

Topical Ciprofloxacin Is Superior to Topical Saline and Systemic Antibiotics in the Treatment of Tympanostomy Tube Otorrhea in Children: The Results of a Randomized Clinical Trial

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Objectives/Hypothesis: To compare the clinical failure rates among children with otorrhea through tympanostomy tubes treated with topical or systemic antibiotics versus topical saline.

Study Design: Randomized, double-blind, controlled patient study.

Methods: A three-armed randomized clinical trial using topical ciprofloxacin or oral amoxicillin or topical saline. The primary outcome was treatment failure defined as presence of otorrhea in at least one ear after 7 days of treatment.

Results: The treatment failure rates were 23% and 70% in the group treated with topical ciprofloxacin and oral amoxicillin, respectively. Treatment failures were seen in 58% of children treated with topical saline. Thus, topical ciprofloxacin significantly reduced treatment failures compared to both oral amoxicillin and topical saline. The most frequent bacteria isolated from treatment failures in general were streptococci and *Moraxella catarrhalis*.

Conclusions: The significant effect of topical ciprofloxacin is probably related to a higher local concentration of antibiotics in the middle ear rather than the result of mechanical rinsing and dissolution of the bacterial load.

Key Words: Tympanostomy tubes, otorrhea, ciprofloxacin, saline, amoxicillin.

Key Words: Level of Evidence: 1a.
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INTRODUCTION

As in many other countries, bilateral insertion of tympanostomy tubes (TT) is the most commonly performed operation in children in Denmark with approximately 60,000 to 70,000 procedures annually. Otorrhea is a frequent complication. Thus, early postoperative tube otorrhea has been reported in about 10% to 20% of children after TT insertion, whereas delayed otorrhea occurs in as many as 68%.^{1,2} Tympanostomy tube otorrhea in young children is caused by pathogens that enter the middle ear from the nasopharynx via the eustachian tube.² The responsible species are the same as those associated with acute otitis media (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).³ Alternatively, pathogens from the external auditory canal, such as *Staphylococcus aureus* might be involved. The duration of episodes with otorrhea should be restricted because day-care attendance might be restrained as well as other social activities, and prolonged otorrhea has been shown to impair quality of life.⁴ The optimal treatment schedule of TT otorrhea is still discussed, especially with reference to the potential ototoxic effects of topical application of various antibiotics with or without steroids, and the risk of microbial resistance.⁵ Previous studies of TT otorrhea have typically examined the efficacy and safety of systemic antibiotics versus placebo, systemic antibiotics in combination with otic drops versus otic drops alone, and comparison between different kinds of otic drops.^{6–15} Thus, the actual recommendations based on these reports are local application of ciprofloxacin otic drops accompanied by massage of the tragus after thorough cleansing and suction of the external ear canal.^{5–15} Furthermore, evidence is gathering that the combination of

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TABLE I.
Demographic Data and Failure Rates in the Total Study Group and in the Three Individual Treatment Groups.

Parameter	Total Study Group	Saline	Ciloxan	Amoxicillin
No.	68	26	22	20
Male/female	40/28	14/12	15/7	11/9
Mean age, mo	22	24	22	20
Age range, mo	7–108	11–63	7–45	10–108
Failure rate	49% (33/68)	58% (14/26)	23% (5/22)	70% (14/20)
Time from TT to otorrhea, d (range)	73 (0–427)	98 (0–305)	106 (0–427)	34 (0–92)
Time from onset of otorrhea to treatment, d (range)	5.7 (1–38)	5.3 (1–12)	6.3 (1–28)	6.4 (1–38)
External otitis	9	4	1	4
Well-functioning TT	60	24	19	17

TT = tympanostomy tube.

dexamethasone and ciprofloxacin is the most effective topical treatment of TT otorrhea.^{10,11,14,15}

With the exception of saline irrigation of the middle ear space at the time of myringotomy and postoperative prophylactic oxymetazoline solution, none of the previous randomized clinical trials (RCTs) have included a control group treated topically with a substance without antibiotics and anti-inflammatory (steroids), or an inactive, nonantibiotic/non-anti-inflammatory substance (placebo) such as saline to test the effect of purely mechanical rinsing.^{8,12,16} In a recent Cochrane review, Vaile et al. requested RCTs that investigate the effects of nonactive substances in the treatment of TT otorrhea, such as placebo and aural toilet.⁸

Therefore, the objective of the present study was to conduct a three-armed randomized double-blind trial to assess the outcome of systemic antibiotics or topical ciprofloxacin or saline rinsing of the external ear canal in children with TT otorrhea.

