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R E S E A R C H A R T I C L E

Effectiveness of amylmetacresol and 2,4-dichlorobenzyl alcohol throat lozenges in patients with acute sore throat due to upper respiratory tract infection: a systematicreview and meta-analysis

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A B S T R A C T

Acute sore throat is an inflammatory symptom characterized by pain, redness, heat and swelling.[1] ‘‘Acute sore throat’’ has used to explain pharyngitis, tonsillitis and laryngitis which occur in a short period of time, which cause from inflammation of the upper respiratory tract.[18] Most common anatomical regions are involved with the pharynx, larynx, tonsils and epiglottis.[2]Sore throat is a common symptom since childhood, an adult may experience two to three sore throats over a period of 12 months.[25,26,14] The non-infective causes of sore throat are usually due to environmental variations, such as seasonal variation, low humidity, second hand smoking, air pollution and a reaction to allergens.[27]Studieshave been found that patients withacute sore throats have showed in significant impact on normal daily activities and functions, including swallowing, talking, eating, working, sleeping and concentration.[14]Literature reviews revealed that bacterial infections (group A b-hemolytic streptococcus) are not the most common causes of sore throats, which contributed to approximately 20% were caused by bacterial infection sore throats in adults.[25] In fact, more than 80% of sore throats in adults are major caused by viral agents, which including of influenza A respiratory syncytial virus, corona virus and rhinovirus.[5,28]Thus, antibiotics are not considered to be the first-line of treatment for uncomplicated acute sore throats.[8]The current study will be considered for inclusion to enable the identification of the current best evidence to examine AMC/DCBA alcohol throat lozenge as an intervention for symptomatic relief in functional benefits in swallowing, throat numbness, relief of pain and reduction severity of throat soreness in patients with acute sore throats due to URTIs, with a further discussion on the implication for future practice. This review was conducted according to an a priori published protocol.

Keywords: inflammatory, DCBA, URTIs, influenza

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Acute sore throat is an inflammatory symptom characterized by pain, redness, heat and swelling.[1] ‘‘Acute sore throat’’ has used to explain pharyngitis, tonsillitis and laryngitis which occur in a short period of time, which cause from inflammation of the upper respiratory tract.[18] Most common anatomical regions are involved with the pharynx, larynx, tonsils and epiglottis.[2]Sore throat is a common symptom since childhood, an adult may experience two to three sore throats over a period of 12 months.[25,26,14] The non-infective causes of sore throat are usually due to environmental variations, such as seasonal variation, low humidity, second hand smoking, air pollution and a reaction to allergens.[27]Studieshave been found that patients withacute sore throats have showed in significant impact on normal daily activities and functions, including swallowing, talking, eating, working, sleeping and concentration.[14]

Literature reviews revealed that bacterial infections (group A b-hemolytic streptococcus) are not the most common causes of sore throats, which contributed to approximately 20% were caused by bacterial infection sore throats in adults.[25] In fact, more than 80% of sore throats in adults are major caused by viral agents, which including of influenza A respiratory syncytial virus, corona virus and rhinovirus.[5,28]Thus, antibiotics are not considered to be the first-line of treatment for uncomplicated acute sore throats.[8] Antibiotics prescribing has progressively increased during the 80s, and in 2000, approximately 60% of patient with acute sore throat caused by URTIs were still prescribed with antibiotics.[29]

The World Health Organization guidelines have discouraged the use of antibiotics for the treatment of viral sore throat.[10] The National Institute for Health and Clinical Excellence guidelines in United Kingdom has suggested a delayed or no antibiotics to be prescript for uncomplicated acute illnesses, including acute sore throat.[8]Furthermore, a reduced unjustified antibiotic usage would reduce the riskdevelopment of antibiotic resistance in the community and primary health care, thus reduce the overall cost burden on the healthcare system.[25]Uncomplicatedacute sore throat presented without complications, such as prolonged fever and difficulty in breathing, can be managed conservatively without the use of antibiotics.[18]The management goals for acute sore throat are to provide symptomatic relief (such as local discomfort and inflammation), prevention of complications.[18]Self management of non-complicated acute sore throat is possible in use of analgesics, local anesthetic, antiseptic and anti-inflammatory agents.[18] Between the two, systemic and local analgesic treatments, the over-the-counter topical remedies such as (1) throat lozenges, (2) gargles and (3) throat sprays, that areused directly to the mouth and throat’s mucosa membrane, and provide more fast symptomatic relief.[29,18] There are obvious differences between the three topical delivery systems, in terms of, onset of action and the amount of active ingredients present in the mouth and throat.[13] Lozenges can be sucked in the oral cavity, that has slowly dissolves and to release the active ingredients directly to the irritated mucosal tissues.[31]Once lozenge dissolves in the mouth, the mouth acts as a reservoir, has prolonged to deliver the active ingredients to the throat.[31] The medicated throat lozenges were being slow releasing action in nature and lasted in an extended period of time, moreover, the convenience of taking throat lozenges will induce patient usually results in a better compliance status.[19]

