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

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Review question/objective: This review aims 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). The objective is 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.

The review question is:

- Are amylmetacresol (AMC 0.6 mg) and 2,4-dichlorobenzyl (DCBA 1.2-mg) alcohol throat lozenges effective in relieving acute sore throat caused by URTIs?

More specifically, the objectives are to:

- Evaluate changes in severity of throat soreness
- Evaluate the pain relief ratings
- Measure functional difficulty in swallowing
- Measure functional throat numbness.

Keywords 2,4-Dichlorobenzyl alcohol; amylmetacresol; lozenge; respiratory infection; sore throat

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Background

Acute sore throat is an inflammatory condition characterized by pain, redness, heat and swelling.[1] It is a term often used to describe pharyngitis, tonsillitis and laryngitis that occur for a short period of time, which result from inflammation of the upper respiratory tract.[2] Four regions are principally involved – the pharynx, the larynx, the tonsils and the epiglottis.[2] On average, regardless of a pandemic influenza year, an adult may experience two to three sore throats over a period of 12 months.[2] The non-infective causes of sore throat are usually due to environmental variations, such as temperature changes, low humidity, second hand smoking, air pollution and a reaction to allergens.[3] Furthermore, it has been found that sore throats have a significant impact on normal daily activities and functioning in a patient, including swallowing, talking, eating, sleeping and concentration.[4] Literature reviews show that bacterial infections are not the most common causes of sore throats; the most common bacterial cause is group A b-hemolytic streptococcus (*Streptococcus pyogenes*), which contributes to approximately 20% of all (overall sore throat or only bacteria caused) sore throats in adults.[5] In fact, up to 80% of sore throats in adults are caused by viruses, such as influenza A respiratory syncytial virus, severe acute respiratory syndrome corona virus and rhinovirus.[5,6] Thus, antibiotics are generally not the first-line of treatment for acute sore throats.[7]

Throughout the 1980s, there was a progressive increase in the overall consumption of antibiotics in the United Kingdom,[8,9] and in the year 2000, antibiotics were still prescribed to over two-thirds of

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patients presenting to general practice with respiratory tract infections, 60% of whom presented with sore throats.[9] The World Health Organization guidelines have discouraged the prescription of antibiotics for the treatment for viral sore throat.[9] The National Institute for Health and Clinical Excellence guidelines in United Kingdom has recommended no antibiotics or a delayed prescription of antibiotics for minor acute illnesses, including sore throat.[8] Furthermore, reduced antibiotic prescription would reduce the development of antibiotic resistance in the community and reduce the overall cost burden on the healthcare system.[10] Delayed prescription of antibiotics (such as using antibiotics only if symptoms worsen) in cases of acute sore throat is viewed as being more cost effective for the healthcare system.[9]

Most cases of acute sore throat without symptoms and signs of complications, such as prolonged fever and difficulty in breathing, can be managed conservatively without the use of antibiotics.[9,10] The management of acute sore throat aims to provide symptomatic relief (such as local pain and inflammation), removal of the underlying causes and prevention of secondary complications.[11] Self-management of non-complicated, simple acute sore throat is possible through the use of analgesics, local anesthetic, antiseptic and anti-inflammatory agents.[9] Between the two, systemic and local analgesic treatments, topical remedies such as throat lozenges, gargles and throat sprays, which are applied directly to the mucous membranes of the mouth or throat, provide more rapid symptomatic relief in patients with acute sore throats.[11] There are clear differences between the three topical delivery systems in the onset of action and the amount of active ingredients present in the mouth and throat.[12] Lozenges are placed in the oral cavity where they slowly dissolve to release the active ingredients directly onto the irritated mucosal tissues.[11] As lozenges dissolve in the mouth, the mouth acts as a reservoir, distributing the lozenge contents to the throat.[10] Therefore, the medicated throat lozenges have the added advantage of being slow releasing and over a prolonged period of time.[10] Furthermore, the convenience of taking lozenges usually results in good compliance.[10]

All AMC/DCBA throat lozenges containing the two core active ingredients: amylmetacresol (AMC; 0.6 mg) and 2,4-dichlorobenzyl alcohol (DCBA; 1.2 mg); both possess antibacterial, antiviral and local anesthetic properties.[4,13] Amylmetacresol and 2,4-dichlorobenzyl alcohol throat lozenges have been marketed in many countries worldwide for pain relief in acute sore throat.[2] Amylmetacresol and 2,4-dichlorobenzyl alcohol throat lozenges have been shown to be safe and efficient in relieving of acute sore throat symptoms,[14] and it produces an immediate symptomatic relief.[15] Local symptomatic pain relief plays an important role in managing acute sore throat.[3] In-vitro evidence has demonstrated the virucidal effect of AMC and DCBA on a number of viruses associated with the common cold;[7] a reduction in viral load is believed to have benefits in reducing the symptoms. The local anesthetic action of AMC/DCBA throat lozenges, a combination of the potent channel blocker – AMC and the reduced potency for sodium channel blockade DCBA – attenuate the effects of AMC, possibly as a result of competitive binding, which acts on a sodium channel blocker, and may be effective in relieving symptoms due to inflammation.[9] Therefore, AMC/DCBA throat lozenge is thought to represent a useful option to meet patients' needs and avoid unnecessary prescription of antibiotics.[9]