MATERIALS AND METHODS

Study Population

The study population was recruited between May 2003 and May 2007 according to the following criteria: Caucasian children younger than 10 years, TT insertion due to secretory otitis media (SOM) for more than 3 months or recurrent acute otitis media (AOM), first episode of otorrhea after TT insertion, TT in situ, and no comorbidity. The exclusion criteria were: children older than 10 years, non-Caucasians, otorrhea due to other ear diseases such as chronic suppurative otitis media or cholesteatoma, presence of other diseases or handicaps, or treatment with systemic or local antibiotics during the preceding 3 weeks. Furthermore, patients taking topical or systemic steroids or nonsteroidal anti-inflammatory drugs were excluded.

All patients were outpatients in the ENT Clinic, Horsens, Denmark, and were treated by two of the authors. Donaldson ventilation tubes were used in all cases.

Study Design

The study was conducted as a randomized, double-blind, controlled study. All TT insertions were performed in the clinic and postoperatively oral and written information about the study was given to the parents about the possibility of participation in the study in case of an episode with otorrhea in the following 12

months. At the onset of otorrhea, the parents contacted the clinic and the child was examined the same day. At enrollment, otomicroscopy with cleansing and suction of the ear canal was performed including swabs for routine microbiological examination.

After written consent was obtained from the parents the children were randomized to one of the following three groups: 1) rinsing the ear canal with 2 × 5 mL saline (without preservatives) through a syringe by the parents three times daily for 1 week; 2) Ciloxan (ciprofloxacin, 3 mg/mL) otic drops, four drops twice daily for 1 week accompanied by massage of the tragus; and 3) amoxicillin, 25 to 50 mg/kg/d divided into three daily doses for one week (according to the Danish National Recommendations: www.medicin.dk). In case of penicillin allergy, erythromycin, 40 mg/kg/d divided into three doses daily for a week was chosen. Only in the presence of a nurse in the clinic, the parents chose a sealed envelope containing a slip of paper describing the specific treatment. Each envelope was marked with a random number from a list of random sequences constructed by the first author, who was not in contact with the patients. The medication was provided directly to the parents, who were instructed to register when the discharge terminated. During the treatment period no other medication was allowed except for mild analgesics. The children could only participate once during the inclusion period.

Outcome Parameters and Definitions

The primary outcome parameter was treatment failure rates after the 7-day treatment schedules. Thus, all patients were re-examined by the two blinded otolaryngologists after 1 week, and it was registered if the ear was dry (success) or otorrhea was still present (failure) irrespective of the amount. In case of bilateral otorrhea, in which only one ear had become dry, the case was registered as a treatment failure. Secondary outcome parameters were complications of otorrhea (otitis externa [redness, edema, and tenderness of the ear canal] and plugging or extrusion of the tubes). In case of failure the otolaryngologist was informed about the randomization group and decided the shift in treatment modality.

The study protocol was approved by the ethics committee (no. VF 20020259). All visits at the clinic including the medication were free of charge, and no compensation for participation was given.

Statistics

A priori, the number of patients in each group was estimated to be 25 based on a minimum relevant difference of 10%.

TABLE II.
The Species Isolated From the Middle Ear Fluid
Prior to Treatment.

Species	Total Study Group			
	Saline	Ciloxan	Amoxicillin	
<i>Haemophilus influenzae</i>	18	3	7	8
<i>Streptococcus pneumoniae</i>	11	4	5	2
<i>Staphylococcus aureus</i>	8	4	2	2
<i>Moraxella catarrhalis</i>	7	3	0	4
Group A streptococcus	4	1	1	2
<i>Pseudomonas aeruginosa</i>	4	1	1	2
Mold	1	0	1	0
Skin flora	2	2	0	0
No growth	6	2	3	1
Missing	16	9	4	3

The Student *t* test was used for comparison of the age, duration from TT insertion to otorrhea, and duration of otorrhea before treatment. The failure rates in the groups were compared by the χ^2 test and occurrence of complications (i.e., otitis externa and plugging of the tubes). A significance level of 5% was chosen.

RESULTS

A total of 68 eligible children were included in the study, 40 boys and 28 girls, with a mean age of 22 months (range, 7–108 months). Twenty-six were in the rinsed the ear canal with saline group, 22 had received Ciloxan, and 20 had been treated with amoxicillin. No significant differences were found among the groups with regard to age and gender ($t < 0.8888$, $P > .3789$) (Table I).

The overall treatment failure rate was 49% (Table I). In the entire study group, the mean duration from the TT insertion to the onset of otorrhea was 73 days (0–427 days), and the mean duration of otorrhea to treatment was initiated was 5.7 days (1–38 days). The duration from the TT insertion to onset of otorrhea was significantly shorter in the amoxicillin treated group than in the saline and the ciprofloxacin treated groups ($t > 2.2687$, $P < .0289$). On the other hand, the duration of otorrhea before treatment did not vary significantly among the three groups ($t < 0.7178$, $P > .4765$).

