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Ear drops for the removal of ear wax (Protocol)

Burton MJ, Aaron K, Warner L

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[Intervention Protocol]

Ear drops for the removal of ear wax

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of ear drops (or sprays) to remove or aid removal of ear wax in adults (aged 18 years and over) and children (aged under 18 years).

BACKGROUND

Description of the condition

Ear wax (cerumen) is a normal bodily secretion that becomes a problem when it blocks the ear canal. People may seek medical attention when they have a sensation of blockage or hearing loss. These symptoms can also be caused by conditions other than wax. Nonetheless, symptoms *attributed* to wax are among the commonest reasons for patients to present to their primary care or general practitioner (GP) with ear trouble.

Wax obstruction is more common in men than in women and is particularly common in the elderly and people with intellectual impairment (Kumar Sinha 2008; Moore 2002; Roeser 1997; Roland 2008). Ear wax removal is the most common ENT procedure performed in primary care; it is performed between four and eight million times each year in the US and the UK (Grossan 1998; Guest 2004).

Wax is part of the self cleaning mechanism of the ear and usually comes out of the ear canal without causing problems. However, when natural expulsion fails, wax is retained in the canal and may become impacted. An occluding wax plug is not associated with poor personal hygiene. Wax may get impacted if people try to clean their ear with cotton buds or when they regularly put things in their ears (for example, earbud-type headphones and hearing aids).

The accumulation of wax may be associated with a sensation of blockage but, conversely, not all patients who feel their ears are blocked actually have a problem related to wax. Wax accumulation has several consequences: (a) it can interfere with the clinician's view of the tympanic membrane; (b) it can cause a conductive hearing loss and hence may interfere with formal hearing assessment; (c) if in contact with the tympanic membrane it can cause discomfort and occasionally vertigo; and (d) it can contribute to infection (Keane 1995). Wax removal can help to solve these problems and potential complications.

Once wax has accumulated enough to cause symptoms or prevent a

clear view of the tympanic membrane, interventions to encourage or secure its removal may be considered. There are several ways in which this may be done and the methods chosen vary around the world.

Self administered remedies include the use of drops to soften or disperse the wax. This may prevent the need for any further intervention. Alternatively, it may make the alternative, mechanical methods of wax removal easier and more effective. The mechanical methods are of two types: dry or wet.

With the dry methods the wax is removed under direct vision using ear curette (a type of surgical instrument), hook or suction. These methods are used in conjunction with an operating microscope. With the wet cleansing methods, ear syringing or irrigation with body temperature water is used to 'wash out' the wax from the ear canal. There are advantages and disadvantages of each of these methods and not all methods are suitable for all patients. In particular, the mechanical methods described in this paragraph are less often undertaken in children.

Description of the intervention

A variety of topical medications are available that can be applied directly into the ear canal with the aim of softening the wax to aid natural expulsion or mechanical removal. The word 'cerumenolytic' has been used to refer to compounds that lead to the disintegration of wax. The liquids used are typically administered in drop or spray form.

Liquids used to remove/soften wax are of several kinds:

- Oil-based compounds, which soften the wax by dissolution (for example, olive or almond oil).
- Water-based compounds, which improve water miscibility (for example, sodium bicarbonate) or water itself.
- A combination of the above.
- Non-water, non-oil-based solutions, such as carbamide peroxide (a hydrogen peroxide-urea compound) and glycerol.

How the intervention might work

The intended mode of action for these medications is to dissolve or soften the wax sufficiently to allow natural expulsion or to make mechanical removal easier.

Why it is important to do this review

Ear wax accumulation is common and may cause considerable problems. The widespread use of ear drops (with or without ear syringing or suction) suggests that many practitioners believe them to be effective (Burton 2009; Hand 2004), although a more recent systematic review has shown weak evidence for cerumenolytics alone in improving wax clearance compared to no treatment (Wright 2015). The Cochrane review of ear drops for the removal of ear wax was last updated in 2009 (Burton 2009); this is a new protocol for the next update of this review. It is important to update this review as it addresses a common clinical problem and aims to collate the available literature to inform the clinician on which type of cerumenolytic is most effective.

