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Children's drops for ear pain in acute otitis media: the CEDAR randomised controlled trial

Submission date
19/09/2014

Recruitment status
No longer recruiting

Registration date
02/10/2014

Overall study status
Completed

Last Edited
16/07/2019

Condition category
Ear, Nose and Throat

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Infection of the middle ear, or acute otitis media (AOM), is a common, painful condition most commonly seen in children under 10. During the infection, germs multiply in the confined space of the middle ear resulting in a build-up of pressure that pushes on, and stretches the ear drum. This causes pain and distress to the child, resulting in sleepless nights (for the child and their family) which then affects both the childs schooling and the parents work day. Concerned parents frequently use painkillers (for example, paracetamol or ibuprofen) and seek advice from primary care (GPs, Walk in Centres, Out of Hours Centres, and Emergency Departments). Although there is world class evidence showing that antibiotics do not help, and NICE advise against their use, the majority of children seen in primary care receive antibiotics, more so for middle ear infections than for any other respiratory infection in childhood. This encourages the parents to become dependent on health care services, making them more likely to consult them for similar illnesses in the future. All of this is expensive for health care providers (consultations, prescriptions and antibiotic resistance) and families (lost time from work and school, travel to primary care centres, buying painkillers). Alternatives to antibiotics (and the dependence on health care services) are urgently needed, especially given the current, very high, public health concerns regarding germ resistance to antibiotics. We want to test one such possible alternative, ear drops than contain benzocaine (a local anaesthetic and numbing nerve blocker) and phenazone (a pain killer). We wish to see whether they could be used to relieve the pain and distress caused by AOM and reduce the dependence of antibiotics to treat the condition. The drops are thought to work by directly numbing the ear drum and are currently available in pharmacies in other countries outside of the UK, including Australia and New Zealand. Other studies have proved inconclusive and no-one has yet investigated if repeated use alleviates pain over a longer period, improves quality of life for children, reduces costs or reduces the use of antibiotics. The CEDAR trial will address all of these issues in children presenting to primary care with acute middle ear infections.

Who can participate?
Children who are suspected of having AOM and complaining of ear pain within the last 24 hours. Parents must give consent for the child to take part in the study. Parents must also be willing to give the child the ear drops, happy to complete a symptom diary and are willing and available to receive follow-up telephone calls as required by the study.

What does the study involve?
The participants take part in either a clinical trial (in which the drops are tested) or an observational study (where the child is just observed over a period of time). For children taking part in the observational study, the usual care for AOM is given and parents are asked to report symptoms daily in a diary. Parents also receive a follow-up telephone call within the first three days of them joining study and then one week later. The childs primary care medical notes are reviewed at 3 months. Children taking part in the clinical trial are randomly allocated into one of three groups. Those in Group 1 are given ear drops containing benzocaine and phenazone. Those in group 2 are given placebo (dummy) drops. Those in group 3 are not given any drops at all. Like those families taking part in the observational study, parents receive follow-up telephone calls and the childs medical notes are reviewed 3 months later.

What are the possible benefits and risks of participating?
Parents of the children being treated in this trial have to give their consent and they can withdraw their child at any time. Health care professionals have to check that it is safe to not give or delay antibiotic treatment to any child taking part. In theory, the ear drops could be toxic to the ear, particularly if they are given to someone with a perforated eardrum. The childs hearing is monitored throughout the trial. There are possibly no direct benefits to taking part but it is possible that pain relief might be experienced by children being given the active or placebo ear drops. There may also be a psychological benefit to the parents as they may feel more able to take action to help their childs illness improve.

Where is the study run from?
The study takes place in up to 120 GP practices and other primary care sites (Children's Emergency Departments, Out of Hours primary care providers) across England and Wales and is run from the Universities of Bristol, Cardiff and Southampton (UK).