The failure rates were 58%, 23%, and 70% in the saline, the ciprofloxacin, and the amoxicillin group, respectively (Table I). Thus, otorrhea occurred significantly less frequent in the ciprofloxacin treated children after 1 week compared to both the saline- and the amoxicillin-treated children ($\chi^2 = 4.8254$, $0.01 < P < .05$ and $\chi^2 = 9.4502$, $P < .0050$). Treatment failure rates did not differ significantly between the saline and amoxicillin group ($\chi^2 = 1.6857$, $P > .05$).

After treatment, a total of nine children (13%) had signs of otitis externa, one in the ciprofloxacin group, and four in each of the other two groups. Eighty-eight percent (60/68) of the tubes were still in place and patent (Table I).

Microbiological data were available in 52 out of 68 children (76%). Pathogens had been isolated from a total

of 43 children (53 isolates). Thirty-two out of 53 isolates (60%) were monocultures, whereas two pathogen species were cocultured in the remaining. The species are listed in Table II. Thus, *Haemophilus influenzae* were the most common bacteria followed by *S. pneumoniae*. In Table III, the treatment failures and successes are depicted in relation to the microbiological findings. Thus, in the saline treated group, 42% of the ears became dry despite the lack of local and systemic antibiotics. The microbiology was known in 17 out of 26 cases in this group (65%). Eleven of the 17 were treatment failures (65%). Pathogens were isolated from eight of the eleven failures dominated by *Streptococcus* species, *M. catarrhalis*, and *S. aureus*. In the six successes, three had *H. influenzae*, one *S. pneumoniae*, one *Pseudomonas aeruginosa*, and one was without growth. In the ciprofloxacin-treated group, microbiological results were available in 18 out of 22 (82%). Five of the 18 (28%) were treatment failures demonstrating growth of streptococci in two, and mold, *P. aeruginosa*, and *S. aureus* in the remaining three cases. On the contrary, seven of the 13 successes were colonized with *H. influenzae*, three were without growth, two *S. pneumoniae*, and one *S. aureus*. Finally, microbiological results were obtained in 16 out of 20 children (80%) treated with amoxicillin. Eleven of the 16 (69%) were treatment failures. *H. influenzae* were isolated from five of the 11 versus three among the five successes. Dividing all pathogens into typical nasopharyngeal and external auditory canal pathogens did not show any correlation to the age of the children.

All *Haemophilus* species demonstrated maximum sensitivity to amoxicillin except one resistant case. *M. catarrhalis* were cultured from three of the treatment failures. In regard to the general resistance pattern, all moraxellae were sensitive to ampicillin/clavulanate, the streptococci were penicillin sensitive, and the *S. aureus* were methicillin sensitive

DISCUSSION

In the present randomized, double-blind study, TT otorrhea was generally still present after 1 week in a total of 49% of 68 children despite various treatment schedules. When treated with saline rinsing of the external ear canal or oral amoxicillin, the incidences of otorrhea (treatment failures) was 58% and 70%, respectively. Treatment with ciprofloxacin otics, however, reduced the occurrence of otorrhea significantly to 23%. Furthermore, complications to otorrhea, such as otitis externa and plugging of the tubes, occurred rather rarely irrespective of treatment modality.

In the light of the frequency of otorrhea, the time needed for inclusion of a sufficient number of children appears extremely long. The reason was the exclusion of children with systemic or local antibiotic treatment for 3 weeks prior to admission to the otolaryngologist. Often the parents had contacted the general practitioner, who had initiated treatment instantly, thereby excluding the child from being enrolled in the study.

The study was carried out according to general rules for central randomization, and therefore the three

TABLE III.
The Microbiology in Relation to Outcome (Failure/Success).

Parameter	Saline	Ciloxan	Amoxicillin
Total no.	26	22	20
No. of known microbiology	17	18	16
Failures	11	5	11
Most frequent species in failures	Streptococci: 4; <i>Moraxella catarrhalis</i> : 3	Streptococci: 2	<i>Haemophilus influenzae</i> : 5; <i>Moraxella catarrhalis</i> : 3
Successes	6	13	5
Most frequent species in successes	<i>Haemophilus influenzae</i> : 3	<i>Haemophilus influenzae</i> : 7; streptococci: 2	<i>Haemophilus influenzae</i> : 3

groups were expected to be identical. However, in regard to one parameter, the amoxicillin treated group differed significantly from the other two groups in terms of the duration from TT insertion to onset of otorrhea. The children in this group did not vary significantly with respect to age, gender, and time with otorrhea before the treatment was initiated. Furthermore, they were included throughout the entire study period and their initial indication for TT insertion (i.e., AOM and/or SOM was not different from the saline and the ciprofloxacin groups). The only obvious explanation might be that a total of five children in the last-mentioned groups had durations of more than 1 year before developing otorrhea, thus increasing the average considerably.