OBJECTIVES

To assess the effects of ear drops (or sprays) to remove or aid removal of ear wax in adults (aged 18 years and over) and children (aged under 18 years).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) including cluster-randomised controlled trials and quasi-randomised trials. We will only use the first phase of cross-over trials.

We will also include trials that randomise patients by ear as we believe it is possible to ensure that the effects of any intervention considered can be localised and the treatment of one ear will not have an effect on the opposite ear.

Types of participants

Adults (aged 18 years and over) and children (aged under 18 years) with ear wax requiring removal because (a) it is symptomatic or (b) it is preventing an adequate view of the ear drum.

We will exclude studies where the majority of patients have wax that is being removed 'routinely' rather than for a specific reason.

Types of interventions

All topical preparations regardless of dose, frequency or duration of use. Active preparations include:

- commercially produced cerumenolytics;
- hydrogen peroxide;
- oil (olive or almond);
- sodium bicarbonate or any other topical preparation;
- water;
- saline.

The main comparators will be: water or saline or no treatment.

The main comparison pairs will be:

- any active treatment *versus* no treatment;

- any active treatment other than water or saline *versus* water or saline;
- water or saline *versus* no treatment.

Other possible comparison pairs will include:
- preparation A *versus* preparation B;
- preparation A with duration of treatment X *versus* preparation A with duration of treatment Y.

Types of outcome measures

Outcomes will be evaluated at the end of treatment or within a week thereof.

Primary outcomes

- Proportion of patients (or ears) with complete clearance of ear wax, as determined by follow-up otoscopy (clearance being complete without the need for additional treatment as determined by each study's clinical aims).
- Adverse effects: discomfort, irritation or pain.

Secondary outcomes

- Extent of wax clearance (difference between degree of obstruction before and after treatment), as determined by follow-up otoscopy.
- Proportion of people (or ears) with relief of symptoms due to wax.
- Proportion of people (or ears) requiring further intervention to remove wax.
- Success of mechanical removal of residual wax following treatment.
- Any other adverse effects recorded in the study.
- Any available data on cost of treatment.

We will not exclude studies solely on the basis that the data are not available relating to any of these outcomes. We will record for each trial the different clinical aims of removing ear wax depending on the clinical site at which each study was carried out.

Search methods for identification of studies

The Cochrane ENT Information Specialist will update the systematic searches for randomised controlled trials and controlled clinical trials previously conducted for the Cochrane review 'Ear drops for the removal of ear wax' (Burton 2009) in April 2008. There will be no language, publication year or publication status restrictions. We may contact the original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:
- the Cochrane Register of Studies ENT Trials Register (search to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL, current issue);
- PubMed (1946 to date);
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- Ovid AMED (1985 to date);
- Ovid CAB abstracts (1910 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
- ISRCTN (search to date);
- Google Scholar (search to date);
- Google (search to date).

In previous searches for the earlier versions of this review, we also searched BIOSIS Previews 1926 to April 2008.
For the Cochrane review 'Ear drops for the removal of ear wax' (Burton 2009), the Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL (Appendix 1). Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). The Information Specialist will update these searches for this new update of the review.

Searching other resources

For the previous review (Burton 2009), we scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. These searches will also be updated.

Data collection and analysis

Selection of studies

KAA and LW will independently screen all the retrieved trials based on the titles and abstracts to identify potentially relevant studies. Both will further assess the full texts of these studies. Any differences will be resolved by discussion and consensus, with involvement of the third author where necessary.

Data extraction and management

KAA and LW will independently extract data from studies. We will use a standardised data collection form. Where a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. If there are differences in the data extracted by different review authors, we will resolve this situation by reference to the original publications and through discussion and consensus, involving a third author as necessary. Where data are missing or unclear, we will contact the original study authors for clarification.

We will extract the following key characteristics of each study: study design, setting, sample size, population, definition of outcomes and how these were collected. We will collect baseline information on prognostic factors or effect modifiers, including duration of symptoms. We will also extract information on the rationale for and aims of wax clearance treatment.

