Oral steroids for hearing loss associated with otitis media with effusion in children aged 2–8 years: the OSTRICH RCT

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Scientific summary

The OSTRICH RCT

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Scientific summary

Background

Otitis media with effusion (OME) affects up to 80% of children by 4 years of age and is the commonest cause of hearing loss in children in the UK. Most episodes resolve spontaneously, but 5% of preschool-aged children have bilateral hearing loss from OME that lasts for ≥ 3 months. Significant hearing loss can affect mood, communication, concentration, learning, socialisation, language development and family function. Antibiotics, topical intranasal steroids, decongestants, antihistamines and mucolytics have all been shown to be ineffective treatments for OME. Use of an autoinflation (AI) device benefits some 4- to 11-year-olds with OME. However, OME is most prevalent, and has most impact on language development, in children who are generally too young to use an AI device. Management options are therefore largely limited to watchful waiting, hearing aids or surgical insertion of ventilation tubes (grommet surgery) through the tympanic membrane (with or without adenoidectomy or tonsillectomy). Subsequently, OME remains the commonest reason for childhood surgery in the UK.

A Cochrane review on oral or topical steroids for OME found a statistically significant benefit from oral steroids plus antibiotics versus antibiotics alone for OME, and a trend towards a significant benefit for oral steroids versus placebo. Studies were generally of poor quality, short term and underpowered.

Objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of a 7-day course of oral steroids in improving hearing at 5 weeks in children with persistent OME symptoms and current bilateral OME and hearing loss as demonstrated by audiometry. Secondary objectives included assessing the effects of a course of oral steroids on OME (as assessed via tympanometry and otoscopy), health-care consultations, insertion of ventilation tubes, adverse effects, symptoms, functional health status, health-related quality of life (HRQoL), longer-term hearing (at 6 months and 12 months) and to assess the cost-effectiveness.

Methods

This was a double-blind, individually randomised, placebo-controlled trial with participants identified and followed up in ear, nose and throat outpatient or paediatric audiology and audiovestibular medicine clinics in Wales and England. Trial sites were selected on the basis of their recruitment potential and being part of a Clinical Research Network.

Eligible participants were children aged 2–8 years with symptoms of hearing loss attributable to OME for at least 3 months, a diagnosis of bilateral OME made on the day of recruitment and audiometry-confirmed hearing loss [> 20 decibels hearing level (dBHL)] averaged within the frequencies of 0.5, 1, 2 and 4 kHz in both ears by pure-tone audiometry (PTA), visual reinforcement audiometry (VRA) or ear-specific play audiometry, or > 25 dBHL averaged within the frequencies of 0.5, 1, 2 and 4 kHz by soundfield VRA or soundfield performance/play audiometry in the better hearing ear on the day of recruitment or within the preceding 14 days. Exclusion criteria included current systemic infection or acute ear infection, cleft palate, Down syndrome, chronic comorbid illness (e.g. diabetes mellitus, renal failure, heart failure), current known sensory hearing loss, oral steroids taken in the preceding 4 weeks and having a condition that increases the child's risk of adverse effects from oral steroids.

Participants were randomised (1 : 1), using random permuted blocks stratified by site and child's age, to a 7-day course of oral soluble prednisolone as a single daily dose (20 mg for children aged 2–5 years or 30 mg for 6- to 8-year-olds) or matched placebo. The primary outcome was acceptable hearing at 5 weeks from randomisation (4 weeks after conclusion of treatment), defined as $\leq$ 20 dBHL averaged within the frequencies of 0.5, 1, 2 and 4 kHz in at least one ear in children assessed by PTA, ear-specific insert VRA or ear-specific play audiometry and $\leq$ 25 dBHL averaged within the frequencies of 0.5, 1, 2 and 4 kHz in children assessed by soundfield VRA or soundfield performance/play audiometry. Secondary outcomes include longer-term (6- and 12-month) hearing, evidence of OME (by otoscopy and tympanometry), health-care consultations for OME, ventilation tube surgery, adverse effects, symptoms, functional health status [as assessed via the Otitis Media Questionnaire (OM8-30)], HRQoL [as assessed via the Paediatric Quality of Life Inventory (PedsQL)] and health utilities [as assessed via the Health Utilities Index, version 3 (HUI3)].