The three groups might also differ regarding compliance. This was not analyzed in the present study, but one might suspect that a higher compliance was obtained among the children receiving local treatment versus the amoxicillin group, in which the failure rates were the highest.

A higher compliance in the amoxicillin treated group might be achieved using only two daily doses instead of three. Rinsing the ear canal with saline through a syringe three times daily might also have caused problems with the compliance due to the limitations of the skills of the parents.

The failure rates reported in previous studies vary between 10% and 22% regarding ciprofloxacin-containing ear drops and 20% and 50% when using oral antibiotics alone.^{5,6,8,10,11,14,15} In comparison, our results demonstrate failure rates exceeding these levels. In general, differences in compliance and additional procedures, such as daily suction, might play a considerable role for treatment results. An important reason for this discrepancy might also be that we evaluated the effect after 1 week, and most other authors have chosen 2 weeks despite similar treatment duration of 1 week. Our definition of failures also seems more rigorous because we demanded that both ears were completely dry to be evaluated as a success. In some studies, outcome parameters, such as time to resolution of TT otorrhea and degree of improvement, have been used making comparison difficult. Most of the recent studies have focused on topical treatment with ciprofloxacin combined with steroids and thereby demonstrated an additional effect of dexamethasone, which evidently relates

to its anti-inflammatory activity.^{5,10,11,14,15} However, the combination of ciprofloxacin and dexamethasone has not yet been approved by the Danish authorities, and therefore these ear drops were not available for the present study.

With the purpose of achieving information about the natural course of TT otorrhea we wanted to study a nontreated group of children. The spontaneous cure rate might be as high as 40%, but the various studies are impeded by the use of some kind of intervention, such as suction and placebo substances.⁶ For ethical reasons we refused to allocate some of the patients to no treatment. Instead we included a group treated with saline rinsing as a control group. Compared to the group treated with an oral antibiotic there was a nonsignificant tendency toward a lower failure rate in the saline-treated group. The mechanism behind this effect might be a mechanical removal and/or dilution of the bacterial load, which also was indicated in a study of prophylactic rinsing of the middle ear at the time of TT insertion.¹⁶ This finding also indicates that the significant effect of ciprofloxacin is not only a mechanical consequence but a result of antimicrobial activity. Thus, saline rinsing might be considered as a supplemental treatment accompanied by quinolone-/steroid-containing eardrops.

From a theoretical point of view, oral amoxicillin should be effective in the treatment of TT otorrhea. The isolated bacteria were dominated by amoxicillin-sensitive strains derived from the upper airways. However, we found the highest frequency of failures among patients treated with amoxicillin, which is in accordance with previous reports.¹⁴ The explanation might be that the drug concentration obtained in the middle ear mucosa is insufficient for eradication of the microorganisms. On the other hand, Ruohola et al. found oral treatment with amoxicillin/clavulanic acid to be superior to placebo.⁶ The results might be influenced by the daily suction of the ear canal. Furthermore, the incidence and severity of adverse effects are considerably higher among patients treated with oral antibiotics compared to ear drops.^{11,14,15} Regarding the ototoxic potential of ear drops, several studies have proved both ciprofloxacin and ciprofloxacin/dexamethasone to be safe even in cases of drum perforations/tympanostomy tubes.^{5,17}

The demographic data of our study population including the microbiological findings are in accordance with the international literature.^{5,9-11,14,15} Besides the clinical

effectiveness, bacterial eradication has been evaluated in relation to the various treatment modalities. As in the present study, *H. influenzae* and *M. catarrhalis* are generally most often represented among failures regardless of treatment.^{9,11,14} Consistent with other studies, we found that treatment with ciprofloxacin resulted in higher microbiological response rates in cases of these strains.^{11,14} Apparently, streptococci seem less responsive to ciprofloxacin compared to oral amoxicillin.¹⁴

All except one of the isolated *H. influenzae* demonstrated maximum susceptibility to amoxicillin. Despite this, only one half was successfully treated with amoxicillin, which might be explained by the previously mentioned bioavailability in the middle ear. Finally, the lack of additional clavulanic acid might explain the failures in cases of *M. catarrhalis* in the present study according to the resistance pattern.

CONCLUSION

The present study supports the superiority of topical treatment with ciprofloxacin in cases of TT otorrhea in terms of clinical effectiveness. However, studies of the spontaneous course of TT otorrhea are missing for comparison.

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