All AMC/DCBA alcohol throat lozenges contained of two main active ingredients Amylmetacresol (AMC; 0.6 mg) and 2,4-dichlorobenzyl alcohol (DCBA; 1.2 mg), which produced antibacterial, antiviral and local anesthetic properties.[4,14] AMC/DCBA alcohol throat lozenges have been marketed in many countries worldwide for symptomatic relief in uncomplicated acute sore throat.[2] AMC/DCBA alcohol throat lozenges have been shown to be safe and efficient effects to facilitate acute sore throat local symptomatic relief.[3]The study evidence demonstrated the virucidal effect of AMC and DCBA would have significant effects in reducing in viral load, and is believed to have benefits of reducing the symptoms.[5] The local anesthetic action of AMC/DCBA alcohol throat lozenges with a combination of potent channel blocker of AMC, and reduced the potency for sodium channel blocksof DCBA which might be effective to reduce symptoms due to inflammation.[5] Therefore, AMC/DCBA alcohol throat lozenge is thought to be an tropical option to meet patients’ needs and avoid unnecessary prescription of antibiotics.[10]

Lozenges containing AMC/DCBA have been reported in several clinical trials in adults,[15-18] all demonstrated significant improvement in symptomatic relief including analgesic, functional, sensorial, benefit in swallowing, throat numbness, relief of pain and reduction in the severity of throat soreness in patients with upper respiratory tract infections (URTIs),[19] thus allowing patients to re-engage in their daily activities and return to their everyday lives.[20] Nowadays, more emphasis is being given on the quality of a patient’s sore throat functional daily activities, which has increased the incidence of antibiotics resistance in the community.[19]

A preliminary search of Cochrane database of systematic review, JBI database of systematic review and implementation reports, PROSPERO, CINAHL and MEDLINE database revealed that there are no systematic

reviewsavailable regarding the evaluation on the effectiveness of AMC/DCBA alcohol throat lozenge in patients with simpleacute sore throat due to URTIs.

The current study will be considered for inclusion to enable the identification of the current best evidence to examine AMC/DCBA alcohol throat lozenge as an intervention for symptomatic relief in functional benefits in swallowing, throat numbness, relief of pain and reduction severity of throat soreness in patients with acute sore throats due to URTIs, with a further discussion on the implication for future practice. This review was conducted according to an a priori published protocol.

Objectives

The aim of this systematic review is to determine the best available evidence related to the effectiveness of amylmetacresol and 2,4-dichlorobenzyl alcohol throat lozenges in patients with acute sore throat due to upper respiratory tract infection (URTI), to evaluate outcomes, including the change in severity of throat soreness, pain relief ratings, measured functional of difficulty in swallowing and functional of throat numbness and risk of adverse effects. Furthermore, the objective of this study was to examine the analgesic properties of amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA) throat lozenge comparing with placebo for the relief of pain in patients with acute sore throat due to URTIs.

2. Materials and Methods

Inclusion Criteria

Types of participants: The current review considered studies that included adult patients, aged 18 years or over, with primary diagnosis of sore throat with a recent onset within four days due to URTI, baseline sore throat score of >6 on the throat soreness scale (TSS) and objective diagnosed by a physician for the presence of tonsillopharyngitis assessment. This study excluded patients with history of allergy or known intolerance to the study, sore throat presented for more than four days, evidence of severe coughing or mouth breathing and children also will be excluded from this study (as clinical trials reported that lozenges are not recommended to be used by young children).

Types of intervention (s) phenomena of interest:

The current review considered studies that evaluate the effectiveness of using AMC/DCBA throatlozenge of any regimen and dosage as treatment with a placebo in patients with acute sore throatcaused by URTIs related to the following interventions:

- Evaluate the change in severity of throat soreness
- Evaluate the pain relief ratings
- Measured functional of difficulty in swallowing
- Measured functional of throat numbness
- Evaluated risk of adverse effects

This study excluded clinical trials with lozenge only contained in one component of AMC/DCBA; the use of various regimens of AMC/DCBA in spray, gargle, gel and intravenous form, used in adults, will also be excluded.

Comparator intervention: The current review will only consider studies that compared to placebo.

Types of studies:

The current review considered experimental study designs including randomized controlled trials. If there are no randomized controlled trials identified, then other experimental study designs including non-randomized controlled trials, quasi-experimental studies, cohort studies and before and after studies for inclusion.

Outcomes: The current review considered studies that include the following outcome measures:

Primary outcomes:

Severity of throat soreness (methodologies can be measured by subjective rating scales, such as TSS, visual analog scale, ordinal scale, categorical scale, verbal rating scores and change from baseline curve [AUC] data analyses).

Secondary outcomes: Pain relief ratings (methodologies can be measured by subjective rating scales, i.e. pain relief scale, visual analog scale, ordinal scale, categorical scale, verbal rating scores and AUC data analyses).

