trials and mostly conducted recruitment and data collection spanning from 2 months for small sample size studies 27, 28 and prolonged up to 3 years to allow sufficient recruitment. 3, 29–31 Planned sample size could not be attained in 2 of the trials due to slow recruitment.

The age range of participants varied from 16-81 years old, with a mean baseline range of 30-39 years in most studies, although bigger trials recruited a higher average of 40-45 years. 20, 23, 32–34 There were 2 exceptions with one study, including subjects, who are at least 12 years old 25 and two studies included children from 4 to 6 years old, but the overall mean age was 20 years or more and the results were distinguished from adults. 29, 35 All studies were found to have a greater proportion of female participants, with a minimum of 52.3% 36 and up to 92.3% in some treatment arms 37 with the highest overall total for all treatment arms at 92.0% in 1 study. 38 Some older studies did not provide the exact

breakdown of the male-female ratio, 28, 39, 40 while a few had no demographic breakdown but mentioned the similarities in age, gender and ethnicity. 41, 42

The assessment of clinical parameters was evaluated mostly in clinical settings, while the one study conducted in community pharmacies involved community-based investigators. 22

Recruited subjects, mostly presented with observable blisters/symptoms/outbreaks within 24-48 hours. 3, 32, 33, 36, 39, 43–46

while some allowed participation if symptoms did not exceed 72 hours. 22, 35 Some studies reported most recruits, especially older subjects had experienced RHL for an average of 20-30 years. 25, 26, 30, 34, 41, 47–51 and some as long as 40-50 years. 46, 52 In most studies, subjects with at least 2-3times positive recurrences annually were recruited 22, 24–27, 53, 34, 38, 48, 49, 52, 54–57, some looked for a minimum of four times per year 20, 33, 41, 58, 59 while two studies looked for only 1 previous RHL episode. 60, 61 Additionally, a trial reported by Busch et al., (2009) required a minimum of 6 episodes annually. 53 A trial by Bolla et al., (1985) warranted at least 12 relapses in a year 21 and 1 evaluated both frequent (≥3 episodes) and infrequent (1 or 2) recurrences by classifying them into different groups. 62

3.4. Interventions and Comparators

The interventions and comparators are described in detail in Supplementary Table 7. The most frequent treatment used among all the eligible studies was the nucleoside analogue Acyclovir. There were 19 trials, that used cream/ointment formulations ranging from 3% to 10% in concentration, with 2 studies testing additional therapeutic benefits in combination with the steroid drug hydrocortisone 34, 56 and 4 studies using the branded Zovirax cream 3, 31, 47, 54 as comparators. Four trials used 200mg or 400mg oral formulations 23, 44, 61, 63, 1 trial compared the therapeutic and prophylactic efficacy for both the peroral capsule administration and topical cream formulation 64 and one trial used a mucoadhesive buccal tablet for continuous administration of the drug sublingually in a single daily dose. 20 The remaining 2 trials used the lip patch 35 and also cutaneous application via iontophoresis. 62 Other nucleoside analogues used for efficacy assessment included Valacyclovir 25, 30, 58, 60 and Famciclovir 48, 50, both given as tablets/capsules, and Penciclovir 39, 52 in cream form. Among all these nucleoside analogues, only 1 study had a direct comparison between 2 of these drugs 36, another study involved the addition of corticosteroid for further benefits 30 while the remaining studies had compared nucleoside analogues with placebos or other interventions.

The next most common treatment used, especially in the newer studies, were a variety of natural/herbal formulations like olive leaf extract, pleuran (beta-glucan), kanuka honey, propolis, tea leaves extract, Melissa herbal extract, rhubarb root extract, and Longovital vitamin-herb supplementation. 22, 27, 29, 31, 65, 32, 33, 34, 35, 43, 55, 59, 66 Due to the nature of some of these formulations, like the inability to mask kanuka honey taste 22, 65 or sensitivity to color and odor of propolis 36

during randomization, the study designs had to be altered and were either open-label or single-blinded trials.

Additionally, some other antivirals, antibacterial agents or chemical compounds included in the analysis were inosine pranobex, monocaprin, doxycycline, 1,5-pentanediol,

tetracaine, Betadine paint, Stoxil ointment (idoxuridine), foscarnet, undecylenic acid, vidarabine monophosphate, thymopentin, butylated hydroxytoluene, ether, levamisole and chloroform 21, 28, 53, 39, 40, 42, 44, 45, 46, 57, 62, 67, 68, 69

Most of these 52 studies had 2 treatment arms, except 9 studies with 3 treatment arms 3, 25, 31, 34, 45, 48, 54, 62, 70 and 2 studies with 4 treatment arms. 50, 64 Another 10 studies did not have placebos as control groups. 3, 22, 31, 65, 32, 33, 36, 43, 47, 55 Although this had weakened study designs, the reasons for excluding placebos were justified because some placebos yielded false results due to the composition of ingredients used 3 and some were due to ethical reasons. 31, 43 Besides, in 2 open-label studies, silica gel and acyclovir cream were differentiated easily due to their texture upon application 47, and Betadine paint colorized the skin compared to the water-miscible idoxuridine ointment. 70 Other examples were the use of patches together with serums and creams in different treatment arms, where the subjects knew the treatment given but the trial was blinded to the assessor, and the odor from camphor in mineral oil enabled subjects to identify the treatment given between chloroform or camphor. 25

Most of the clinical study duration on TTH trials for individual subjects ranged from three to fourteen days or until the lesion had healed, 31, 32, 34, 38, 39, 57, 62 while prophylactic studies for subjects took up to 9 months with followup periods. 66, 69 The frequencies of treatment given varied from 3 to 6 times daily, some as often as 8 times daily or every 2 hours. 28, 31, 49, 52, 67 Two studies required application only once at the start of trial 62, 70 while several studies had specified instructions to follow throughout the trial duration. 20, 21, 25, 38, 41, 44, 48, 60, 66, 69

3.5. Outcomes of Interest

All the outcomes of interest are described in detail in supplementary Table 8. The primary outcome in the most eligible studies is TTH which was reported in 37 studies. Among these, 21 studies showed statistical significance in the improvement of lesions, from randomization to normal skin and complete loss of crusts.

Across all secondary outcomes included in this analysis, 27 studies showed results in pain reduction, 7 studies with the reduction in episodic duration of lesions, 25, 26, 34, 40, 41, 49, 66

3 studies each with the improvement of total symptom scores 53, 44, 59 and superior Global Efficacy Assessment mean scores, 35, 36, 50 7 studies evaluating superiority testing, also known as the time to complete encrustation or epithelialisation, 28, 31, 32, 33, 37, 54, 57 eight studies contributing to itchiness decrement 27, 53, 33, 37, 39, 43, 47, 57 2 studies assessed bleeding tendency 27, 43 and 1 study also determined both irritation reduction and mucosa color change. 43 Among all the studies which included duration of episodes, only 2 studies did not provide statistically significant results, 44,67 while it was finely balanced across pain reduction results with 13 studies showing the statistical significance and 14 studies with no significant differences. For superiority testing, 4 of 7 studies had a significantly better time to full encrustation outcomes, 32, 33, 37, 54 2 of 3 studies had significantly better Global Efficacy Assessment mean scores 35,38 and only 1 of 3 studies had significant enhancements in total symptom scores. 53

For the prevention aspect, the primary outcome was the incidence of recurrence which was reported in 13 studies. Six of these trials 20, 21, 23, 24, 34, 58 showed statistically significant results to stipulate longer mean times to the first recurrence and extended symptom-free periods.