Baseline data were collected by the recruiting clinician and study nurses. A parent/legal guardian was asked to complete a questionnaire booklet that included the OM8-30, the PedsQL and the HUI3. If appropriate, a child's version of the questionnaire booklet was also completed by the participant, comprising the child self-report version of the PedsQL. Parents/legal guardians were asked to complete a diary at home over the first 5 weeks. The diary was completed daily in the first week to record treatment adherence. Thereafter, it was completed weekly for 4 weeks to record symptoms, adverse events and health-care resource use, additional medication taken, time off school/nursery and parental time off work. Follow-up assessments were conducted at week 5 (4 weeks post completion of treatment) and at 6 and 12 months, when completion of the questionnaire booklets and the clinical assessments (e.g. audiometry, tympanometry and otoscopy) were repeated, as well as questions about the use of NHS resources, additional medication taken, time off school/nursery and parental time off work. Although the follow-up of participants continued for 12 months, after the 5-week assessment, all participants resumed 'usual care'.

A total of 302 participants were required to demonstrate a change in the proportion of children with resolved hearing loss at 5 weeks post randomisation, from 20% in a control group to 35% in an intervention group, with 80% power at a 5% significance level. We selected a conservative estimate of 1.75 for our effect size (ratio of proportions) because we considered that a 15% absolute increase in the rate of resolution at 5 weeks would represent a clinically meaningful benefit that could result in a meaningful reduction in operations.

The primary analyses were by intention to treat (ITT) using a multilevel logistic regression model, adjusting for site, child's age and time to follow-up, with comparisons presented as the absolute difference in proportions and the adjusted odds ratio (OR), with a 95% confidence interval (CI) and the *p*-value. A number of potential effect modifiers and confounders (age, history of atopy, season randomised, recent use of antibiotics for ear infection, number of previous episodes, duration of symptoms, household smoking, deprivation score and previous tonsillectomy or adenoidectomy) were entered into the primary regression analysis, with interaction terms, in order to conduct prespecified subgroup analyses. Secondary outcomes with a binary outcome (present/absent) measured over multiple follow-up time points, such as satisfactory hearing and presence of effusion, were analysed using repeated measures logistic regression. For continuous secondary outcomes, such as the PedsQL, HUI3 and OM8-30 scores, repeated measures linear regression models (using transformations as necessary) investigated differences between the treatment groups and over time (5 weeks and 6 and 12 months), adjusting for baseline. Child symptoms were combined and examined weekly over time. A Cox regression model was used to test differences in time to insertion of ventilation tubes. The cost-effectiveness analysis was from the perspective of the UK NHS and Personal Social Services. The costs of the course of oral steroids were calculated and combined with the differences in costs between the intervention and control groups to determine the overall costs associated with the intervention. The resource utilisation of both groups (consultations, medications, operations, equipment, etc.) and treatments associated with adverse events were assessed through the completion of self-completed questionnaires at baseline, 5 weeks, 6 months and 12 months, and translated into costs using appropriate published unit costs. The difference in the overall costs between groups was compared with the differences in outcomes, including quality-adjusted life-years (QALYs) computed from the HUI3 and utilities derived from mapping responses to the OM8-30 questionnaire. A series of one-way sensitivity analyses were conducted to assess

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the impact of parameter variation on baseline estimates of the cost-effectiveness ratios, and a probabilistic sensitivity analysis was undertaken to determine the extent to which the intervention can be regarded as representing value for money.

Results

Participants were recruited from 20 sites between March 2014 and April 2016. A total of 1018 children were assessed for eligibility, with 389 children (38%) being randomised. The main reasons for exclusions were failure to meet the hearing loss criteria ($n = 264$), failure to meet other inclusion criteria ($n = 239$) and parental decision to not participate ($n = 124$). The baseline demographics of the randomised children were well balanced. Slightly more boys were randomised, and the majority identified as white. Around 30% of randomised children were on the waiting list for ventilation tube insertion. The method of audiometry was balanced across the trial groups. Over 85% of ears were tested over four frequencies (0.5, 1, 2 and 4 kHz) using ear-specific methods, with around 80% tested over four frequencies using the soundfield. Hearing loss was slightly worse in the oral steroid group, and most children had mild to moderate hearing loss. Over 95% of ears had type B (flat) tympanograms. A total of 316 children (81%) attended all three assessments, 14 attended the 5-week assessment only, four attended only the 6- and 12-month assessments, 38 attended two of the three assessments and four missed their 5-week assessment but returned for the 6- and 12-month assessments. Over 90% of participant diaries were returned; 98% reported initiating treatment and 88% reported taking all or some medication for all 7 days, with most reporting taking the medication fully as prescribed.