Difficulty in swallowing (methodologies can be measured by subjective rating scales, i.e. visual analog scale, ordinal scale, categorical scale, verbal rating scores and AUC data analyses).Throat numbness (methodologies can be measured by subjective rating scales, i.e. visual analog scale, ordinal scale, categorical scale, verbal rating scores and AUC data analyses).Risk of adverse effects (such as allergic/hypersensitivity reactions).

Search strategy: The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of PubMed, CINAHL and Embase (via EBSCO) database was first undertaken, followed by an analysis of the text words, contained in the title and abstracts, as well as the index terms used to describe the review. A second search using all identified keywords and index terms was then being undertaken across all included databases. Third, the reference lists of all identified reports and articles were assessed to identify further additional studies. This review considered studies published nationally and internationally in bothEnglish and Chinese languages, as these are the languages understood by the reviewers. Studies published after 1958 was considered for inclusion in this review. The year 1958 was chosen as a date when AMC/DCBA throat lozenge was invented and started being used on human subjects. The databases searched include PubMed, CINAHL, Embase, Medline and Cochrane Central Register for Controlled Trials. The search for unpublished studies included clinical trial registers obtaining full data, if possible, by contacting the authors, Google scholar, ProQuest Dissertations and Theses. Electronic databases to be searched for primary publications written in Chinese will include Electronic theses dissertations system and Chinese Electronic Periodical Services.

Searching other resources: The current review will be identifying additional articles from the searches named above. Furthermore, relevant pharmaceutical companies (Strepsils Reckitt Benckiser Healthcare International, Hull, United Kingdom) of AMC/DCBA alcohol throat lozenges

will be contacted and the manufacturer was requested to provide information on both published and unpublished trials.

Initial keywords used:

- 2,4-dichlorobenzyl alcohol, AMC/DCBA, lozenge and amylmetacresol
- Sore throat and throat soreness
- Upper respiratory tract infection and respiratory infection
- The full search strategy is provided in appendix I.

Method of the review:

Prior to inclusion in the review, retrieved papers meeting the inclusion criteria were assessed by two independent reviewers (C.M. and A.D.) for methodological validity using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistical Assessment and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements arising between two reviewers were resolved through a discussion or with a third reviewer (A.G.).

Data extraction: Quantitative data will be extracted from papers included in the review from JBI-MAStARI (Appendix III). The data were extracted independently by two reviewers (C.M. and A.D.). The data extracted included specific details about the interventions, population, study methods and outcomes of significance to the review question and specific objectives. Author of primary studies were contacted for missing information or to clarify questions about the data.

Data synthesis:

When possible, quantitative data were pooled in statistical meta-analysis using Review Manager 5.3. (Copenhagen: The Nordic Cochrane Centre, Cochrane). All results were subject to double data entry by two reviewers (C.M. and A.D.). Effect sizes (expressed as a risk ratio [RR] for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals (CIs) were calculated for analysis. Statistical heterogeneity was assessed using the standard Chi-square, I^2> 50% to represent substantial heterogeneity. In the presence of significant heterogeneity (P <0.05), a random effects meta-analysis was used. Where high levels of heterogeneity are found, they will be explored by the pre-specified subgroup analyses based on the regimen and dosage of AMC/DCBA alcohol throat lozenge and different study designs included this review. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentations where appropriate.

3. Results and Discussion

Description of studies:

Four studies were retrieved for methodological validity assessment using the JBI-MAStARI tools (Appendix II). Finally, 4 studies published between 2009 and 2012 met all inclusion criteria for the review and quality appraisal, flow diagram is shown in figure 1. The excluded studies and their reasons for exclusion are listed in Appendix IV and included studies and their findings and conclusions can be found in Appendix V.

Studies within this review included randomized controlled trials, as stated in the inclusion criteria in the review protocol. Of the 4 studies, 2 had two groups; an intervention group (IG) and a control group (CG) receiving usual care, 2 had three groups, two intervention group (IG) and a control group (CG) receiving usual care. In all RCTs, throat lozenges containing 0.6mg AMC and 1.2mg DCBA were applied with intervention group, control group were treated with sugar-based non-medicated place lozenge.All of these studies were conducted in the UK; four studies were conducted in community.

Type of population

Included studies involved 1035 participants were aged 16 years and above, with a median age of 31 years and over in four studies. There were reported mild adverse effects in 4 studies. The participants involved in 4 included studies were primary diagnosis of sore throat with a recent onset within the past four days, due to upper respiratory tract infection. All participants had a baseline sore throat score of >6 on the throat soreness scale (TSS); objective confirmation by a physician for the presence the tonsillopharygitis assessment (TPA).

Type of outcome measure

The included studies, comprised of primary endpoints measured were the change from baseline at 2 hours in severity of throat soreness. The included studies comprised of secondary endpoints measured included change from baseline in 0-120 minutes in throat soreness using the 11-point throat soreness scale, which ranged from 0=not sure to 10=very sore). Difficulty in swallowing (was using a 100mm visual analogue scale (VAS) from ‘not difficult’ to ‘very difficult’ to swallow) and has assessed as change from baseline in 0-120 minutes.