The absence of adverse events was reported in 16 studies while there were no recorded events in nine studies. 28, 52, 56, 59, 61, 62, 63, 66, 69. Most were mild to moderate side ef-

fects such as headache, nausea, diarrhoea, dry lips, application site reactions(pain, dryness and burning), numbness, skin smarting or facial exacerbations, while rare issues reported in a small number of trials include skin desquamation or flaky skin, 26, 71 dysgeusia, 41 hyperuricaemia 44 and

nasopharyngitis/upper respiratory tract infection. 34 One study had also reported side effects in 6 subjects in both thymopentin and placebo groups but was only classified as temporary mild repercussions without specifying them. 21

3.6. Risk of Bias and Quality of Studies

The results for RoB assessments were shown in Fig. 2, supplementary Figures S1 and S2. For studies with TTH outcomes, 36 studies assessed assignment to intervention effect using intention-to-treat (ITT) and 'as treated' analyses with an overall bias of 41.7% of some concern, while one

Fig. 3. Network plot on the efficacy of interventions in management of herpes labialis. Abbreviations: ABT = acyclovir buccal tablet; ACY, acyclovir; ACY + HCT, acyclovir + hydrocortisone; AMP, vidarabine monophosphate; BHT, butylated hydroxytoluene; BM, balm mint(Lo-701) melissa extract; COM, compeed cold sore patch; EGCG, epigallocatechin-3- gallate; ETR, ether; FAM, famciclovir; FSN, foscarnet; HEP, herspatch serum patch; KH, kanuka honey; NaCl, sodium chloride solution; OLE, olive leaf extract; PBO, placebo; PCV, penciclovir; PLN, pleuran; TC, tetracaine; UA, undecylenic acid; VCY + CLO, valacyclovir + clobetasol.

study assessed adherence to intervention effect using 'perprotocol' analysis with an overall high risk of bias. For studies with recurrence outcomes, all 13 studies used the ITT analysis for intervention allocation evaluation with the overall bias of some concern at 46.2%.

3.7. Comparing Effectiveness of Interventions used for the Management of Herpes Labialis with Primary Treatment Outcome Time-to-Healing(Network Meta-Analysis)

There were 26 studies with sufficient reported data included for this analysis. Fig. 3 shows the network plot connecting 21 interventions (including placebo) which analyzed the TTH of herpes labialis lesions, where each node represented a treatment arm, node size illustrated the total number of subjects using that intervention and the width of connecting lines reflecting the number of trials included. Placebo was the most common comparator used in these studies and was used as the reference group in the analysis. Assessments in comparing the efficacy between the 20 interventions (other than placebo) involved in the analysis resulted in 11 interventions which significantly lowered the TTH of herpes labialis lesions when compared to placebo. Of all the interventions implicated, the combination of oral valacyclovir with the addition of topical clobetasol was found to be the most effective with a mean difference (MD) of healing time of -3.50 (95% CI - 5.22 to -1.78), followed by vidarabine monophosphate (AMP) [MD -3.22 (95% CI -4.59 to -1.85)] and olive leaf extract (OLE) [MD -3.17 (95% CI -49.24 to 42.90)]. Interestingly, the placebo had lower TTH compared to topical ether, undecylenic acid cream and oral pleuran, with MD (95% CI) of 0.70 (-1.67 to 3.07), 0.44 (-0.08 to 0.96) and 2.60 (1.48 to 3.72) respectively. Table 4 showed all the mean differences between the interventions which were evaluated.

Using the SUCRA method, the combination of oral valacyclovir and topical clobetasol was likely ranked as the best treatment (93.0%), followed by cutaneous topical application of vidarabine monophosphate (91.7%) and topical epigallocatechin-3-gallate (86.3%) (Table 1). On the other hand, the least efficacious treatment shown was oral pleuran (2.4%) followed by undecylenic acid cream (12.3%) and topical ether (17.3%). The SUCRA ranking graphs were shown in Fig. 4 and the league table for various indirect comparisons between the agents and available direct comparisons was provided in Fig. 5. The NMA results were comparable with most of the available direct comparison data.

A global inconsistency test results demonstrated that there was no significant inconsistency observed among the trials (P >.05) and was shown in Supplementary Table S9. Inconsistency explored by (SIDE)

approach is shown in Supplementary Table S10 and the results showed 'agreement' between the direct and indirect evidence for all the comparisons. P-values equal to or greater than.05 suggested that there was no statistically significant inconsistency. We also performed a Loop-specific approach to detect inconsistency shown in Supplementary Table S10 with all closed triangular loops (formed by three treatments). Inconsistency factor (IF) indicated the differences between direct and indirect estimates and the corresponding 95% confidence interval for each IF in each closed triangular or quadratic loop was presented in Supplementary Table S11. Inconsistent loops were distinct loops that featured IFs with 95% confidence intervals incompatible with zero. For example, for the triangular loop of evidence involving drug comparisons, the relative risk for estimating the effect differs between direct and indirect evidence by 0.95 but exhibited a 95% confidence interval inclusive of 0, indicating the possibility of featuring no difference. Direct comparisons with pair wise metaanalysis by random effects method is provided as Supplementary Figure S3. This is because most of the agents have not been directly compared with each other or placebo and have only been tested against a single agent of investigators choice.

Table 1. SUCRA ranking of different interventions for treatment.

Intervention	Mean difference (95% CI)	SUCRA value (%)	P-value
VCY + CLO	-3.50 (-5.22 to -1.78)	93.0	.000
AMP	-3.22 (-4.59 to -1.85)	91.7	.000
EGCG	-2.77 (-4.46 to -1.08)	86.3	.001
FAM	-2.09 (-2.53 to -1.65)	79.8	.000
TC	-2.10 (-2.64 to -1.55)	79.8	.000
HEP	-1.42 (-2.16 to -0.67)	64.9	.000
ACY + HCT	-1.28 (-1.90 to -0.66)	60.1	.000
PCV	-1.20 (-1.72 to -0.68)	56.9	.000
OLE	-3.17 (-49.24 to 42.90)	54.1	.893
COM	-1.05 (-1.79 to -0.30)	51.5	.006
NaCl	-1.02 (-2.35 to 0.32)	50.6	.135

BM	-0.91 (-2.06 to 0.24)	47.3	.120
ACY	-0.92 (-1.44 to -0.40)	46.5	.001
BHT	-0.75 (-3.10 to 1.60)	44.5	.531
KH	-0.49 (-1.23 to 0.25)	32.9	.191
ABT	-0.38 (-0.90 to 0.14)	30.8	.155
FSN	-0.20 (-1.29 to 0.89)	27.0	.718
ETR	0.70 (-1.67 to 3.07)	17.3	.562
UA	0.44 (-0.08 to 0.96)	12.3	.100
PLN	2.60 (1.48 to 3.72)	2.4	.000

Abbreviations: ABT = acyclovir buccal tablet; ACY = acyclovir; ACY + HCT = acyclovir + hydrocortisone; AMP = vidarabine monophosphate; BHT = butylated hydroxytoluene; BM = balm mint (Lo-701) melissa extract; COM = Compeed cold sore patch; EGCG = epigallocatechin-3-gallate; ETR = ether; FAM = famciclovir; FSN = foscarnet; HEP = Herspatch serum patch; KH = kanuka honey; NaCl = sodium chloride solution; OLE = olive leaf extract; PCV = penciclovir; PLN = pleuran; TC = tetracaine; UA = undecylenic acid; VCY + CLO = valacyclovir + clobetasol.

Publication bias in the network for TTH outcome was assessed using a comparison-adjusted funnel plot as shown in Supplementary Figure S4 which showed evidence of publication bias.

3.8. Comparing Effectiveness of Intervention used for the Prevention of Herpes Labialis with Primary Prevention Outcome Total Number of Recurrences (Network Meta-Analysis)

For this outcome, 7 studies had sufficient reported data to be analyzed. Fig. 6 displayed a network map, analyzing the recurrence of herpes labialis which connected 5 interven-

tions. Similar to the primary treatment outcome, each node indicated a treatment arm, node size represented the total number of subjects in that particular intervention and the thickness of connecting lines featured the number of trials involved. The reference group used was the placebo.

All 4 interventions excluding placebo from seven studies that were involved in the analysis had no significant differences in the total number of herpes labialis recurrences when compared to placebo. Based on the mean differences in the frequency of recurrences among the interventions included for

comparisons, inosine pranobex [0.36 (95%CI 0.09- 1.45)] showed the least RR, although this was not statistically

Table 2. SUCRA ranking curve of different interventions for prevention outcome.

