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Topical versus oral antibiotics, with or without corticosteroids, in the treatment of tympanostomy tube otorrhea

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ABSTRACT

Objective: Antibiotic treatment is the standard of care for tympanostomy tube otorrhea. This meta-analysis aims to evaluate the efficacy of topical antibiotics with or without corticosteroids versus oral antibiotics in the treatment of tube otorrhea in children.
Data Sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and ProQuest.
Review Methods: The above databases were searched using a search strategy for randomized controlled trials for optimal treatment of tube otorrhea in the pediatric population. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed. Primary outcome was cure (i.e. clearance of otorrhea) at 2–3 weeks. Secondary outcomes were microbiological eradication and complications such as dermatitis and diarrhea. The incidence of these events was defined as dichotomous variables and expressed as a risk ratio (RR) and number needed to benefit (NNTB) in a random-effects model.
Results: We identified 1491 articles and selected 4 randomized controlled trials which met our inclusion criteria. Topical treatment had better cure (NNTB = 4.7, pooled RR = 1.35, $p < 0.001$) and microbiological eradication (NNTB = 3.5, pooled RR = 1.47, $p < 0.001$ among 3 of the studies) than oral antibiotics. Oral antibiotics had higher risk of diarrhea (pooled RR = 21.5, 95% CI 8.00–58.0, $p < 0.001$, Number needed to harm (NNTH) = 5.4) and dermatitis (pooled RR = 3.14, 95% CI 1.20–8.20, $p = 0.019$, NNTH = 32). The use of topical steroids in addition to topical antibiotics was associated with a higher cure rate (pooled RR = 1.59, $p < 0.001$ vs pooled RR = 1.57, $p = 0.293$).
Conclusion: Topical antibiotics should be the recommended treatment for management of tympanostomy tube otorrhea in view of its significantly improved clinical and microbiological efficacy with lower risk of systemic toxicity as compared to oral antibiotics. Further research is necessary to confirm the benefits of topical corticosteroids as an adjunct to topical antibiotics.

1. Introduction

Tympanostomy tube insertion is the most common otolaryngologic day-surgery procedure performed in the pediatric population. In the US, nearly 1 in 15 children would have undergone a tympanostomy tube insertion by 3 years of age [1]. Indications for tube insertion include persistence of middle ear effusion, recurrent middle ear infections, or infections recalcitrant to oral antibiotic therapy [2]. It has been shown to significantly restore hearing, reduce effusion prevalence, reduce incidence of recurrence of otorrhea, and improve disease-specific quality of life for children with otitis media with effusion or recurrent acute otitis media [3].

Acute otorrhea is the most common observed complication of tympanostomy tube, with a mean incidence of 26% (range, 4%–68%) in observational studies and up to 83% with prospective surveillance [4,5]. Tube otorrhea is usually sporadic and painless [6], but may be accompanied with foul odor, pain and pyrexia [3]. It is postulated to be a manifestation of a recurrent acute otitis media, with bacterial superinfection or infection. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [7,8] are often implicated as the predominant bacteria. Treatment is usually with broad-spectrum antibiotics, which can be delivered either orally or with topical eardrops.

Trials comparing topical and oral antibiotics in children with tube otorrhea have had relatively small sample sizes. But independently they suggest that otic drops are as effective as, or more effective than, oral treatment. Despite these evidence in the

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literature, a survey conducted in 2013 showed that 54% of surveyed emergency medicine physicians used oral antibiotics to treat tube otorrhea, as compared to 9% of surveyed otolaryngologists [9].

A systemic search identified randomized controlled trials (RCTs) that directly compared topical and oral antibiotics in the treatment of acute tube otorrhea, and a meta-analysis was conducted.

2. Methods

The reporting of our systemic review was guided by the PRISMA Statement [10].

2.1. Systematic search strategy and study selection

Studies were selected and screened according to the research question and PICO criteria. We sought all RCTs that studied the efficacy of topical versus oral antibiotics in pediatric patients with acute tube otorrhea. The PICO criteria used were: pediatric humans with acute tube otorrhea; topical antibiotics with or without topical corticosteroids versus oral antibiotics; cure rates at specific time intervals, microbiological eradication as well as median time to cessation where possible; and RCTs only.

Initial database searches were conducted in August 2015. PubMed, EMBASE, Cochrane Central Register of Controlled Trials and ProQuest were searched using the terms as shown below. Search results were screened to remove duplicate, non-peer reviewed, and review articles. All articles were de-identified (blinded title, authors, journal name, and year of publication) before selection. Two authors independently selected abstracts according to the research question and PICO criteria. Disagreements between the authors were resolved by consensus. The stages and reasons for exclusions are presented in Fig. 1.