Sore throat relief (was using 7-point categorical scale: no relief; or slight, mild, moderate, considerable, almost complete, or complete relief) and has assessed as change from baseline in 0-120 minutes.Only three included studies were examined throat numbness, which has using 5-point categorical scale: none, mild, moderate, considerable, complete numbness, these were assessed as change from baseline in 0-120 minutes. Area under curve (AUC) from 0 to 2 hours for the change from baseline in severity of throat soreness, difficulty swallowing, sore throat relief, throat numbness. Only two included studies were examined the change from baseline in severity of throat soreness, difficulty swallowing, sore throat relief, at the end of day 1, at 24 hour after first dose and at the end of day 2 and 3.

Other reported outcomes

Four studies were reported on significant improvement effects in subjective rating scales of the general conditions in patients treated in intervention group, compared with control group on various components of consumer questionnaires. Wade (2011) found on emotional benefits were reported in patients treated with AMC/DCBA throat lozenge compared with placebo group.

Methodological quality

The methodological quality was assessed using the 10-item JBI-MAStARI standardized critical appraisal tool. Concerning randomization (question 1); overall 4/4 studies

were considered truly random with clear explanation of the randomization procedure (Table 1). Blinded participants criteria (question 2) was applicable in 4/4 studies. Blinded allocation (question 3) was clearly described in 4/4 studies. A description of outcomes among subjects who withdrew (question 4) was stated in 4/4 studies. 4/4 studies were defined as unclear as they lacked an explanation of the blinded assessment procedure (question 5). 4/4 studies demonstrated group equivalency at baseline (question 6). In total, 4/4 studies adequately described both intervention and control groups (question 7). All studies met criteria for question 8 related to a consistent and clear measurement of outcomes across groups. All studies were considered adequate on criteria for question 9 and 10 as outcomes were deemed to be measured in a reliable way and analyzed using appropriate statistical analysis.

Findings of the review

A total of 4 factors were identified in this review of which all 4 factors with included trials identified that could be combined in meta-analysis given the homogeneity of the outcomes measured and patient population of the studies.

Primary Outcome

Severity of throat soreness was conducted in all 4 included studies, pooling data revealed no significant heterogeneity (Tau^2= 0.00, Chi^2= 6.51, *P* =0.16, I^2=39%). A meta-analysis using the random-effects model found a significant difference in the AUC results for the change from baseline to 2 hours post dose in severity of throat soreness of AMC/DCBA warm lozenge and AMC/DCBA cool lozenge compared to placebo. The summary of mean difference in severity of throat soreness is -1.22 (95%CI = -1.27, -1.18; *P*<0.00001) (Figure 2).

Two included trials reported the differences of severity of sore throat over 3 days. Pooling data revealed no significant heterogeneity (Tau^2= 0.00, Chi^2= 3.86, *P* =0.05, I^2=74%). The weighted mean differences was -1.84 (95%CI = -1.90, -1.77; *P*<0.00001) (Figure 3), suggested that AMC/DCBA alcohol throat lozenge group induced significantly different mean change from baseline in severity of throat soreness data obtained at the end of day 3 compared with placebo group.

Secondary Outcome

Sore throat relief

Three included studies reported the effects on sore throat relief for AMC/DCBA alcohol throat lozenge compared to placebo. Subgroup analysis was done to compare results from wade et al study with different regimen of AMC/DCBA warm lozenge and AMC/DCBA cool lozenge. Pooling data revealed no significant heterogeneity (Tau^2= 0.00, Chi^2= 3.33, *P* =0.34, I^2=10%), and the overall effect score was significant (Z=23.92, *P*<0.00001). The weighted mean difference was 1.07 (95% CI = 0.98, 1.16; *P*<0.00001) (Figure 4). Suggesting AMC/DCBA lozenges induced significant sore throat relief change in the AUC results for the change from baseline in 2 hours post dose.

Difficulty in swallowing

All four trials reported difficulty in swallowing, no statistical heterogeneity was found across the trials (Tau^2= 0.05, Chi^2= 6.00, *P* =0.20, I^2=33%). A meta-analysis using the random-effects model revealed significant differences in difficulty in swallowing between AMC/DCBA lozenge and placebo groups in the AUC result for the change from baseline to 2 hours post dose. The weighted mean difference was -11.16 (95% CI = -11.54, -10.79; *P*<0.00001) (Figure 5), suggesting that AMC/DCBA lozenge has significant improvement in difficulty in swallowing compared with placebo lozenge.

Two included studies reported the difficulty in swallowing over 3 days. Pooling data revealed significant heterogeneity (Tau^2= 0.00, Chi^2= 0.45, *P* =0.50, I^2= 0%). The weighted mean difference was -17.09 (95% CI = -17.39, -16.80; *P*<0.00001) (Figure 6). The meta-analysis showed the difference between treatments in the change from baseline in difficulty in the change from baseline in difficulty in swallowing gradually increased over the 3-day period.