When is the study starting and how long is it expected to run for?
January 2015 to December 2017

Who is funding the study?
National Institute of Health Technology Assessment Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2014-004016-11

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
2305; HTA 13/88/13

Study information

Scientific Title
What is the clinical and cost effectiveness of benzocaine/phenazone ear drops on antibiotic consumption and ear pain in children aged between 6 months and 10 years presenting to primary care with acute otitis media (AOM)? An individually randomised, placebo controlled three-arm superiority trial with cost-effectiveness analysis, qualitative evaluation and a parallel observational cohort study

Acronym
CEDAR

Study objectives
The main aim of the CEDAR trial is to investigate the clinical and cost effectiveness of benzocaine/ phenazone (hereon ®active) ear drops (otic solution) compared to 'no drops' (usual care) for reducing antibiotic consumption in children aged between 6 months and 10 years presenting to primary care with AOM. The key secondary aim is to investigate clinical and cost effectiveness of active compared to placebo drops for ear pain.

Main research questions:
1. Do active drops lead to a lower proportion of children consuming antibiotics by day 7 compared with no drops (usual care)?
2. Do active drops provide superior pain relief in the first 24 hours compared to placebo drops?

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central Oxford A Research Ethics Committee, 03/02/2016, ref: 15/SC/0376

Study design
Individually randomised 3 arm UK multi-centre double-blind superiority trial in primary care with cost effectiveness analysis, nested qualitative evaluation and parallel observational cohort study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet.

Health condition(s) or problem(s) studied
Acute otitis media in children

Interventions
Randomsed controlled trial:
Eligible, consented children will be randomised in a ratio of 1:1:1 to receive either:
1. Usual care: patients will receive the current best standard of care according to NICE guidelines, i.e. advice about symptom management using OTC analgesics (paracetamol, ibuprofen), with or without a delayed antibiotic prescription.
2. Active treatment: patients will receive usual care plus topical anaesthetic ear drops (benzocaine 14mg/mL and phenazone 54mg/mL otic solution in glycerol with preservative hydroxyquinoline sulphate). The dosage, method and frequency of administration are yet to be confirmed by the Trial Steering Committee and will be described in instructions to be submitted for REC review. Patients will receive the intervention for up to 8 days, or as long as the child's ear pain persists, whichever period is shorter. The parents of participating children will be followed up daily for 8 days. If the child's ear pain persists beyond the 8 day period, we will follow them up weekly, to a maximum of 28 days from randomisation. At three months, sites will undertake a review of the child's medical notes, and parents will be asked to complete a quality of life questionnaire.
3. Placebo treatment: as for 2), but with otic solution of glycerol with preservative 8-hydroxyquinoline sulphate (i.e. excluding the active drugs).

Observational study:
Children will receive usual care and follow-up as for the RCT.

For both the Randomised Controlled Trial and the Observational Cohort Study:
Daily symptom diary, weekly telephone follow-up and review of participants' primary care medical notes at 3 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
1. Benzocaine 2. Phenazone

Primary outcome measure
Any antibiotic consumed by day 7 (measured using symptom diary and telephone call at 1 week)

Secondary outcome measures
Key secondary outcome:
Ear pain over first 24 hours using the parent completed, validated numerical rating scale successfully used in our previous trials (symptom diary and telephone call in first three days) and child completed Faces Pain Scale Revised (FPS-R)14 for children aged <5 years

Other secondary outcomes:
1 Daily symptom severity (until resolution, expected by 8 days for most children) including episodes of distress/crying, disturbed sleep, interference with normal activity, appetite, fever and hearing problems
2. Adverse events (symptom diary)
3. Ear drop and rescue analgesia consumption (symptom diary)
4. Parent satisfaction with, and opinion of, treatment allocation and future intention to use drops (with/without prior GP consultation if drops were to become available over-the-counter) at 7 days
5. Preference based quality of child life measured (baseline, 24 hours, 7 days and 3 months) using CHU-9D18 (for children age >5 years)
6. NHS costs up to 7 days (symptom diary) and contacts to 3 months (primary care medical notes review)
7. Child's school/nursery absences, parent lost productivity and other expenses up to 7 days (symptom diary)
8. Child's quality of life (OMQ-14,19 modified for <3 years) at baseline and 3 months (postal questionnaire)
9. Qualitative outcomes to assess acceptability, barriers and adherence, a purposeful sample of parents and clinicians will be asked to participate in qualitative interviews to explore experiences of, and attitudes to AOM and its treatment