Lozenges containing AMC/DCBA have been reported in several clinical trials in adults[14-17] and have demonstrated significant greater improvement for symptomatic and pain relief, such as difficulty swallowing and throat numbness, and a reduction in the severity of throat soreness in patients with upper respiratory tract infections (URTIs),[15] thus allowing patients to resume their daily activities.[18] 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.[15]

A preliminary search of the Cochrane Database of Systematic Reviews, *JBI Database of Systematic Reviews and Implementation Reports*, PROSPERO, CINAHL and MEDLINE located no systematic reviews that have evaluated the effectiveness of AMC/DCBA alcohol throat lozenges in patients with acute sore throat due to URTIs.

This systematic review will identify the current best evidence to examine AMC/DCBA alcohol throat lozenges as an intervention for symptomatic relief and functional benefits in swallowing, throat numbness and pain, and reduction in the severity of

throat soreness in patients with acute sore throats due to URTIs, with a further discussion on the implications for future practice.

Inclusion criteria

Types of participants

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

Types of interventions

The current review will consider studies that evaluate the effectiveness of using AMC/DCBA throat lozenge of any regimen and dosage as treatment with a placebo in patients with acute sore throat caused by URTIs related to the change in severity of throat soreness, pain relief ratings, difficulty in swallowing and throat numbness. This study will exclude clinical trials with lozenges only contained in one component of AMC/DCBA; the use of various concentrations 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 have been compared to placebo (sugar-based, non-medicated lozenge).

Outcomes

The current review will consider studies that include the following outcomes:

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 (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).

Types of studies

The current review will consider randomized controlled trials for inclusion. 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 will be considered for inclusion.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed, CINAHL and Embase (via EBSCO) will be 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 will then be undertaken across all included databases mentioned below. Refer to Appendix I for details on how key search terms will be combined. Third, the reference lists of all identified reports and articles will be searched for additional studies. This review will consider studies published nationally and internationally in both English and Chinese languages, as these are the languages understood by the reviewers. Studies published after 1958 will be considered for inclusion in this review. The year 1958 was chosen as AMC/DCBA throat lozenges were first introduced and started being used on human subjects then.

The databases to be searched include PubMed, CINAHL, Embase and Cochrane Central Register for Controlled Trials.

The search for unpublished studies will include 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 systems and Chinese Electronic Periodical Services.

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 will be requested to provide information on both published and unpublished trials.

Initial keywords to be used will be:

- 2,4-dichlorobenzyl alcohol, AMC/DCBA, lozenge and amylmetacresol
- Sore throat and throat soreness
- Upper respiratory tract infection and respiratory infection.

Assessment of methodological quality

Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistical Assessment and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements will be resolved through a discussion or with a third reviewer.

Data extraction

Quantitative data will be extracted from papers included in the review from JBI-MAStARI (Appendix III). The data extracted will include specific details about the interventions, population, study methods and outcomes of significance to the review question and specific objectives. Data will be extracted independently by two reviewers before conferring, and a third will be used if there is any disagreement. If there is information missing in the relevant studies, the corresponding authors will be contacted and given opportunities to clarify the information. Multiple, independent data extractors will be used to minimize errors during the extraction process.

Data synthesis

Quantitative research findings will, where possible, be pooled in statistical meta-analysis using Review Manager 5.3. (Copenhagen: The Nordic Cochrane Centre, Cochrane). All results will be subject to double data entry. The outcomes of this study will be assessed by the change from baseline curve (AUC) in 0–120 min and three-day period in severity of throat soreness, sore throat relief, difficulty in swallowing and throat numbness. Effect sizes expressed as risk ratio for categorical data (adverse effects) and weighted mean differences for continuous data (mean severity of throat soreness, mean sore throat relief ratings, mean difficulty in swallowing and mean numbness of throat) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statically using the standard Chi-square, $I^2 > 50\%$ to represent substantial heterogeneity. 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 lozenges 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 presentation where appropriate.

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Appendix I: Search strategy

1	Amylmetacresol or cresol
2	Dichlorobenzyl alcohol or benzyl alcohol
3	Upper respiratory tract infection or respiratory tract infection
4	Sore throat or phayngitis or exp throat soreness
5	1 or 2
6	5 and 3 and 4

Appendix II: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_____Date_____

Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4. Was there a control group?	☐	☐	☐	☐
5. Was there multiple measurements of the outcome/conditions both pre and post the intervention/exposure?	☐	☐	☐	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	☐	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix III: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number