Throat Numbness

Throat numbness was assessed in two studies, substantial statistical heterogeneity was found across the two trials (Tau^2= 0.04, Chi^2= 5.49, *P* =0.06, I^2=64%). By pooling the two trials together, a meta-analysis using the random-effects model found a significant differences in throat numbness between AMC/DCBA and placebo lozenge groups in the AUC results for the change from baseline to 2 hours post dose, the weighted mean difference was 0.44 (95% CI = 0.16, 0.72; *P* =0.002) (Figure 7).

Adverse Events

Adverse events and number of patients with at least one adverse event were reported in all four included trials. In total 14.7% of the participants treated with AMC/DCBA alcohol throat lozenge had adverse events compared to 17.3% in the placebo groups. Most of reported adverse events were mild such as: headache, cough, chills, pyrexia and congestion. Majority of the adverse events were related to participants' progression of URTIs. Four included trials reported adverse events, a statistical heterogeneity was found (Tau^2= 0.09, Chi^2= 6.72, *P* =0.15, I^2= 40%). A meta-analysis using the random-effects model found significantly fewer adverse events in participants who received AMC/DCBA alcohol throat lozenge (14.7% AMC/DCBA vs 17.3% placebo; risk ratio = 0.77; 95% CI = 0.50, 1.20; *P* =0.25) (Figure 8).

Discussion

The results of this systematic review show that AMC/DCBA alcohol throat lozenges are consistently more effective for sore throat reduction caused by URTIs in adult patients compared to a placebo non-medicated throat lozenge in AUC for the change from baseline to 2 hours after first dose and at the end of day 3. Sucking candy is a popular therapy and is likely that lozenge to reduced the pain, such as: by increasing saliva flow and reducing mouth dryness.[20] Lozenges are an effective format for release of active ingredients to the throat, and have a long lasting period of time to dissolves in the mouth, which provided a constant delivery of the active ingredients to the affected region.[18] Lozenges containing the active ingredients AMC/DCBA are broadly available over-the-counter and have been shown to be highly effective for symptomatic relief of acute sore throat.[1,15]

This meta-analysis included four RCTs that compared the severity of throat soreness of AMC/DCBA and placebo throat lozenge group. The summarized observed throat soreness reduction of -1.23 (95% CI = -1.27, -1.19), for AMC/DCBA lozenge were significantly better than placebo, assessed by AUC for the change from baseline to 2 hours post dose; and severity throat soreness reduction was -1.84 (95% CI = -1.90, -1.77) at the end of day 3 were significantly greater for AMC/DCBA throat lozenge group compared with placebo lozenge groups.

This review identified four randomized trials published 2010 to 2012, (involving 1035 participants) that assessed the effectives of AMC/DCBA alcohol throat lozenge in the relief of patient with acute sore throat due to URTIs. AMC/DCBA alcohol throat lozenge also provides sore throat relief and improves in throat soreness, difficult in swallowing and numbness of throat for the duration of 2 hours. However, the included studies have report uncertain risk of bias due to lack of assessing outcomes of blinding to the treatment allocators.The two included studies examined severity of sore throat and difficulty in swallowing over 3 days, there was high heterogeneity in the meta-analysis and the possibility of the low number of events and trials to evaluate this outcomes.

One of the included studies has analyzed variants excipients of AMC/DCBA alcohol throat lozenge (AMC/DCBA cool lozenge and AMC/DCBA warm lozenge). Despites explored subgroups meta-analyses, which shows that AMC/DCBA alcohol throat lozenges have reduced in severity of sore throat, relief in pain, improves difficulty in swallowing and throat numbness.

Limitation

This review has some limitations to the findings of this systematic review. Four of included studies were analyzed the efficacy endpoints at AMC/DCBA alcohol throat lozenge were the AUC from baseline to 2 hours for the change from baseline in severity of throat soreness, sore throat relief, difficulty in swallowing and throat numbness. Different from other studies, only two of included studies efficacy endpoints have reported severity of throat soreness and difficulty in swallowing over 3 days, other outcomes endpoints such as throat numbness, sore throat relief have not reported.

The included RCTs were all sponsored by the manufacturer and all of them were published from United Kingdom. Selection bias is not sufficiently described, there were few dropouts and it is not reported, as participant flow chart as stipulated by CONSORT-statements was only available for two included trials. This review has restriction of studies to English and Chinese, one other trial were published in German, and we could only extracts the information available in English abstracts and this lack of information limited our ability to assess the risk of bias and to include the data in our meta-analysis.