Overall study start date
01/01/2015

Completion date
31/12/2017

Eligibility

Key inclusion criteria
Randomised Controlled Trial:
1. Children presenting within 72 hours of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)
2. Legal guardian (hereon parent) available to give immediate verbal (telephone) and written (within 24 hours) consent
3. Parent-reported ear pain in 24 hours pre-enrolment (unless child too young to report pain, when GP-ascertained otoscopic evidence alone sufficient)
4. GP-ascertained otoscopic evidence of acute inflammation (operationalised as per our previous trial6 as: dullness or cloudiness with erythema; or bulging)

5. Clinician willing to use a NICE recommended no or delayed antibiotic strategy
6. Parent able to give ear drops
7. Parent willing to able to complete symptom diary
8. Parent willing and available to receive follow-up telephone calls within first three days and at one week post recruitment

Children with cystic fibrosis (CF) and severe learning difficulties will be included, to maintain generalizability. We are not aware of evidence that AOM is different in children with CF, and the treating clinician will be responsible for deciding if children are safe to receive delayed antibiotics. Parents will be able to complete pain scores for children with severe learning difficulties.

Observational Cohort Study:
1. Children presenting within 72 hours of suspected AOM onset (other preceding respiratory tract infection symptoms may be longer)
2. Legal guardian (hereon parent) available to give immediate verbal (telephone) and written (within 24 hours) consent
3. Parent-reported ear pain in 24 hours pre-enrolment (unless child too young to report pain, when GP-ascertained otoscopic evidence alone sufficient)
4. GP-ascertained otoscopic evidence of acute inflammation (operationalised as per our previous trial) as: dullness or cloudiness with erythema; or bulging)
5. Parent willing to able to complete symptom diary
6. Parent willing and available to receive follow-up telephone calls within first three days and at one week post recruitment

Participant type(s)
Patient

Age group
Child

Sex
Both

Target number of participants
501 for the Randomised Controlled Trial, plus up to 501 additional participants for the Observational Cohort Study

Total final enrolment
106

Key exclusion criteria
Randomised Controlled Trial:
1. Requirement for immediate oral antibiotic for AOM (e.g. NICE recommend for children under 2 years with bilateral AOM or otorrhoea) or another infection
2. Alternative source of pain
3. GP-ascertained otoscopic appearances consistent with fever or crying (pink drum alone)
4. Diagnosis more suggestive of otitis media with effusion (glue ear)
5. Suspected or confirmed perforation (theoretical but unconfirmed risk of ototoxicity from active drops, seen in 7% of children with AOM5)
6. Known sensitivity to study medicine; child requiring immediate hospitalisation

Observational Cohort Study:
None

Date of first enrolment
01/09/2016

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
University of Bristol
Centre for Academic Primary Care
School of Social and Community Medicine
Canynge Hall
39 Whatley Road
Clifton
Bristol
United Kingdom
BS8 2PS

Study participating centre
University of Cardiff
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University of Southampton
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Sponsor type
University/education

Website
http://www.bris.ac.uk/red

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Planned publication of study results in peer-reviewed academic journals
2. Provision of a summary of the trial findings to recruiting sites and parents of participating children who have expressed interest
3. Production of tailored summaries for commissioners and key stakeholders

Intention to publish date
31/01/2019

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2019	16/07/2019	Yes	No
HRA research summary			28/06/2023	No	No