For our specified outcomes, we will extract the findings of the studies on an available case analysis basis. That is, we will include data from all patients available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

In addition to the pre-specified information about study characteristics and aspects of methodology relevant to risk of bias (see below), we will extract the following summary statistics for each trial and each outcome:

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data are not available, we will extract the values for change from baseline.
- For binary data: the numbers of participants experiencing an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appear to be approximately normally distributed or if the analysis that the investigators performed suggests parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we may convert them into binary data.

We have specified the time point of interest for the outcomes in this review. Some studies may report data at multiple time points, but we will only extract the data available from the latest time point within the interval between 'end of treatment' and one week post-treatment.

Assessment of risk of bias in included studies

KAA and LW will independently assess the risk of bias of each included study. We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* and we will use the Cochrane 'Risk of bias' tool (Handbook 2011). With this tool we will assess the risk of bias as 'low', 'high' or 'unclear' for each of the following six domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective reporting;
- other sources of bias.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. proportion of patients (ears) with complete clearance of ear) using risk ratios (RR) with 95% confidence intervals (CI). For the key outcomes presented in the 'Summary of findings' table, we will also express the results as absolute numbers, based on the pooled results and compared to the assumed risk. We may also calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk will usually be either (a) the median of the risks of the control groups in the included studies (this being used to represent a 'medium-risk population') or, alternatively, (b) the average risk of the control groups in the included studies, this being the 'study population' (Handbook 2011). If a large number of studies are available, and if it is appropriate, we will also present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For outcomes measured on a continuous scale, we will use the mean difference (MD) with a standard deviation (SD), or a standardised mean difference (SMD) if different scales have been used to measure the same outcome. We aim to provide a clinical interpretation of the SMD values.

Unit of analysis issues

The treatment options chosen for this review are administered topically to one or both ears. The results are expected to be reported as parallel-group studies. We will analyse the data based on randomisation between-patient or within-patient controls. We will follow the advice in the *Cochrane Handbook for Systematic Reviews of Interventions* when considering if, and how, to pool data from studies with between-patient and within-patient controls (Handbook 2011).

Dealing with missing data

Where data relating to an outcome of interest are not reported, but the methods of the study suggest that the outcome has been measured, we will try to contact study authors by email to obtain this information. We will also do this if some of the data required for

meta-analysis are unreported, unless the missing data are standard deviations. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If it is impossible to estimate these, we will contact the study authors.

We will not make any imputations other than those for missing standard deviations. We will extract and analyse all data using the available case analysis method.

Assessment of heterogeneity

We will assess both clinical and statistical heterogeneity. Clinical heterogeneity may be present even in the absence of statistical heterogeneity. We will examine the included trials for evidence of differences in the types of participants recruited, interventions, controls or outcomes measured.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi^2 test (with a significance level set at P value < 0.10) and the I^2 statistic. The latter calculates the percentage of variability that is not due to chance. I^2 values over 50% suggest substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

We will assess two aspects of reporting bias: between-study publication bias and within-study outcome reporting bias.

Publication bias (between-study reporting bias)

If sufficient trials (more than 10) are available for an outcome we will use a funnel plot to assess publication bias. If we observe asymmetry, we will conduct a more formal investigation using the methods proposed by Egger 1997.

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report with those listed in the study protocol whenever possible, or - if the protocol is not available - with those listed in the methods section. If results are mentioned, but not reported in a way that allows analysis, we will seek further information from the study authors in order to try and reduce bias in the meta-analysis. If further information is not available, this will be reflected in a designation of 'high' risk of bias. Where there is insufficient information to judge the risk of bias, we will note this as an 'unclear' risk of bias (Handbook 2011).

Data synthesis

We will use Review Manager 5.3 to carry out meta-analyses (RevMan 2014). Where possible we will analyse data to give a summary measure of effect. If no or minimal heterogeneity is seen, we will use a fixed-effect model for meta-analysis to measure the effect. Where considerable heterogeneity is observed, we will use a random-effects model. We will analyse data separately where combinations of interventions are presented.

For dichotomous data, we will analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. We will analyse time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data are from the same scale, we will pool mean values obtained at follow-up (endpoint data) with change outcomes and report this as a MD. If the SMD has to be used as an effect measure, we will not pool endpoint and change data.