Intervention	Mean difference (95% CI)	SUCRA value (%)	P-value
IP	0.36 (0.09-1.45)	89.2	.150
ACY	0.64 (0.31-1.32)	67.8	.228
VCY	1.00 (0.52-1.91)	33.7	.992
ACY + HCT	1.10 (0.39-3.09)	27.1	.851

Abbreviations: ACY = acyclovir; ACY + HCT = acyclovir + hydrocortisone; IP = inosine pranobex; VCY = valacyclovir.

significant. From the results found in Table 2, none of these interventions was superior to placebo in reducing the recurrence of herpes labialis. Comparatively, the ranking according to SUCRA values also pointed out that inosine pranobex was the best-ranked intervention (89.2%), followed by acyclovir (67.8%), valacyclovir (33.7%) and lastly, the combination of topical acyclovir and hydrocortisone (27.1%). Fig. 7

displayed the SUCRA ranking graphs for these interventions while Fig. 8 provided the league table for several indirect comparisons.

A global inconsistency test was similarly performed to detect inconsistency for the overall network. The results found significant inconsistencies among all the trials involved (P <.05)as shown in Supplementary Table S12. The node splitting approach also suggested statistically significant inconsistency as shown in Supplementary Table S13. The loop-specific approach to detecting inconsistency is shown in Supplementary Table S14. The funnel plot in Supplementary Figure S5revealed a significant publication bias in the 7 studies involved in recurrence outcomes.

4. Discussion

To the best of our knowledge, this is the first NMA conducted for assessing the comparative efficacy of interventions utilised in the treatment as well as prevention of herpes labialis. The overall NMA findings of the 2 primary outcomes provided comparisons between results from established RCTs, some of which were empirically examined before in systematic reviews but not quantitatively. Hence, this NMA included both head-to-head trials and placebocontrolled studies to reveal how different the results would be observed by using direct and indirect comparisons between the interventions in each primary outcome, while also allowing assessments of bias being reported among any 2 treatments in the network and the efficacious impact of each intervention when ranked numerically. 72

Our study explored the comparative efficacy of 20 different interventions with antiviral properties in terms of reduced lesion healing time for herpes labialis and provided evidence-based hierarchies on their efficacy and acceptability. Data from 26 RCTs involving over 6000 participants demonstrated that all interventions apart from the topical ether, topical undecylenic acid and oral pleura were more efficacious than placebo in terms of lowering TTH, with 10 of these interventions significantly reducing the time for the lesions to heal completely. Although acyclovir was the most frequently used intervention and comparator across all the trials, it was ranked below the other antiviral drugs (famciclovir and penciclovir), chemical/medicinal compounds (vidarabine monophosphate, tetracaine, Compeed cold sore patch, and Herspatch serum) and the herbal EGCG tea leave extract in reducing the healing time of disease.

An important finding was the combination therapy of antivirals with steroids had increased efficacy, thus lowering TTH outcomes to a greater extent as demonstrated by the high SUCRA rankings and values of the valacyclovir and clobetasol combination and acyclovir with hydrocortisone compared to single antiviral interventions. Hence, in terms of

the probability of being the best treatment and by ranking, the combination therapy of oral valacyclovir and topical clobetasol was the best option in our NMA with current evidence in reducing the healing time of herpes labialis lesions. These findings are in compliance with preclinical studies by

Harmenberg et al., (2003) and Awan et al., (1998) where the addition of 1% hydrocortisone in the topical ME-609 treatment containing 5% acyclovir had significantly better efficacy than 5% Zovirax cream, 1% hydrocortisone alone or without treatment, respectively in adoptive transfer of immunity (ATI) mouse models, suggesting dual characteristics of this combination therapy to activate the healing process of herpes labialis lesions by inhibiting viral duplication and regulating inflammatory reactions. 73, 74 Some clinical studies also supported these findings where corticosteroids demonstrated increased clinical activity when combined with antivirals in various herpes simplex virus infections, such as faster median healing times and the aborted number of herpes labialis lesions in a combination of famciclovir with fluocinonide, 75 reducing the number of activated inflammatory mechanism pathways and improving disturbances in consciousness in herpes encephalitis, 76, 77 and decreased continuation of stromal inflammation to rapidly improve herpes simplex stromal keratitis by reducing its duration. 78

In general, long-term use of low potency steroids such as hydrocortisone is regarded as mostly safe to use on huge surface regions such as the face, lips, slender, thin skin and children's tender skin, while higher potency topical corticosteroids like clobetasol are useful for more extreme skin infections and on palms or soles due to the thicker skin layers. 79 Although the application of these potent steroids to the face, groin or skin impediment should be avoided, rare circumstances may require their use and only for short durations, up to a maximum of 2 weeks with gradual tapering of the treatment regimen for maintenance and also prevent side-effects. 80

In contrast, although the network plot featuring 4 different interventions from 7 RCTs for preventing recurrences of herpes labialis also demonstrated some evidence of efficacy and appropriateness in decreasing recurrence rate, none of them were statistically significant compared to placebo. In terms of rankings, SUCRA values presented inosine pranobex as the best treatment compared to single antiviral agents or in combination with steroids. Additionally, the loop-specific approach could not estimate heterogeneity in the triangular loop of acyclovir, acyclovir plus hydrocortisone and placebo treatments as observations were obscure and the asymmetrical nature of funnel plots revealed publication bias from the seven trials involved. Thus, as there was no statistical significance when

comparing the interventions, we could only conclude from SUCRA rankings and values that oral inosine pranobex was the most effective treatment among the four interventions analyzed.

In terms of safety, most of the treatments analyzed had either no reported adverse events or minimal localised reactions at application sites like dry skin or inflammation at comparable rates to placebo, demonstrating general assurance of the safe use of the treatments included in the analysis. Although there were also common side-effects reported like headache, nausea, and diarrhoea, these were not specified for the interventions involved in most studies due to infrequent reporting and were also deemed unrelated to study treatments, hence NMA could not be executed adequately.

A previous meta-analysis conducted by Chen et al., (2017) focused on nucleoside antiviral drugs demonstrated significant efficacy (including TTH outcome) and safety of these drugs being used in treating herpes labialis, with valacyclovir shown to be superior to acyclovir with no significant heterogeneity, while limited data prevented further analysis for famciclovir and penciclovir. 81 These results were consistent with our quantitative NMA results where all the nucleoside antiviral drugs included were ranked highly according to SU- CRA values and also had significant mean differences in healing time reduction of herpes labialis lesions, thus allowing our study to correspondingly position other interventions to be ranked together after assessing all direct and indirect estimates cumulatively.

Recent systematic reviews by Hammer et al., (2018) and Rosa et al., (2015) also revealed three common topical antiherpetics (acyclovir, penciclovir and docosanol) were only marginally superior to placebo in lesion healing time reduction 82, 83 and the clinical recurrence decrement was statistically significant for topical acyclovir with addition of hydrocortisone when compared to placebo only 84 As mentioned above, our study could not include docosanol but it can be estimated to be comparable in efficacy and rankings with acyclovir and penciclovir to reduce lesion healing time, while the combination of acyclovir and hydrocortisone had similar results in preventing recurrence although there was no statistical significance as our NMA also included 3 other interventions, namely inosine pranobex, acyclovir alone and valacyclovir.

One of the latest NMAs by Al-Zoobaee et al., (2020) revealed acyclovir was superior to valacyclovir in preventing herpes labialis recurrences, but this was studied in cancer patients in an immunocompromised population. 7 Hence, the results could not be compared with this study but set a benchmark in identifying the best RHL treatment for a different population. Another NMA by Fu et al., (2018) studied multiple antiviral interventions in facial paralysis caused by Bell's palsy which could possibly be associated with the involvement of the same herpes simplex virus, but it was not conclusively proven. 85 Furthermore, there were systematic reviews in non-pharmacological treatments for herpes labialis which involved low-level laser and photodynamic therapy by

Al-Maweri et al., (2018) 86 and Lotufo et al., (2020) 87 respectively, but both reviews revealed high variabilities of study designs and inconsistency of laser parameters causing heterogeneity suggested the need for well-designed RCTs in future comparative research to effectively assess efficacy and safety outcomes against antiviral therapies.