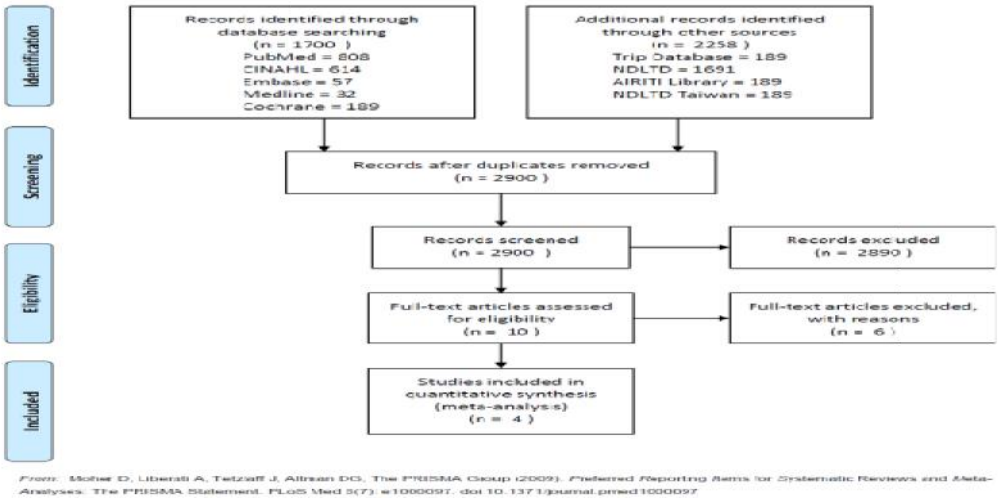

Fig 1: Flow chart of literature search and study selection

Table 1: Assessment of methodological quality

References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Wade et al	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	9/10
Macnally et al	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	9/10
Thomas MI	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	9/10
Mcnally et al	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	9/10
	4/4	4/4	4/4	4/4	0/4	4/4	4/4	4/4	4/4	4/4	

This table shows the results of critical appraisal for the included studies (listed in the first column). Refer to Appendix II for question 1-10 in the relevant MAStARI critical appraisal instruments. Q1, Q2, Q3 – study population representativeness (inclusion and exclusion criteria). Q4 – Confounding factors identified and addressed. Q5 and Q7 – Outcomes criteria relevant and standardized in assessment. Q6 and Q8 – Follow-up duration sufficient. Q9 and Q10 – Appropriate statistical techniques. U= unclear; Y= Yes

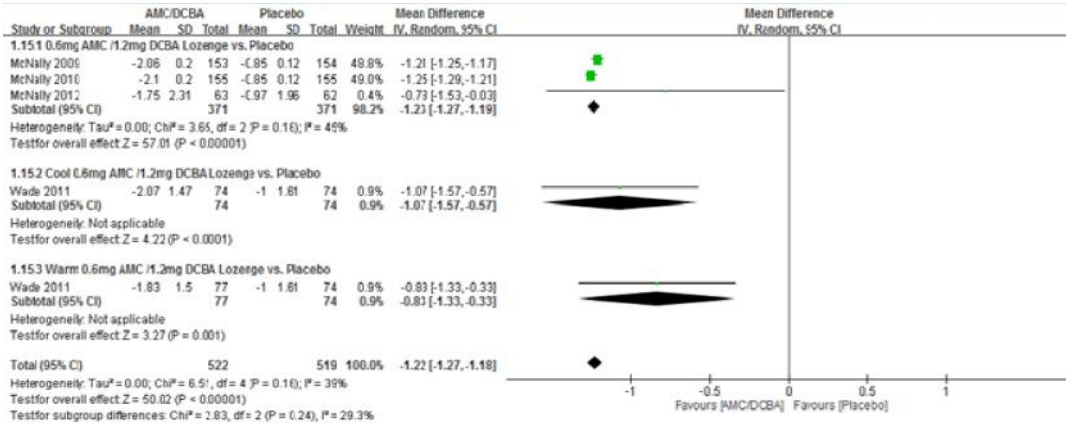

Fig 2: Meta analysis for severity of throat soreness by types of Cool / Warm AMC/DCBA lozenge formulation (forest plots of mean difference within a random effect model by types of AMC/DCBA lozenge for severity of throat soreness for included studies)

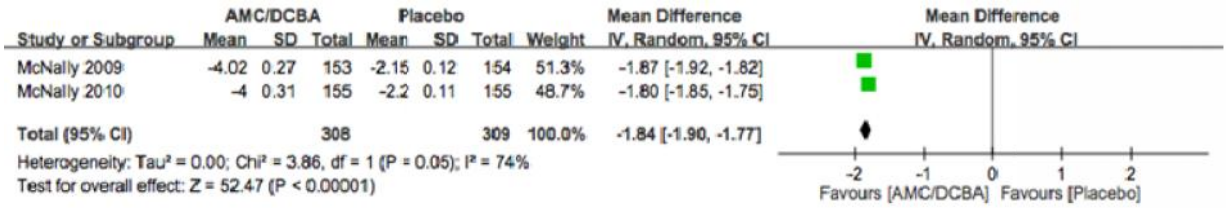

Fig 3: Meta analysis for AUC from baseline to 3 days for severity of throat soreness by AMC/DCBA throat lozenge (forest plots of mean difference within a random effect model by AMC/DCBA lozenge for severity of throat soreness for included studies)