When statistical heterogeneity is low, the differences in treatment effects seen when using methods based on a random-effects versus a fixed-effect model are trivial. When statistical heterogeneity is high we will use the random-effects method as this provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

We will conduct some subgroup analyses even if statistical heterogeneity is not observed. These analyses are planned as the factors indicated are suspected to be potential effect modifiers. They include:

- severity of wax occlusion of the ear canal: total obstruction versus partial;
- alternative types of preparation: water-based versus oil-based.

When studies have a mixed group of patients - total obstruction/impaction versus partial - we will analyse the study as one of these subgroups (rather than as a mixed group) if more than 80% of patients belong to one category.

In addition to the subgroups above, we will conduct the following subgroup analysis in the presence of statistical heterogeneity:

- patient age (children versus adults).

Sensitivity analysis

We will carry out sensitivity analyses to determine whether or not the findings are robust based on the decisions made in undertaking the review. We plan analyses for the following factors (where possible):

- model chosen: fixed-effect *versus* random-effects;
- risk of bias of included studies (excluding studies with high risk of bias);
- methods of outcome measurement (evaluating the impact of including data where the validity of the measurement is unclear).

Studies at high risk of bias are defined as those that have a high risk of allocation or concealment bias (or both) and a high risk of attrition bias (overall loss to follow-up of > 20% or differential follow-up observed, or both).

GRADE and 'Summary of findings' table

We will use the GRADE approach to rate the overall quality of evidence. We will use the GDT tool (http://www.guidelinedevelopment.org/) for the *main comparison pairs* listed in the Types of interventions section. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: 'high', 'moderate', 'low' and 'very low'. A rating of 'high' quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate. A rating of 'very low' quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have any serious limitations as 'high quality'. However, several factors can lead to the *downgrading* of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision;
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

CENTRAL	EMBASE (Ovid)	PubMed
#1 MeSH descriptor: [Cerumen] explode all trees #2 Cerumen* or cerumin* or earwax or (ear and wax) or (ears and wax) or (ear and impaction) or (ears and impaction) or (ear and impacted) or (ears and impacted) #3#1 or #2	1 cerumen/ 2 cerumen impaction/ 3 exp ceruminolytic agent/ 4 (Cerumen* or cerumin* or earwax or (ear and wax) or (ears and wax) or (ear and impaction) or (ears and impaction) or (ear and impacted) or (ears and impacted)).tw. 5 1 or 2 or 3 or 4	#1 "CERUMEN" [Mesh] OR CERUMEN* [tiab] OR CERUMIN* [tiab] OR earwax [tiab] OR (EAR [tiab] AND WAX* [tiab]) OR (EARs [tiab] AND wax* [tiab]) OR (EAR [tiab] AND impacted [tiab]) OR (EARs [tiab] AND impacted [tiab]) OR (EAR [tiab] AND impaction [tiab]) OR (EARs [tiab] AND impaction [tiab])
Web of Science	**CINAHL (EBSCO)**	**ICTRP**
#1 TS=(Cerumen* OR cerumin* OR earwax OR (ear AND wax) OR (ears AND wax) OR (ear AND impaction) OR (ears AND impaction) OR (ear AND impacted) OR (ears AND impacted))	S1 TX Cerumen* OR cerumin* OR earwax OR (ear AND wax) OR (ears AND wax) OR (ear AND impaction) OR (ears AND impaction) OR (ear AND impacted) OR (ears AND impacted)	cerumen* OR cerumin* OR earwax OR ear AND wax OR ear AND impacted OR ear AND impaction

CONTRIBUTIONS OF AUTHORS

Martin Burton: critically revising the protocol for essential intellectual content; senior author.

Ksenia Aaron: critically revising the protocol for essential intellectual content.

Laura Warner: assisting KAA in critically revising the protocol.

DECLARATIONS OF INTEREST

Martin Burton is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol.

Ksenia Aaron: none known.

Laura Warner: none known.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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NOTES

This is a new protocol for a planned update of the Cochrane review 'Ear drops for the removal of ear wax' (Burton 2009). The original review will be withdrawn on completion of the update.