A total of 17 children did not have their hearing assessed at 5 weeks, either because of loss to follow-up or because the audiologist was unable to carry out the assessment. In the ITT population of 363 children, 132 demonstrated acceptable hearing at 5 weeks: 59 out of 180 (33%) children in the placebo group and 73 out of 183 (40%) children in the oral steroid group. The between-group difference of 7.1% (95% CI –2.8% to 16.8%) results in a number needed to treat of 14.1 (95% CI number needed to treat to harm = 35.7 to ∞ to number needed to treat to benefit = 6.0). At the 5-week follow-up, the odds of having acceptable hearing were 32% higher for children randomised to receive oral steroids (OR 1.36, 95% CI 0.88 to 2.11; $p = 0.164$) than for children randomised to receive a placebo. The sensitivity analyses using a per-protocol population showed no significant difference between the groups. The complier average causal effect analysis found an increase to 8.0% in the difference between groups after adjusting for full adherence. For all subgroups, no differences in treatment effects were found and the *p*-values for the interaction term (treatment group by subgroup) in the model ranged from 0.04 to 0.74.

There was a considerable increase in acceptable hearing at 6 and 12 months compared with 5 weeks, with a constant 7–8% difference between treatment groups at each time point. There was no overall difference in acceptable hearing between groups and no differential effect of treatment over time. There was no significant difference in the proportion of children with tympanometric evidence of resolution of OME at each time point; however, as a time-dependent variable, improvement over time was significantly greater in the oral steroid group ($p = 0.007$). Between the 5-week and 6-month follow-ups, around 22% of children in both groups had ventilation tubes inserted, and between 6 and 12 months, 14% and 13% of children in the placebo and oral steroid groups, respectively, had ventilation tubes inserted. There was no evidence of a difference between treatment groups at each follow-up time point, but there was a differential treatment effect over time ($p = 0.017$). Functional health status and quality of life (QoL) improved over time in both groups, but there were no statistical or meaningful differences between treatment groups. There were no significant differences in the number of health-care consultations or time off school, nursery or work. The weekly symptom scores were generally low with a skewed distribution. The scores in both treatment groups reduced over time with no difference. Only one participant (in the placebo group) had a serious adverse event (i.e. asthma exacerbation requiring hospitalisation). Potential adverse events were reported by 22 (12.9%) and 25 (14.0%) children during week 1 in the placebo and oral steroid groups, respectively, with no apparent difference between the groups. Gastrointestinal symptoms were reported by

11 (4.7%) and 7 (3.9%) children, and behavioural changes were reported in 3 (1.8%) and 7 children (3.9%) in the placebo and oral steroid groups, respectively.

The primary cost-effectiveness analysis demonstrated an incremental cost of achieving an additional hearing resolution at 5 weeks as a result of oral steroid treatment of £690, which increased to £3052 at 12 months. The primary cost–utility analysis (incremental cost per QALY gain at 12 months) found evidence for oral steroids being dominated by placebo (i.e. less effective and more costly). However, the differences in costs and outcomes were small and not statistically significant, with the sensitivity analyses suggesting considerable uncertainty. The results need to be interpreted in the context of the clinical effectiveness findings.

Conclusions

If effective, a short course of oral steroids for OME would have been very appealing, as it is generally well tolerated and would avoid more burdensome and expensive interventions, such as ventilation tube surgery or hearing aids. Although the study found an absolute increase of 7.1% in the proportion of children treated with steroids with acceptable hearing at 5 weeks after randomisation, which was maintained at 6 and 12 months, these differences were not statistically significantly different. The study did not identify any subgroup that received a meaningful advantage from steroid treatment. In addition, the study did not find any differences in functional health status and QoL measures between the treatment groups. Therefore, even if the small benefit seen in terms of hearing resolution is not a chance finding, it is unlikely to be clinically significant.

This trial has produced unique data about the generally favourable natural history of problems associated with persistent OME with proven bilateral hearing loss. These data can help to inform a shared decision-making approach to the management of OME, including the watchful waiting option. Studies exploring the optimal ways of sharing natural history and intervention effect data with parents, as well as further evaluations of alternative pathways, will help to improve the management of this common and important problem.

The Oral STeroids for the Resolution of otitis media with effusion In CHildren (OSTRICH) trial findings suggest that any benefit from a short course of oral steroids for OME is likely to be small and of questionable clinical significance, and unlikely to be cost-effective and, therefore, cannot be recommended for routine use.

Trial registration

This trial is registered as ISRCTN49798431 and EudraCT 2012-005123-32.

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