NMAs are being used to assess pharmacotherapeutic strategies due to the popularity and ability of this method to conduct evaluations of relative efficacies among treatment regimens without the need for head-to-head comparisons. 84, 88

Combining the application of systematic reviews and quantitative results with mutually comparable and related studies leads to corresponding direct and indirect evidence being discovered 89 and hence our current findings can facilitate the development of high-quality guidelines while being useful for health practitioners to determine the best treatment options, analyze benefits and/or shortcomings of each treatment and prioritise future planning of research in specific analytical approaches which were not estimated before, such as choosing specific comparators or control groups in subsequent trials. 90

There were a few limitations in our study. Firstly, the variabilities of each RCT, such as publication years spanning different decades, small-scale single-center trials to large multicenter RCTs, and novel pharmacological and non-pharmacological management options for herpes labialis involved potential bias. These were observed in several high to unclear risks of bias, particularly in the domains for

outcome measurement and selection of reported results. Secondly, most of the interventions were only tried and tested in single trials and hence comparison with pair-wise data wouldn't be legitimate. While most RCTs were blinded to subjects and assessors, open-label designs due to the inability to mask treatment characteristics such as kanuka honey taste, visible patches or formulations of different creams and ointments may still influence results outcome as well, hence the vigilance of adequate analysis and bias evaluations must be considered when extracting data for all studies involved. Moreover, the diversity in administration routes and different dosages of included interventions and comparators could also affect results as some antivirals like acyclovir were commonly given orally, topically, or both simultaneously. Hence, each RCT would need to compare treatments with similar routes or standardized dosages, otherwise results inclined towards either systemic administration or frequent external applications, creating bias in primary outcomes and adverse events such as application site irritation. Lastly, the lack of defined adverse events and detailed data for these occurrences undermined the strength of this study is evaluating safety concerns of all antiviral interventions, regardless of primary prevention or management outcomes. While adverse events were reported in some studies, the categorisation among participants encountering these side effects was too

inconclusive as all observed adverse events were cluttered together among treatment arms or collectively quantified. Hence, inconsistencies across trials would reveal no signs of adverse events among participants either in treatment or placebo arms.

5. Conclusions

Our results indicated that many antiviral medications were proven effective in reducing TTH with no statistically significant inconsistencies and publication bias across the incorporated trials. The combination of oral valacyclovir and topical clobetasol therapy was found to be the best-ranked and most effective treatment in the reduction of herpes labialis healing time. Most of the trials did not report any major adverse effects implying the safety of the majority of tested interventions. Additional superior

quality RCTs are warranted to determine the most efficacious intervention in preventing the recurrence of herpes labialis.

Author Contributions

"Conceptualization DVG and KKH.; methodology, DVG and SKV.; software, SKV.; validation, KKH, SKV, ABN and SMS; formal analysis, KKH and SKV; investigation, DVG and KKH.; resources, DVG.; data curation, DVG and KKH.; writing— original draft preparation, KKH.; writing—review and editing, DVG and MKM.; visualization,; supervision, DVG and MKM.; project administration DVG and MKM.; funding acquisition, DVG All authors have read and agreed to the published version of the manuscript."

Acknowledgments

Nil

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.jebdp.2022. 101778.

References

1. Herpes & Shingles: Symptoms & treatments - life extension [Internet]. [cited 2021 Sep 19]. Available from: https://www. lifeextension.com/protocols/infections/herpes- and- shingles

2. Birek C, Ficarra G. The diagnosis and management of oral herpes simplex infection. Curr Infect Dis Rep. 2006 Jun;8:181–188.

3. Boes H, Goulioumis V, Wechsler A, Zimmer S, Bizhang M. Clinical study on the effectiveness of three products in the treatment of Herpes simplex labialis. Scientific Reports. 2020 Apr 15;10:6465.

4. Esmann J. The many challenges of facial herpes simplex virus infection. Journal of Antimicrobial Chemotherapy. 2001 Feb 1;47(suppl_1):17–27.

5. Zeichner J. Acyclovir buccal adhesive tablet. Clinical insights - practical dermatology [Internet]. 2016 Jan [cited 2021 Mar 22]; Available from: https://practicaldermatology.com/pdfs/0116 _ insert.pdf

6. Álvarez DM, Castillo E, Duarte LF, et al. Current antivirals and novel botanical molecules interfering with Herpes simplex virus infection. Front Microbiol. 2020 Feb 11;11:139.

7. Aribi Al-Zoobaee FW, Yee Shen L, Veettil SK, Gopinath D, Maharajan MK, Kunnath Menon R. Antiviral agents for the prevention and treatment of Herpes simplex virus Type-1 infection in clinical oncology: a network meta-analysis. Int J Environ Res Public Health. 2020 Nov 30;17:8891.

8. Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. Journal of Clinical Epidemiology. 2017 Mar 1;83:65–74.

9. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015 Jun 2;162:777–784.

10. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology. 2005 Apr 20;5:13.

11. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.

12. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011].The Cochrane Collaboration. [Internet]. 2011. Available from: http: //handbook.cochrane.org/.

13. Dias S, Caldwell DM. Network meta-analysis explained. Archives of Disease in Childhood -Fetal and Neonatal Edition. 2019;104:F8–F12.

14. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirecttreatment-comparison and network-meta-analysis studies: report of the ISPOR task force on indirect treatment comparisons good research practices: part 2. value health. 2011 Jun;14:429– 37.

15. Krahn U, Binder H, König J. Visualizing inconsistency in network meta-analysis by independent path decomposition. BMC Medical Research Methodology. 2014 Dec 16;14:131.

16. Higgins J, Jackson D, Barrett J, Lu G, Ades A, White I. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012 Jun;3:98–110.

17. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods. 2016 Mar;7:80–93.

18. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005 Oct 15;331:897–900.

19. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLOS ONE. 2013 Oct 3;8:e76654.

20. Bieber T, Chosidow O, Bodsworth N, et al. Efficacy and safety of aciclovir mucoadhesive buccal tablet in immunocompetent patients with labial herpes (LIP Trial): a double-blind, placebo-controlled, self-initiated trial. J Drugs Dermatol. 2014 Jul;13:791–798.

21. Bolla K, Djawari D, Kokoschka EM, et al. Prevention of recurrences in frequently relapsing herpes labialis with thymopentin. A randomized double-blind placebo-controlled multicenter study. Surv Immunol Res. 1985;4(1):37–47 Suppl.

22. Semprini A, Singer J, Braithwaite I, et al. Kanuka honey versus aciclovir for the topical treatment of herpes simplex labialis: a randomised controlled trial. BMJ Open. 2019 May 1;9:e026201.

23. Spruance SL, Hamill ML, Hoge WS, Davis LG, Mills J. Acyclovir prevents reactivation of Herpes simplex labialis in Skiers. JAMA. 1988 Sep 16;260:1597–1599.

24. Raborn GW, Martel AY, Grace MGA, McGaw WT. Herpes labialis in skiers: randomized clinical trial of acyclovir cream versus placebo. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. 1997 Dec 1;84:641–645.

25. Spruance SL, Jones TM, Blatter MM, et al. High-dose, short- -duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. Antimicrob Agents Chemother. 2003 Mar;47:1072–1080.

26. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of Herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Antimicrob Agents Chemother. 2002 Jul;46:2238–2243.

27. Zhao M, Zheng R, Jiang J, et al. Topical lipophilic epigallocatechin-3-gallate on herpes labialis: a phase II clinical trial of AverTeaX formula. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2015 Dec 1;120(6):717–724.

28. Taylor CA, Hendley JO, Greer KE, Gwaltney Jr JM. Topical treatment of Herpes labialis with chloroform. Archives of Dermatology. 1977 Nov 1;113:1550–1552.

29. Urbancikova I, Hudackova D, Majtan J, Rennerova Z, Banovcin P, Jesenak M. Efficacy of pleuran (β-Glucan from pleurotus ostreatus) in the management of Herpes simplex virus type 1 infection. Evidence-Based Complementary and Alternative Medicine. 2020 Apr 13;2020:e8562309.

30. Hull C, McKeough M, Sebastian K, Kriesel J, Spruance S. Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. Journal of the European Academy of Dermatology and Venereology. 2009;23:263–267.

31. Saller R, Büechi S, Meyrat R, Schmidhauser C. Combined herbal preparation for topical treatment of Herpes labialis. Complement Med Res. 2001;8:373–382.

32. Jautová J, Zelenková H, Drotarová K, Nejdková A, Grünwaldová B, Hladiková M. Lip creams with propolis special extract GH 2002 0.5% versus aciclovir 5.0% for herpes labialis (vesicular stage): randomized, controlled double-blind study. Wien Med Wochenschr. 2019 May;169:193–201.

