

# Ofloxacin Otic Drops vs Neomycin–Polymyxin B Otic Drops as Prophylaxis Against Early Postoperative Tympanostomy Tube Otorrhea

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**Objectives:** To evaluate the incidence of tympanostomy tube (TT) sequelae, tube otorrhea, and tube obstruction immediately postoperatively in patients receiving TT for otitis media and to compare patients receiving postoperative otic drops with controls.

**Design:** Blinded randomized control trial.

**Setting:** A tertiary pediatric otolaryngology practice.

**Subjects:** The study population comprised 306 patients undergoing TT placement.

**Interventions:** The 306 patients were enrolled into the following 3 groups: (1) those receiving no postoperative otic drop prophylaxis (control group), (2) those receiving ofloxacin otic drops (FLOX group), and (3) those receiving neomycin sulfate–polymyxin B sulfate–hydrocortisone otic drops (COS group).

**Results:** Overall otorrhea rates postoperatively were 14.9% for the control group, 8.1% for the FLOX group, and 5.5% for the COS group. When controlling for dis-

ease severity, the rate of otorrhea was significantly higher for the control group than for both the FLOX ( $P=.04$ ) and COS ( $P=.01$ ) groups. Nonpatent, plugged, tube rates were added to otorrhea rates for a TT failure analysis postoperatively. The control group demonstrated a significantly greater failure rate (29.9%) than both the FLOX (12.1%) and COS (7.7%) groups. The only differences between the patients in the 2 groups receiving drops were that ofloxacin was more well liked by patients ( $P=.04$ ) and caused less pain ( $P=.004$ ).

**Conclusions:** Nonpatency and otorrhea are the most frequent sequelae immediately following TT placement. Few studies have compared different treatment regimens in a randomized controlled trial. These results demonstrate that otic drops clearly provide benefit postoperatively in preventing TT plugging and otorrhea but primarily in patients who have middle ear fluid at the time of TT placement. In addition, consideration of drop choice should be based on patient tolerance and medication safety profiles.

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**T**YMPANOSTOMY TUBE (TT) placement is a frequently performed surgical procedure, is the most common reason a child receives general anesthesia in the United States, and represents significant medical expenditures, given its common use in the management of otitis media.<sup>1,2</sup> Despite this frequency, there exist gaps in our knowledge about treatments related to this procedure and especially those done in randomized controlled trials. Postoperative TT otorrhea (TTO) is the most common sequelae and occurs at a rate of 2% to 17%.<sup>2,3</sup> Nonpatent or plugged tubes from drainage or blood is another relatively frequent sequelae. Otic drops are frequently used for several days postoperatively to alleviate these difficulties; however, to our knowledge, no large randomized controlled trial has been performed examining the efficacy of several different treatment regimens.

At a rate of between 500 000 to 1 million TT procedures performed annually in the United States,<sup>1</sup> a significant amount of health care dollars are expended annually on prophylactic use of otic drops following this procedure with very little data on their efficacy. The present study was undertaken to attempt to answer the questions: (1) Do prophylactic otic drops provide benefit in reducing otorrhea and tube nonpatency? (2) Are there subsets of patients who receive more benefit from these treatments? and (3) Are there differences between otic drops in preventing otorrhea and tube plugging?

## METHODS

This study received institutional review board approval from Children's Hospital of Wisconsin, Milwaukee, prior to its initiation; all subjects had signed informed consent prior to en-

rollment; and a data safety monitoring board, through the National Outcomes Research Center at Children's Hospital of Wisconsin, provided periodic data assessment throughout the trial. No previous data were available comparing these specific groups, but based on previous published literature, sample size was calculated for patient enrollment assuming a 10% difference between treated and untreated patients, with an  $\alpha$  level of .05 and a power level of 0.80.

A total of 306 patients scheduled for placement of TT for otitis media were recruited from an academic pediatric otolaryngology practice. Inclusion criteria included any child undergoing TT placement for otitis media. Exclusion criteria included the following: patients with syndromic conditions, patients with known craniofacial abnormalities, patients with other chronic illness or other severe medical conditions, and patients with known sensorineural hearing loss. Consecutive patients scheduled for TT placement who did not meet exclusion criteria were offered participation in the study. After signing informed consent, the patients were randomized to 1 of 3 groups for postoperative use of otic drops: (1) no drops (control group), (2) ofloxacin (Floxin Otic; Daiichi Pharmaceutical, Montvale, NJ) otic drops (FLOX group) and (3) neomycin sulfate-polymyxin B sulfate-hydrocortisone suspension (Bausch and Lomb, Tampa, Fla) otic drops (COS group). Random allocation was achieved using random number selection by the research coordinator, and group allocation was kept concealed until completion of the trial.