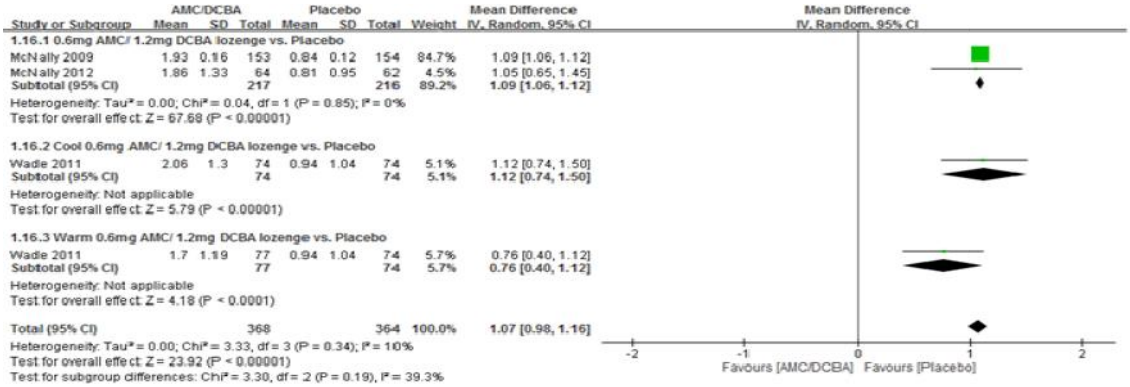

Fig 4: Meta analysis for sore throat relief by types of Cool / Warm AMC/DCBA lozenge formulation (forest plots of mean difference within a random effect model by types of AMC/DCBA lozenge for sore throat relief for included studies)

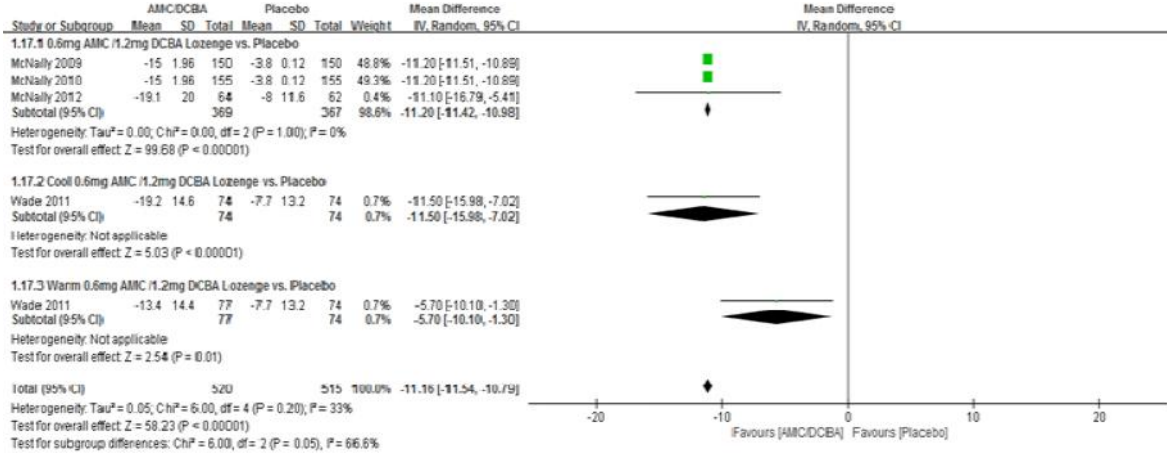

Fig 5: Meta analysis for difficulty in swallowing by types of Cool / Warm AMC/DCBA lozenge formulation (forest plots of mean difference within a random effect model by types of AMC/DCBA lozenge for difficulty in swallowing for included studies)

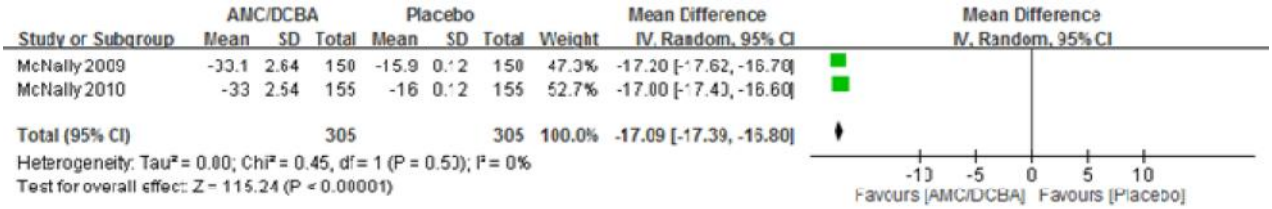

Fig 6: Meta analysis for AUC from baseline to 3 days for difficulty in swallowing by AMC/DCBA throat lozenge (forest plots of mean difference within a random effect model by AMC/DCBA lozenge for difficulty in swallowing for included studies)