33. Arenberger P, Arenbergerova M, Hladíková M, Holcova S, Ottillinger B. Comparative study with a lip balm containing 0.5% propolis special extract GH 2002 versus 5% aciclovir cream in patients with Herpes labialis in the papular/erythematous stage: a single-blind, randomized, two-arm Study. Curr Ther Res Clin Exp. 2017 Oct 14;88:1–7.

34. Hull CM, Harmenberg J, Arlander E, et al. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. Journal of the American Academy of Dermatology. 2011;64:696 Apr 1e1-696.e11.

35. Wölbling RH, Leonhardt K. Local therapy of herpes simplex with dried extract from Melissa officinalis. Phytomedicine. 1994 Jun 1;1:25–31.

36. Lin L, Chen X, Cui P, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. Journal of Dermatological Treatment. 2002 Jan;13:67–72.

37. Van Vloten WA, Swart RNJ, Pot F. Topical acyclovir therapy in patients with recurrent orofacial herpes simplex infections. Journal of Antimicrobial Chemotherapy. 1983;12:89–93 Jan 1suppl_B.

38. Veltri J, Boon R, Böhling A, Wilhelm K-P, Bielfeldt S. A randomized exploratory study to investigate the inflammatory response during an ultraviolet-radiation-induced cold sore episode. Dermatol Ther (Heidelb). 2021 Jun;11:983–994.

39. Kaminester LH, Pariser RJ, Pariser DM, et al. A double-blind, placebo-controlled study of topical tetracaine in the treatment of herpes labialis. Journal of the American Academy of Dermatology. 1999 Dec 1;41:996–1001.

40. Rowe NH, Brooks SL, Young SK, et al. A clinical trial of topically applied 3 percent vidarabine against recurrent herpes labialis. Oral Surg Oral Med Oral Pathol. 1979 Feb;47:142–7.

41. Russell AS, Brisson E, Grace M. A double-blind, controlled trial of levamisole in the treatment of recurrent Herpes labialis. The Journal of Infectious Diseases. 1978 May 1;137:597–600.

42. Spruance SL, Krueger GG, MacCalman J, Overall JC, Klauber MR. Treatment of recurrent Herpes simplex labialis with levamisole. Antimicrob Agents Chemother. 1979 May;15:662–665.

43. Toulabi T, Delfan B, Rashidipour M, et al. The efficacy of olive leaf extract on healing herpes simplex virus labialis: a randomized double-blind study. Explore (NY). 2021 Jan 29:S1550-8307(21)00004-5.

44. You Y, Wang L, Li Y, et al. Multicenter randomized study of inosine pranobex versus acyclovir in the treatment of recurrent herpes labialis and recurrent herpes genitalis in Chinese patients. J Dermatol. 2015 Jun;42:596–601.

45. Skulason S, Holbrook WP, Thormar H, Gunnarsson GB, Kristmundsdottir T. A study of the clinical activity of a gel combining monocaprin and doxycycline: a novel treatment for herpes labialis. Journal of Oral Pathology & Medicine. 2012;41: 61–67.

46. Freeman DJ, Wenerstrom G, Spruance SL. Treatment of recurrent herpes simplex labialis with topical butylated hydroxytoluene. Clinical Pharmacology & Therapeutics. 1985;38: 56–59.

47. Zschocke I, Reich C, Zielke A, Reitmeier N, Reich K. Silica gel is as effective as acyclovir cream in patients with recurrent herpes labialis: results of a randomized, open-label trial. Journal of Dermatological Treatment. 2008 Jan 1;19:176–181.

48. Spruance SL, Bodsworth N, Resnick H, et al. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. J Am Acad Dermatol. 2006 Jul;55:47–53.

49. Boon R, Goodman JJ, Martinez J, Marks GL, Gamble M, Welch C. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. Clinical Therapeutics. 2000 Jan 1;22:76–90.

50. Spruance SL, Rowe NH, Raborn GW, Thibodeau EA, D'Ambrosio JA, Bernstein DI. Peroral famciclovir in the treatment of experimental ultraviolet radiation-induced Herpes simplex labialis: a double-blind, dose-ranging, placebo-controlled, multicenter trial. The Journal of Infectious Diseases. 1999 Feb 1;179:303–310.

51. Spruance SL, Crumpacker CS. Topical 5 percent acyclovir in polyethylene glycol for herpes simplex labialis: antiviral effect without clinical benefit. The American Journal of Medicine. 1982 Jul 20;73:315–319.

52. Spruance SL, Crumpacker CS, Schnipper LE, et al. patient-initiated treatment of herpes labialis with topical 10% acyclovir. Antimicrob Agents Chemother. 1984 May;25:553–555.

53. Busch R, Graubaum H-J, Gruenwald J, Faergemann J. Therapeutic effect of 1,5-pentanediol for herpes simplex labialis: a randomized, double-blind, placebo-controlled clinical trial. Advances in therapy. 2009 Aug 1;26:719–727.

54. Horwitz E, Pisanty S, Czerninski R, Helser M, Eliav E, Touitou E. A clinical evaluation of a novel liposomal carrier for acyclovir in the topical treatment of recurrent herpes labialis. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. 1999 Jun 1;87:700–705.

55. Ahadian H, Karbasi A, Ghanea S. Comparison of the effectiveness of mellisan gel and acyclovir 5% cream in the improvement of recurrent Herpes labialis. 2015;7.

56. Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J, Spruance SL. Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced Herpes labialis. Antimicrob Agents Chemother. 2002 Jun;46:1870–1874.

57. Shafran SD, Sacks SL, Aoki FY, et al. Topical undecylenic acid for Herpes simplex labialis: a multicenter, placebo-controlled trial. The Journal of Infectious Diseases. 1997 Jul 1;176:78–83.

58. Baker D, Eisen D. Valacyclovir for prevention of recurrent herpes labialis: 2 double-blind, placebo-controlled studies. Cutis. 2003 Mar;71:239–242.

59. Koytchev R, Alken RG, Dundarov S. Balm mint extract (Lo-701) for topical treatment of recurring herpes labialis. Phytomedicine. 1999 Oct 1;6:225–230.

60. Miller CS, Cunningham LL, Lindroth JE, Avdiushko SA. The efficacy of valacyclovir in preventing recurrent herpes simplex virus infections associated with dental procedures. The Journal of the American Dental Association. 2004 Sep 1;135:1311–1318.

61. Spruance SL, Stewart JCB, Rowe NH, McKeough MB, Wenerstrom G, Freeman DJ. Treatment of recurrent Herpes simplex labialis with oral acyclovir. The Journal of Infectious Diseases. 1990 Feb 1;161:185–190.

62. Sr Gangarosa LP, JM Hill, Thompson BL, Leggett C, Kissing JP. Iontophoresis of vidarabine monophosphate for Herpes orolabialis. The Journal of Infectious Diseases. 1986 Dec 1;154:930–934.

63. Raborn GW, McGaw WT, Grace M, Tyrrell LD, Samuels SM. Oral acyclovir and herpes labialis: a randomized, double-blind, placebo-controlled study. The Journal of the American Dental Association. 1987 Jul 1;115:38–42.

64. Spruance SL, Freeman DJ, Stewart JC, et al. The natural history of ultraviolet radiation-induced herpes simplex labialis and response to therapy with peroral and topical formulations of acyclovir. J Infect Dis. 1991 Apr;163:728–734.

65. Fingleton J, Corin A, Sheahan D, et al. Randomised controlled trial of topical kanuka honey for the treatment of cold sores. Advances in Integrative Medicine. 2014 Dec 1;1:119–123.

66. Pedersen A. LongoVital® and herpes labialis: a randomised, double blind, placebo-controlled study. Oral Diseases. 2001;7:221–225.

67. Bernstein DI, Schleupner CJ, Evans TG, et al. Effect of foscarnet cream on experimental UV radiation-induced herpes labialis. Antimicrob Agents Chemother. 1997 Sep;41:1961–1964.

68. Spruance SL, Crumpacker CS, Haines H, et al. Ineffectiveness of topical adenine arabinoside 5 ' -monophosphate in the treatment of ecurrent Herpes simplex labialis. N Engl J Med. 1979;300:1180–1184.

69. Guinan ME, MacCalman J, Kern ER, Overall Jr JC, Spruance SL. Topical ether and Herpes simplex labialis. JAMA. 1980 Mar 14;243:1059–1061.