Patients with fluid demonstrated in 1 or both middle ear spaces at the time of TT placement were instructed to use their drops for a total of 10 days. If no fluid was present, patients were treated for a total of 3 days.

A consistent operative technique was used in all patients, with myringotomy performed in the anterior inferior quadrant and placement of a Teflon-coated, fluoroplastic Armstrong beveled TT (Gyrus ENT, Bartlett, Tenn). A significant portion of the patients enrolled in the study had their procedure performed by resident trainees under the supervision of an attending surgeon. All patients were seen postoperatively by day 14, with a majority seen between days 10 and 14. All assessments made at the follow-up appointment regarding TTO and tube patency were made with the observer blinded to the patient's treatment group. These assessments were made by the attending surgeon. Patients were instructed to return their unused otic drops at the time of follow-up to assess for compliance of treatment regimen. Tubes were considered patent if the entire lumen and promontory middle ear mucosa could be visualized on otoscopy. Otoscopic findings were corroborated by tympanometry.

A 5-item questionnaire was given to the caregiver who accompanied the child at the initial postoperative visit. This questionnaire was completed prior to being seen by the physician and was collected without being reviewed by the physician. The questionnaire was designed to assess compliance and patient satisfaction with the drops used (**Table 1**). The analysis of these questionnaires was completed in a blinded fashion.

All statistical assessments were performed in consultation with an epidemiologist and statistician at the National Outcomes Research Center at Children's Hospital of Wisconsin. Otorrhea and tube plugging rates were compared between the 3 arms using  $\chi^2$  analysis. Analysis of each treatment arm vs control was performed with  $\chi^2$  analysis and the Fisher exact test. Otorrhea and tube plugging rates for all 3 groups and each treatment arm individually vs control was performed correcting for operative findings using the Mantel-Haenszel  $\chi^2$  test. Postoperative survey results were analyzed by the Wilcoxon 2-sample test (nonparametric).  $P \leq .05$  was considered significant. In addition, 95% confidence intervals were calculated using the exact method for rate analysis. The failure rates were not adjusted for disease severity in these calculations. A failure rate

**Table 1. Five-Question Survey Administered on Follow-up Visit Assessing Parent Perceptions of Drops Prescribed and the Compliance With This Therapy**

Question	Ofloxacin Sulfate vs Neomycin-Polymyxin B*	P Value
Child disliked drops?	Ofloxacin drops liked better	.04
Child had pain with drop administration?	Ofloxacin drops were less painful to administer	.004
Drops given as instructed?	No difference between drops	.59
Drops not given because of pain?	No difference between drops	.30
Drops helped child?	No difference between drops	.37

\*Neomycin sulfate-polymyxin B sulfate-hydrocortisone.

reduction was calculated to compare the treatment groups with the control group. The failure rate reduction was taken by subtracting the intervention failure rate (FLOX or COS group) from the control group failure rate (**Table 2**). For the purposes of this study, any change in the absolute failure rate greater than 5% was considered clinically significant given the high degree of success expected in TT placement and the very low risk or associated adverse effects of administering postoperative drops.

In the survey data analysis, the authors used the survey data in questions 1, 2, and 3 as an ordinal scale of 1 to 5 (1=always, 2=almost always, 3=sometimes, 4=almost never, and 5=never).

All funding and materials for this study were provided through the Division of Pediatric Otolaryngology, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, and the National Outcomes Research Center at Children's Hospital of Wisconsin, Milwaukee.

## RESULTS

A total of 306 patients were enrolled between February 2002 and December 2003, and 29 patients were excluded from the final analysis. Of these patients, 14 ended up having their surgery cancelled or postponed and were not reenrolled into the study. Fifteen patients did not keep their immediate postoperative follow-up by 2 weeks and were excluded from analysis. Of these 29 patients, 12 were in the control group, 11 were in FLOX group, and 6 were in the COS group. All other patients who began the trial completed the trial in their assigned group. Therefore, 277 patients were analyzed; 87 were in the control group, 99 were in the FLOX group, and 91 were in the COS group. There were no significant demographic differences between the groups based on age, sex, or race (**Table 3**). Middle ear effusion (MEE) was present in 42 (48%) of 87 patients in the control group, 61 (62%) of 99 patients in the FLOX group, and 52 (57%) of 91 patients in the COS group.