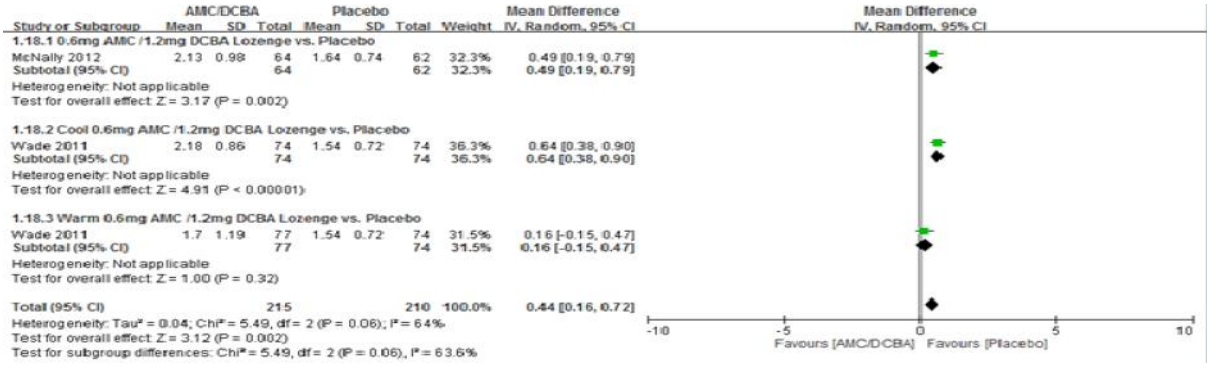

Fig 7: Meta analysis for throat numbness by types of Cool / Warm AMC/DCBA lozenge formulation (forest plots of mean difference within a random effect model by types of AMC/DCBA lozenge for throat numbness for included studies)

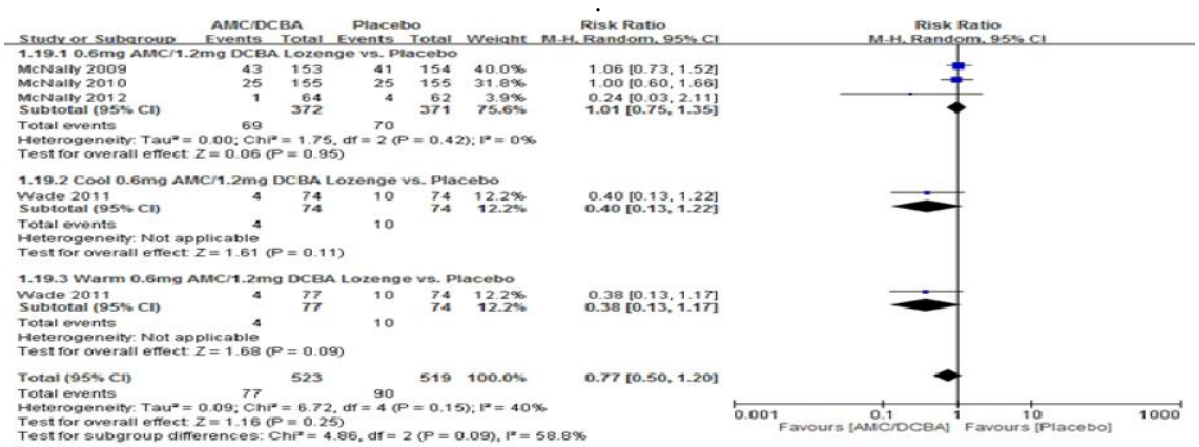

Fig 8: Meta analysis for Adverse Effects by types of Cool / Warm AMC/DCBA lozenge formulation (forest plots of risk ratio within a random effect model by types of AMC/DCBA lozenge for adverse events for included studies)

4. Conclusion

Findings of this review suggest that AMC/DCBA alcohol throat lozenges are well-tolerated and provide safe, fast and effective treatment option to be provided for uncomplicated acute sore throat relief in patients with URTIs.

Implication for practice

The review found AMC/DCBA alcohol throat lozenge provides safe and effective relief for acute sore throat caused by URTIs. The review found the beneficial effects of AMC/DCBA alcohol throat lozenge, which has showed significantly reduced in severity throat soreness, relief of difficulty in swallowing and patient can feel analgesic effects working soon after first lozenge administration. Studies demonstrated that continued used AMC/DCBA over a 3-day period provides significantly greater improvement in throat soreness, and better easing of throat numbness. This would reduce unnecessary in antibiotic prescription, to minimized bacterial resistance and unnecessary exposure to potential adverse effects and reduce cost for health care systems. AMC/DCBA alcohol throat lozenges suggest to be one of effective OTC regimen, proven in effective relief of the physical symptoms, hence provide more symptom-free days, and a better quality of daily living, and this review advices the use of AMC/DCBA alcohol throat lozenge as an option in self-care of uncomplicated acute sore throat caused by URTIs.

Implication for research

Additional high-quality and large randomized controlled studies of the AMC/DCBA alcohol throat lozenges for improving sore throat will be necessary. Any further trial should analyze the standard efficacy endpoints trial of physical symptoms for the AMC/DCBA alcohol throat lozenges. Satisfaction to be measured (Correction) in any of the review studies and would be a useful addition to any of

the future trial. There also will be some evidence from this review that the various results may occur when population is drawn from various countries and populations.

Conflict of Interest: We declare no conflict of interest.

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