70. Simmons A. An open-label study conducted to evaluate the efficacy of betadine® cold sore paint. DRM. 1997;195(2):85–88 Suppl.

71. Raborn GW, McGaw WT, Grace M, Percy J, Samuels S. Herpes labialis treatment with acyclovir 5% modified aqueous cream: a double-blind randomized trial. Oral Surg Oral Med Oral Pathol. 1989 Jun;67:676–679.

72. Cote MP, Lubowitz JH, Brand JC, Rossi MJ. Understanding network meta-analysis (NMA) conclusions requires scrutiny of methods and results: introduction to NMA and the geometry of evidence. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2021 Jul;37:2013–2016.

73. Harmenberg JG, Awan AR, Alenius S, et al. ME-609: a treatment for recurrent Herpes simplex virus infections. Antivir Chem Chemother. 2003 Aug 1;14:205–215.

74. Awan AR, Harmenberg J, Kristofferson A, Field HJ. Herpes simplex virus zosteriform lesions with adoptive transfer of immune cells: a murine model which mimics human recurrent disease. Antiviral Research. 1998 Apr 1;38:43–53.

75. Spruance SL, McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet Radiation-induced Herpes simplex labialis: a pilot study. The Journal of Infectious Diseases. 2000 Jun 1;181:1906–1910.

76. Lizarraga KJ, Alexandre LC, Ramos-Estebanez C, Merenda A. Are steroids a beneficial adjunctive therapy in the immunosuppressed patient with Herpes simplex virus encephalitis? CRN. 2013;5:52–55.

77. Nakano A, Yamasaki R, Miyazaki S, Horiuchi N, Kunishige M, Mitsui T. Beneficial effect of steroid pulse therapy on acute viral encephalitis. ENE. 2003;50:225–229.

78. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic eye disease study: a controlled trial of topical corticosteroids for Herpes simplex stromal keratitis. Ophthalmology. 1994 Dec 1;101:1883–1896.

79. Ference JD, Last AR. Choosing topical corticosteroids. AFP. 2009 Jan 15;79:135–140.

80. Rathi SK, D, Souza P. Rational and ethical use of topical corticosteroids based on safety and efficacy. Indian J Dermatol. 2012;57(4):251–259.

81. Chen F, Xu H, Liu J, et al. Efficacy and safety of nucleoside antiviral drugs for treatment of recurrent herpes labialis: a systematic review and meta-analysis. J Oral Pathol Med. 2017 Sep;46:561–568.

82. Hammer K, Dietz J, Lo TS, Johnson E. A systematic review on the efficacy of topical Acyclovir, Penciclovir, and Docosanol for the treatment of Herpes simplex labialis. EMJ Dermatol. 2018:118–123 6[1].

83. Rosa MID, Souza SL, Farias BFD, Pires PDS, Dondossola ER, Reis MEFD. Efficacy of topical 5% Acyclovir-1% Hydrocortisone cream (ME-609) for treatment of Herpes labialis: a systematic review. An Acad Bras Ciênc. 2015;87:1415–1420 Aug 42 suppl.

84. Rajadurai SG, Maharajan MK, Veettil SK, Gopinath D. Comparative efficacy of antifungal agents used in the treatment of oropharyngeal candidiasis among HIV-infected adults: a systematic review and network meta-analysis. J. Fungi. 2021;7:637. doi: 10.3390/jof7080637.

85. Fu X, Tang L, Wang C, et al. A network meta-analysis to compare the efficacy of steroid and antiviral medications for facial paralysis from bell ´s palsy. Pain Physician. 2018 Nov;21:559–569.

86. Al-Maweri SA, Kalakonda B, AlAizari NA, et al. Efficacy of low-level laser therapy in management of recurrent herpes labialis: a systematic review. Lasers Med Sci. 2018 Sep 1;33:1423–1430.

87. Lotufo MA, Tempestini Horliana ACR, Santana T, et al. "Efficacy of photodynamic therapy on the treatment of herpes labialis: a systematic review". Photodiagnosis and photodynamic therapy. 2020 Mar 1;29:101536.

88. Shen Loo Y, Yee Wong T, Veettil SK, Se Wong P, Gopinath D, Mooi Ching S, Kunnath Menon R. Antifungal agents in preventing oral candidiasis in clinical oncology: A network metaanalysis. Oral Dis. 2021;27:1631–1643 OctEpub 2020 Sep 28. PMID: 32762108. doi: 10.1111/odi.13588.

89. Santos E, Ferreira R, Marques A. How to perform and interpret a network meta-analysis for indirect and mixed comparisons: key methodological strategies. Rev Enf Ref. 2016:133–140 Mar 29;IV SérieN o 8.

90. Roever L, Biondi-Zoccai G. Network meta-analysis to synthesize evidence for secision making in cardiovascular research. Arq Bras Cardiol. 2016 Apr;106:333–337.

Fig. 1. PRISMA flow diagram of literature search.

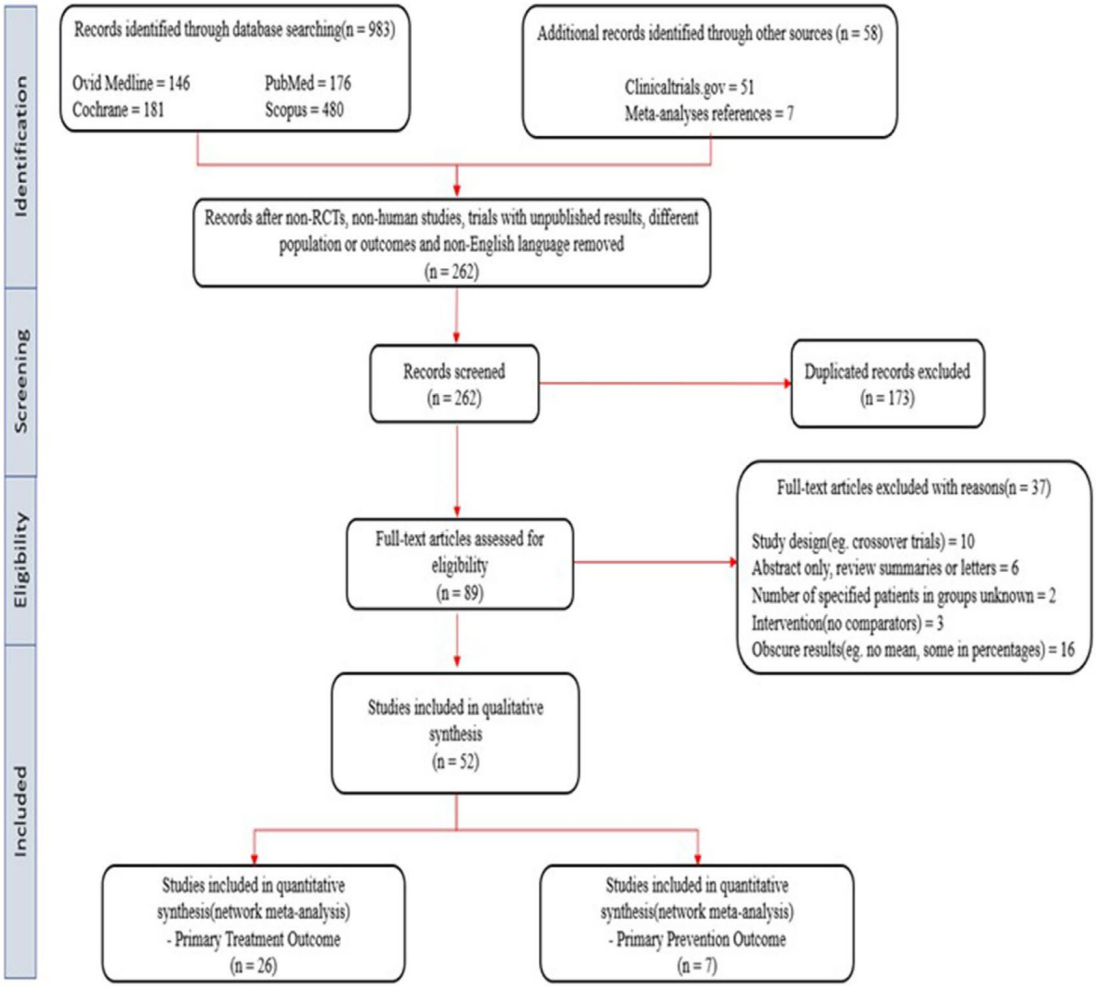

Fig. 2. Risk of bias assessment for studies with TTH outcomes.