The postoperative otorrhea rates were greatly increased in patients who demonstrated MEE at the time of TT placement (**Table 4**). A significantly higher percentage of patients developed otorrhea when middle ear fluid was present compared with tubes placed in ears with dry middle ear spaces (Table 4). This impact of MEE at the time of TT placement was taken into consideration in performing the statistical assessment of the differences between treatment arms. A higher rate of MEE, as seen in

**Table 2. Tube Failure Rates in Groups\***

Failure Rate							
Control Group		FLOX Group		COS Group		Failure Rate Reduction of Ofloxacin Sulfate, % (95% CI)	Failure Rate Reduction of Neomycin–Polymyxin B, % (95% CI)
No. of Tube Failures/No. of Tubes Placed	% (95% CI)	No. of Tube Failures/No. of Tubes Placed	% (95% CI)	No. of Tube Failures/No. of Tubes Placed	% (95% CI)		
52/174	29.9 (23.2-37.3)	24/198	12.1 (7.9-17.5)	14/182	7.7 (4.3-12.6)	17.8 (8.8-27.3)	22.2 (13.4-31.5)

Abbreviations: CI, confidence interval; COS, neomycin sulfate–polymyxin B sulfate–hydrocortisone; FLOX, ofloxacin sulfate.

\*Both the FLOX and COS groups had a statistically significant reduction in failure rates compared with the control group. There was no statistically significant difference in failure reduction between the FLOX and COS groups.

**Table 3. Demographics of Patients in Trial**

Demographic	Control Group (n = 87)	FLOX Group (n = 99)	COS Group (n = 91)
Sex, No. (%)			
M	48 (55)	54 (55)	49 (54)
F	39 (45)	45 (45)	42 (46)
Race, %			
White	76	72	80
Black	12	15	12
Hispanic	10	6	4
Other	2	6	4
Age at tube insertion, mo (range)	22.6 (6.0-80.0)	22.5 (8.0-144.0)	26.0 (5.0-146.0)

Abbreviations: COS, neomycin sulfate–polymyxin B sulfate–hydrocortisone; FLOX, ofloxacin sulfate.

the FLOX group, was interpreted as overall greater disease severity in this group. When controlling for disease severity in this fashion, there existed a significantly higher rate of otorrhea for patients in the control group compared with patients in both of the prophylactic otic drop groups (all  $P < .04$ ) (**Table 5**). There were no differences in otorrhea rates between the 2 groups receiving drops.

In addition to otorrhea, a failure analysis of TT placement was assessed by adding tube nonpatency rates to otorrhea. The postoperative tube patency rates were lower for the control group than for the otic drop groups (85.1% for the control group, 96.0% for the FLOX group, and 97.8% for the COS group). In this tube failure analysis, tube failure rates were significantly higher in the control group than in either of the 2 otic drop groups (Table 2). These differences were present even without controlling for the increased disease severity seen in the FLOX group. When using the limits of the 95% confidence intervals for TT failure rates to assume the narrowest difference between treated patients and controls, there was greater than a 5% drop in failure rates of patients treated with otic drops compared with control patients. There were no differences between the 2 groups receiving otic drops.

The compliance of the patients receiving otic drops, pain associated with drop use, and how well the otic drops were tolerated were assessed in a postoperative ques-

tionnaire (Table 1). The ofloxacin drops were more well liked and caused less pain compared with the neomycin–polymyxin B drops, although this did not appear to lessen the compliance with the prescribed therapy based on otic drop use.

Aside from TTO or tube obstruction, no adverse events resulted in association with this investigation.

#### COMMENT

Prophylactic otic drops are frequently prescribed for varying periods following TT placement. Despite this practice, to our knowledge, no large randomized controlled trial comparing various treatment groups with control patients have been published that examine a variety of factors including otorrhea, tube patency, and patient tolerance of treatment. In assessing this use of otic drops, consideration should be given to cost, efficacy, patient compliance, patient satisfaction with treatment, duration of treatment, and treatment risks and benefits. The present study demonstrates that, in a setting of MEE, patients have less difficulty with postoperative otorrhea and tube plugging when otic drops are administered following TT placement.