2.2. Data extraction

The extracted data comprised the year of publication, participant numbers, the two intervention arms, the study design, and study findings. The outcomes investigated included cure (defined as the absence of otorrhea), microbiological eradication and any complications or treatment-related adverse effects. For all studies, data were extracted independently by two authors (JC, KWP). Any differences in reporting were reconciled by jointly revisiting the relevant publication.

2.3. Statistical analysis

All statistical analyses were performed with STATA Version 13.0. Meta-analysis of binomial data using the random-effects model was performed to derive a summary estimate of relative risks. The random-effects model was used because it takes into account both variation caused by sampling error and also random variation of the underlying effect sizes between studies. The effect of topical versus oral antibiotics in terms of cure rates and microbiological eradication were calculated using relative risks with its p-value. Significant difference was set at $p < 0.05$ for all analyses. A fixed-effects (weighted with inverse variance) or a random-effects model was used where appropriate, after computing the chi-squared and I^2 statistics. When $p < 0.05$ or $I^2 > 50\%$, the assumption of homogeneity was rejected and a random effects model was adopted. Random-effect estimates were used when there was significant between-study heterogeneity. Peter's test was used to test for evidence of publication bias when the heterogeneity variance tau-squared was less than 0.1.

3. Results

We found 1360 potentially relevant articles after duplicates were removed. Of these, only 4 [11–14] fulfilled the inclusion criteria. These 4 studies were published between years 1998 and 2014. These studies were analyzed as intention to treat. Patient with negative microbiology at baseline were excluded from analysis of efficacy of microbiological eradication.

The 4 studies included 560 subjects with tube otorrhea (277 received topical antibiotics while 283 received oral antibiotics). Other study design characteristics are summarized in Table 1. The Jadad score is summarized in Table 2. All studies were single blinded as the intervention was the route of administration of medications, which made patient-blinding not feasible.

Data from the four eligible studies were pooled for meta-analysis. Results showed that patients who received topical treatment demonstrated a statistically significant improvement in resolution rates at the defined endpoint of 2–3 weeks (pooled relative risk [RR] = 1.35, 95% Confidence Interval [CI] 1.21–1.50, $p < 0.001$, Number needed to benefit [NNTB] = 4.7). Fig. 2 shows the Forest plot and the standard relative risk for patients who received topical versus oral antibiotics. There was little evidence for publication bias for small-study effects (intercept = 73.9, 95% CI –363 to 511, t = 0.73, p = 0.542). However, heterogeneity was high ($I^2 = 80.8\%$). Subgroup analysis showed that patients who used topical antibiotics with steroids (pooled RR = 1.59, 95% CI 1.34–1.89, $p < 0.001$, NNTB = 3.0) reported significantly improved cure rates at 2–3 weeks ($I^2 = 5.3\%$). However, patients who used topical antibiotics alone had a statistically non-significant improvement (pooled RR = 1.57, 95% CI = 0.68–3.67, p = 0.293, $I^2 = 82.4\%$).

Microbial eradication results were included in 3 of the above 4 studies. Topical treatment was also shown to have improved eradication rates compared to oral antibiotics (pooled RR = 1.47, 95% CI 1.27–1.70, $p < 0.001$, NNTB = 3.5) (Fig. 3). There was similarly little evidence for publication bias for small-study effects (intercept = –55.3 95% CI –911 to 801, t = –0.82, p = 0.562).

In addition, side effects were much less common with topical antibiotics than with oral antibiotics. Three of the above studies reported numbers in terms of side effects. The two most common adverse reactions reported were gastrointestinal disturbances (i.e. diarrhea) and dermatitis. Oral antibiotics carried a significantly higher risk of diarrhea (pooled RR = 21.5, 95% CI 8.00–58.0, $p < 0.001$, number needed to harm (NNTH) = 5.4) and dermatitis (pooled RR = 3.14, 95% CI 1.20–8.20, p = 0.019, NNTH = 32).

4. Discussion

Antibiotics reduce otorrhea, fever and pain from otitis media. A meta-analysis performed by Rovers et al concluded that oral antibiotics were more effective than placebo in the treatment of children with acute otitis media and otorrhea (NNTB = 3) [15] with regard to the above outcomes. In adults with chronic suppurative otitis media, topical antibiotics are more efficacious in reducing otorrhea than either oral [16] or intramuscular [17]antibiotics, possibly because the tympanic membrane perforation permits a higher local drug concentration to be achieved with topical antibiotic therapy. For pediatric patients with tube otorrhea, studies have shown failure rates of between 10% and 23% with ciprofloxacin-containing ear drops versus 20%–70% with oral antibiotics alone [12,13,18–20].

The most recent clinical practice guidelines by the American Academy of Otolaryngology-Head and Neck Surgery suggest a strong recommendation for topical antibiotics over oral antibiotics based on Grade B aggregate evidence [21], based on 3 RCTs performed between 1998 and 2010. We included a fourth well-designed study which was recently published, and conducted a meta-analysis to statistically analyze the utility of topical versus oral antibiotics in