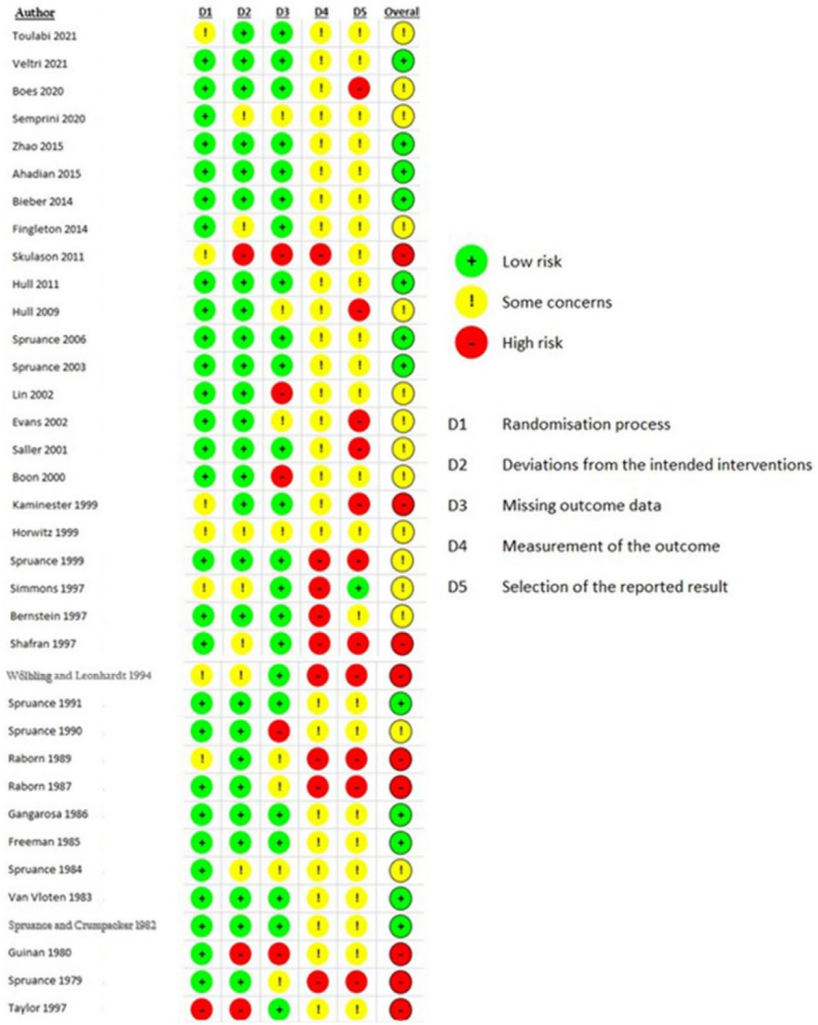

Fig. 3. Network plot on the efficacy of interventions in management of herpes labialis. Abbreviations: ABT=acyclovir buccal tablet; ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; AMP, vidarabine monophosphate; BHT, butylated hydroxytoluene; BM, balm mint(Lo-701) melissa extract; COM, compeed cold sore patch; EGCG, epigallocatechin-3-gallate; ETR, ether; FAM, famciclovir; FSN, foscarnet; HEP, herspatch serum patch; KH, kanuka honey; NaCl, sodium chloride solution; OLE, olive leaf extract; PBO, placebo; PCV, penciclovir; PLN, pleuran; TC, tetracaine; UA, undecylenic acid; VCY+CLO, valacyclovir + clobetasol.

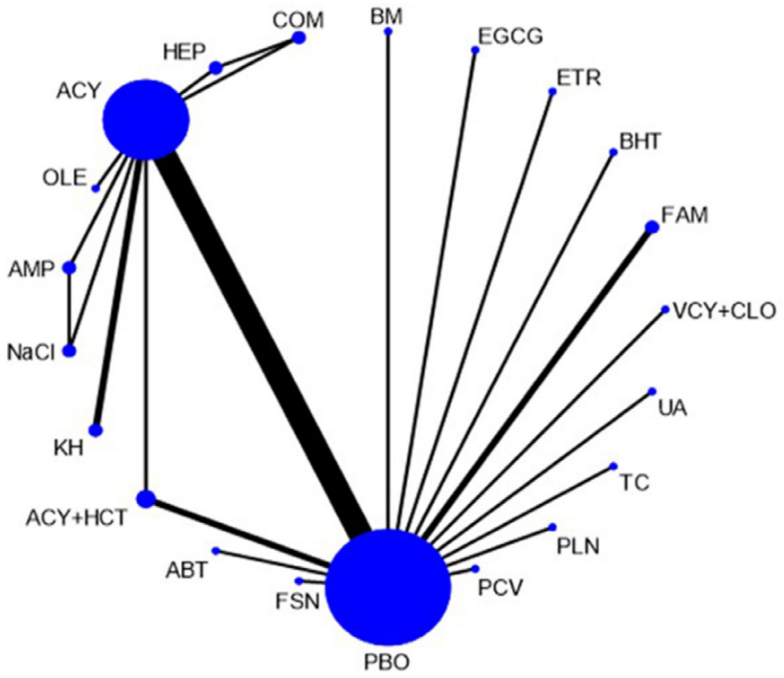

Fig. 4. SUCRA ranking curve graphs for time-to-healing treatment outcome. Abbreviations: ABT, acyclovir buccal tablet; ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; AMP, vidarabine monophosphate; BHT, butylated hydroxytoluene; BM, balm mint(Lo-701) melissa extract; COM, compeed cold sore patch; EGCG, epigallocatechin-3-gallate; ETR, ether; FAM, famciclovir; FSN, foscarnet; HEP, herspatch serum patch; KH, kanuka honey; NaCl, sodium chloride solution; OLE, olive leaf extract; PBO, placebo; PCV, penciclovir; PLN, pleuran; TC, tetracaine; UA, undecylenic acid; VCY+CLO, valacyclovir + clobetasol.

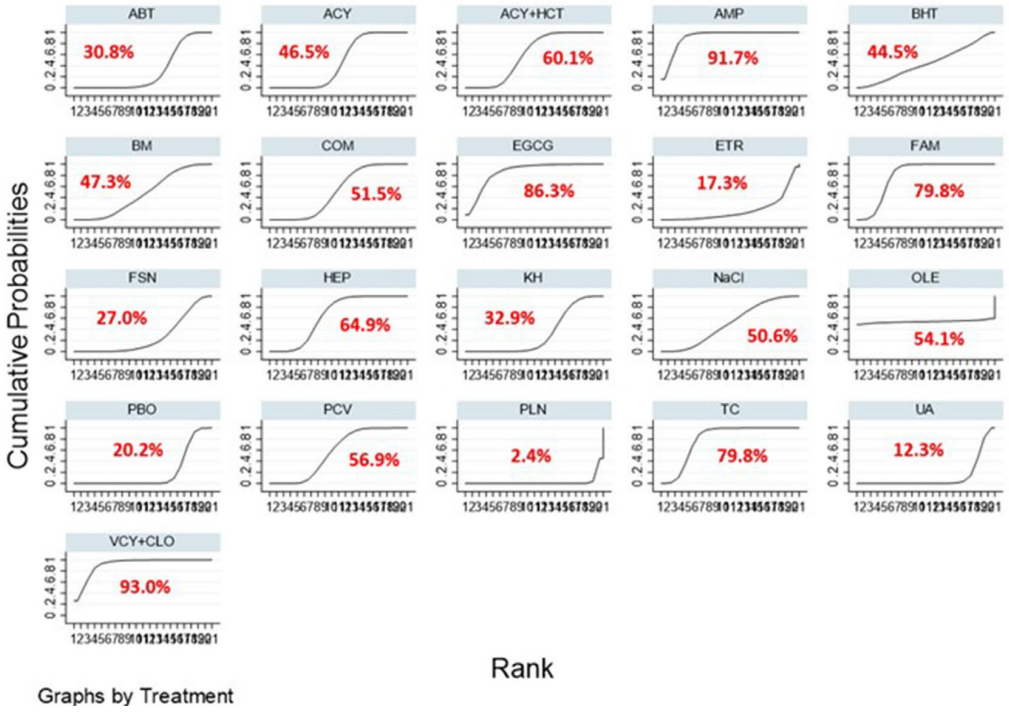

Fig. 5. League table of the network meta-analyses comparing the effects of all interventions in reducing time-to-healing in days (mean) and 95% CI. Bolded and shaded results indicated statistical significance and the treatment specified in the column was more efficient than the one in the row. Abbreviations: ABT=acyclovir buccal tablet; ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; AMP, vidarabine monophosphate; BHT, butylated hydroxytoluene; BM, balm mint(Lo-701) melissa extract; COM, compeed cold sore patch; EGCG, epigallocatechin-3-gallate; ETR, ether; FAM, famciclovir; FSN, foscarnet; HEP, herspatch serum patch; KH, kanuka honey; NaCl, sodium chloride solution; OLE, olive leaf extract; PBO, placebo; PCV, penciclovir; PLN, pleuran; TC, tetracaine; UA, undecylenic acid; VCY+CLO, valacyclovir + clobetasol.