A previous meta-analysis<sup>4</sup> assessing the benefit of prophylactic drops following TT placement found significant difficulties with previous studies and recommended further investigations. However, the overall recommendation of that study was in favor of the administration of prophylactic drops following TT placement.<sup>4</sup> Although subsequent studies have examined this benefit of prophylactic otic drops following TT placement, conclusions have been hampered by study design and lack of power to allow for definitive conclusions.<sup>5</sup> In addition, these studies have failed to examine other factors such as tube patency rates and patient satisfaction with treatment. A recently published large patient series has also suggested that other preparations, such as oxymetazoline hydrochloride, may also provide equal benefit to antibiotic otic drops at a reduced cost; however, these preparations were not the focus of the proposed investigation.<sup>6</sup>

The present study was designed with these questions in mind and was constructed with a large enough patient enrollment to allow for adequate power to examine the benefit of otic drops in treated patients vs controls, as well

**Table 4. Otorrhea Rates by Treatment Group Stratified by Presence of MEE at Time of TT Placement\***

Otorrhea Rate	Control Group		FLOX Group		COS Group	
	No. of Tubes With Otorrhea/ No. of Tubes	% (95% CI)	No. of Tubes With Otorrhea/ No. of Tubes	% (95% CI)	No. of Tubes With Otorrhea/ No. of Tubes	% (95% CI)
Total otorrhea rate	26/174	14.9 (10.0-21.1)	16/19	8.1 (4.7-12.8)	10/182	5.5 (2.7-9.9)
Otorrhea rate in dry ears	4/90	4.4 (1.2-11.0)	0/75	0.0 (0.0-4.8)	0/78	0.0 (0.0-4.6)
Otorrhea rate in ears with MEE	22/84	26.2 (17.2-37.0)	16/123	13.0 (7.6-20.3)	10/104	9.6 (4.7-17.0)
Difference in otorrhea rates: dry vs MEE	NA	21.8 (11.4-32.1)	NA	13.1 (7.1-19.0)	NA	9.6 (4.0-15.3)

Abbreviations: CI, confidence interval; COS, neomycin sulfate-polymyxin B sulfate-hydrocortisone; FLOX, ofloxacin sulfate; MEE, middle ear effusion; NA, not applicable; TT, tympanostomy tube.

\*Each group demonstrated a significantly higher otorrhea rate when MEE was present at the time of TT placement compared with dry middle ears at the time of TT placement.

**Table 5. Statistical Assessment of Differences Between Rates of Otorrhea in Groups\***

Variable	All Groups	FLOX Group vs Control Group	COS Group vs Control Group	FLOX Group vs COS Group
All patients	.08	.10	.04	.31
No MEE	.14	.22	.20	No otorrhea in either group
MEE present	.07	.09	.03	.20
All: adjusted for disease severity (MEE)†	.02	.04	.01	.42

Abbreviations: COS, neomycin sulfate-polymyxin B sulfate-hydrocortisone; FLOX, ofloxacin sulfate; MEE, middle ear effusion.

\*Data are given as *P* values (significant difference at  $P \leq .05$ ). Both treatment groups demonstrated a significant reduction in otorrhea compared with the control group.

†The final assessment was adjusted for disease severity (rate of MEE prevalence) because of a significantly increased rate of otorrhea seen in patients in whom MEE was present.

as to allow for comparisons of 2 commonly used otic drops. The drops chosen for this study were selected because ofloxacin represented the only otic preparation for middle ear use approved by the Food and Drug Administration at the study's initiation, and neomycin-polymyxin B represented the most widely used otic drop prior to the introduction of ofloxacin to the market. Finally, additional factors that frequently enter into consideration of the use of otic drops, tube patency, and patient satisfaction with this treatment were assessed in this investigation.