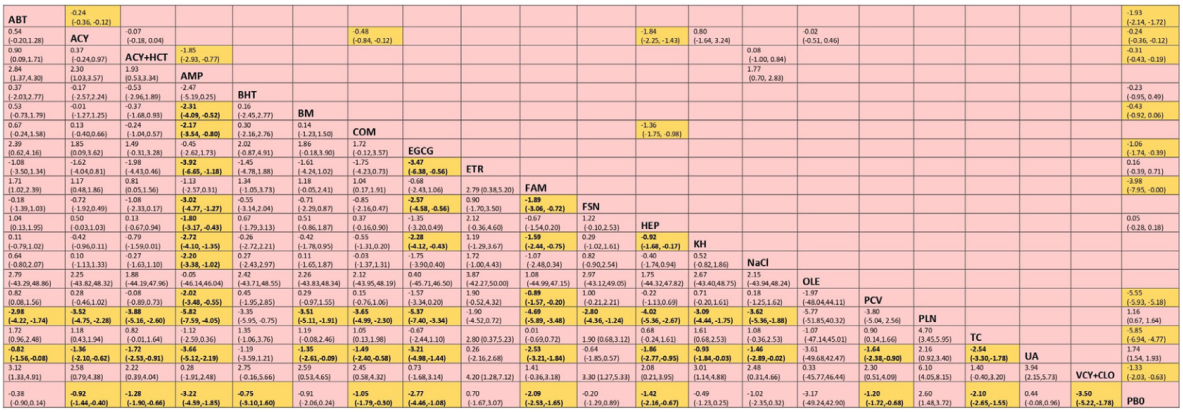

Fig. 6. Network plot on the efficacy of interventions used in the prevention of herpes labialis. Abbreviations: ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; IP, inosine pranobex; PBO, placebo; VCY, valacyclovir.

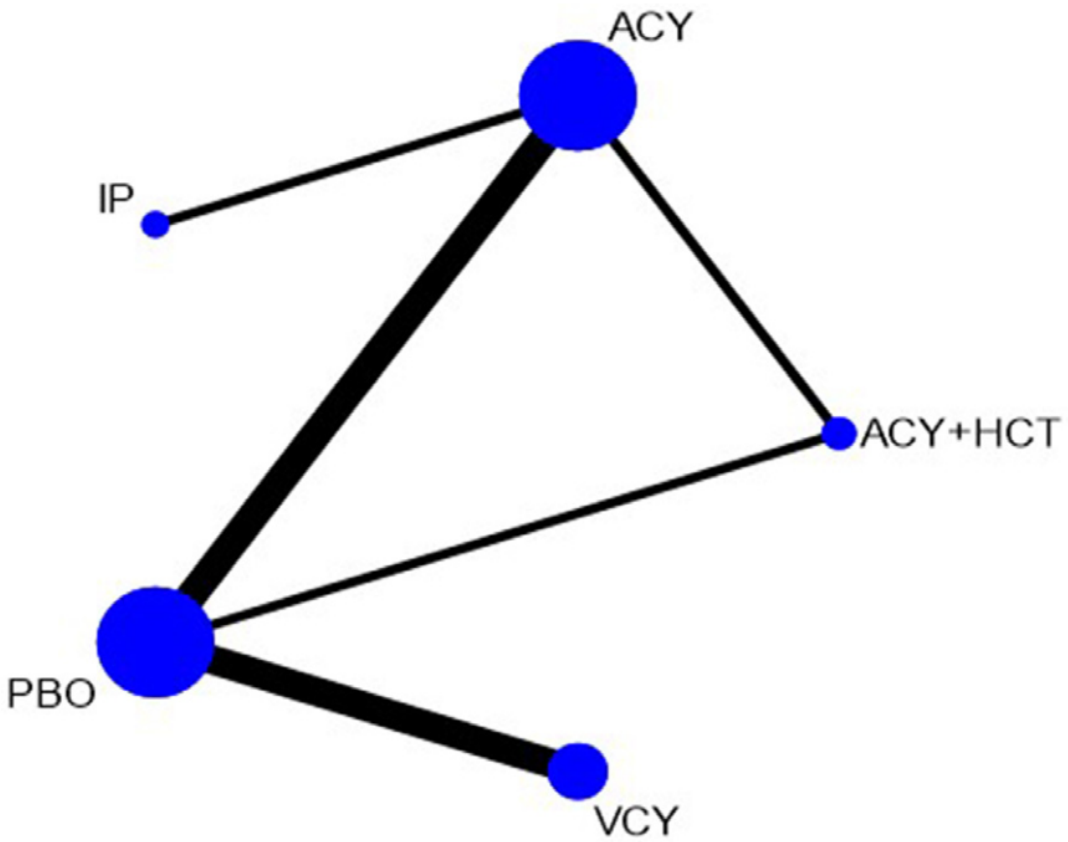

Fig. 7. SUCRA ranking curve graphs for the recurrence outcome. Abbreviations: ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; IP, inosine pranobex; PBO, placebo; VCY, valacyclovir.

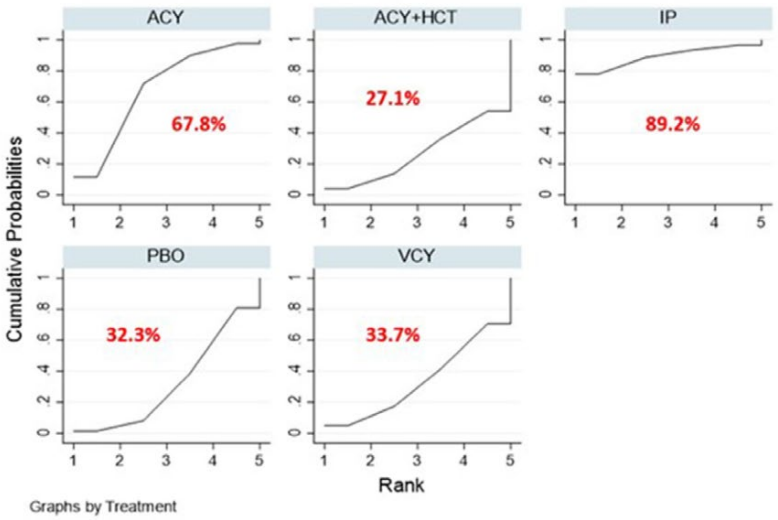

Fig. 8. League table of the network meta-analyses comparing the effects of all interventions in reduction of recurrence. None of the interventions was superior to each other. Abbreviations: ACY, acyclovir; ACY+HCT, acyclovir + hydrocortisone; IP, inosine pranobex; PBO, placebo; VCY, valacyclovir.

ACY				
0.58 (0.21,1.61)	**ACY+HCT**			
1.79 (0.54,5.95)	3.10 (0.64,15.01)	**IP**		
.64 (0.24,1.70)	1.11 (0.33,3.74)	0.36 (0.08,1.68)	**VCY**	
0.64 (0.31,1.32)	1.10 (0.39,3.09)	0.36 (0.09,1.45)	1.00 (0.52,1.91)	**PBO**