The present study demonstrates that patients receive benefit from the use of otic drops compared with control patients in the prophylaxis of postoperative TTO (Table 5). Similar to a previously published study that demonstrated approximately a 7% reduction in postoperative TTO when drops were used in all patients,<sup>7</sup> the present investigation revealed approximately a 7% reduction in TTO for the FLOX group and a 10% reduction in the COS group. However, the raw percentage of postoperative TTO needs to be considered in the light of the percentage of patients who had MEE at the time of TT placement. Because the presence of middle ear fluid at the time of TT placement significantly increases the chances of postoperative TTO, again demonstrated in this study (Table 4), calculations were performed taking into consideration the rate of MEE in each treatment group. Although this was a randomized trial, the FLOX group had a higher percentage of patients with MEE at the time of TT compared with the COS group, which had more than the control group. When correcting for this "severity" of preoperative disease, both the FLOX and COS

groups demonstrated significantly less postoperative TTO compared with the control group, and there were no statistical differences between the 2 treatment groups (Table 5, row 4). The importance of MEE at the time of TT placement is further highlighted in Table 4, which shows that the control patients with dry middle ear at the time of TT placement had an otorrhea rate of only 4%, but this significantly increased to 26% when MEE was present. Similarly, when one compares the postoperative TTO rate in patients with dry ears across all 3 groups (Table 5, row 2), there were no significant differences between the groups.

Tube patency following TT placement is of significant importance. In addition to a plugged tube not achieving the intended purpose of the surgical procedure, additional procedures or otic drops are often required to attempt to get the tube unplugged. There is often, also, a great deal of patient/parent dissatisfaction when then surgical procedure results in a plugged tube postoperatively. Tube plugging generally comes from 2 sources: mucoid fluid continuing to drain from the middle ear space after the tube is placed and blood clotting within the lumen of the tube. In examining the potential benefit of prophylactic drops following TT placement, the tube plugging rate was added to the postoperative TTO rate for a tube failure analysis. The benefit of prophylactic otic drops following TT placement becomes even more pronounced when considering both the difficulty of postoperative TT otorrhea and tube plugging (Table 2), for which both treatment groups had significantly lower failure rates compared with the controls. There were no sta-

tistical differences between the 2 treatment groups. Expressed another way, when comparing the rates of TTO plus tube plugging of treated patients vs controls, there was an almost 18% to 22% increased rate of tube failure if postoperative drops were not used. Even if the limits of the 95% confidence intervals were used to assume the least possible difference between using drops and not using drops, there was an almost 9% to 13% reduction in failure rates with the use of prophylactic drops. Most parents have high expectations regarding the success rate of TT placement, and there is very little risk or negative adverse effects in using prophylactic otic drops postoperatively. Given these factors, we believe that these rates of risk reduction in tube failure are clinically significant. Again, it can be noted, however, that these differences exist primarily in patients who demonstrate MEE at the time of TT placement.

A final consideration in determining the use of prophylactic otic drops following TT placement is patient satisfaction with the therapy. This was assessed by means of a postoperative questionnaire in this study. As demonstrated in Table 3, patients appeared to have less pain and dislike in the administration of ofloxacin drops compared with neomycin-polymyxin B drops. One possible explanation for this may be the overall more neutral pH found in the ofloxacin preparation<sup>8</sup> (pH of 6.5±0.5) compared with the overall more acidic neomycin-polymyxin B drops<sup>9</sup> (pH range, 3.0-7.0). Although the assessment of tolerance of a medication by children can be subject to interpretation bias, the use of caregivers as surrogates to assess patient tolerance of an intervention is well accepted in pediatric clinical research. Care was also taken throughout the study to avoid giving the parents information or direction that might bias their decision of the tolerance of the various otic preparations. Furthermore, the individuals responsible for assessing the survey responses were blinded to the patient's study group.

In conclusion, the use of prophylactic otic drops following TT placement appears warranted based on their ability to achieve lower rates of otorrhea and higher rates of tube patency. In patients without MEE at the time of TT placement, the benefit of prophylactic drops is far less clear. In light of recently developed quinolone otic preparations for which there is no concern regarding ototoxicity,<sup>10,11</sup> the use of postoperative drops has an even more favorable risk-benefit profile. Considering ototoxicity, patient tolerance of drop administration and the equivalent efficacy of ofloxacin and neomycin-polymyxin B in limiting the difficulties of otorrhea and tube plugging seen in control patients, ofloxacin would appear to be a superior choice for postoperative TT prophylactic otic drops. Additional areas of study should focus on the optimal time for drop administration following TT placement and blinded randomized controlled trials investigating nonantibiotic-containing preparations as well as the recently developed quinolone-steroid otic drops, which were approved by the Food and Drug Administration for middle ear use. In light of the frequency of TT placement, high-quality studies in these areas are needed to guide practitioners and patients and to avoid therapy based on empirical data. Such studies would truly have the potential to affect a large group of patients with significant implications regarding health care expenditures.

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