# Abstract:

**Objectives:** To determine the effectiveness of ciprofloxacin 0.3% antibiotic eardrops in preventing clinically significant postoperative otorrhea and tube obstruction following grommet insertion in children.

**Design:** 3-arm double-blinded randomized controlled trial. Randomisation in 1:1:1 ratio into two interventional and one control arm. The interventional groups received either 5 drops of topical ciprofloxacin 0.3% eardrops in each ear intraoperatively or intraoperatively and for 5 days postoperatively. The control group received no drops. Patients were assessed by blinded assessors at 6 weeks postoperatively.

**Setting:** The study was conducted in a large tertiary health network “Blinded for review”.

**Participants**: All children, 17 years and under, undergoing bilateral MEVT surgery with or without concurrent upper airway surgery for recurrent acute otitis media and chronic otitis media with effusion were approached.

**Main Outcome Measures:** Presence of postoperative otorrhea and ventilation tube obstruction at 6 weeks postoperatively.

**Results:** 256 pediatric patients completed the study with a median age of 4.02 years. 153 participants were male. Intraoperative antibiotics were more effective than control in preventing otorrhea (RR=0.341, 95%CI 0.158–0.738, NNT= 11.25, p=.006). Postoperative antibiotics were more effective than control in preventing ventilation tube obstruction (RR=0.424, 95%CI 0.193 to 0.930, NNT=14.7 p=.032).

**Conclusion:** Intraoperative topical ciprofloxacin was effective at preventing early postoperative otorrhea and a prolonged course was effective at preventing ventilation tube obstruction. Future studies on this topic should seek to clarify whether particular subgroups of patients benefit more from prophylactic topical antibiotics and model for cost-effectiveness.

**Trial Registration:** This trial was registered prospectively on the *“Blinded for review”.* Clinical Trials Registry (*“Blinded for review”.*) on the 28th of June 2018. Available at URL:   
*“Blinded for review”.*

# Key Points:

* Postoperative otorrhea and ventilation tube obstruction are common postoperative complications of middle ear ventilation tube (MEVT) insertion.
* The use of perioperative topical antibiotic drops as prophylaxis remains a contentious topic in the ENT community.
* This RCT demonstrated effectiveness of perioperative ciprofloxacin ear drops at preventing postoperative otorrhea and ventilation tube obstruction at 6 weeks postoperatively
* The routine use of topical ciprofloxacin ear drops around the time of grommet surgery reduced rates of postoperative otorrhea 65% when compared to control.
* A prolonged course of topical ciprofloxacin following intraoperative application reduced the incidence of ventilation tube obstruction by 54% when compared to control.

# Introduction:

Insertion of middle ear ventilation tubes (MEVTs) are effective in reducing the frequency of recurrent acute otitis media (rAOM) and improving conductive hearing loss in chronic otitis media with effusion (cOME). It is the most common surgical procedures performed in the pediatric population in the United States, with 667,000 cases performed per year.(1)

Overall, the efficacy and safety of this procedure has been demonstrated over the past 70 years since its introduction by Armstrong in the 1950s. (2) However two common complications, early postoperative otorrhea and ventilation tube obstruction, can reduce the quality of life of patients and caretakers, result in reduced longevity of the ventilation tube and the need for repeat medical and surgical intervention. (3)

Factors which are thought to contribute to these complications include intrinsic factors such as patient age, gender and anatomical variation, as well as extrinsic factors such as contamination during surgery, timing of surgery and childcare attendance. (4, 5)

To reduce these complications, prior studies have suggested antiseptic preparation of the external ear canal prior to tube insertion(6), insertion of antibiotic coated ventilation tubes (7, 8), postoperative oral antibiotic prophylaxis (9), application of intraoperative and postoperative topical antibiotic or isotonic saline drops (10) as well as intraoperative irrigation of the middle ear cleft (11).

The use of topical antibiotics has garnered the most evidence in the last 20 years, especially with the introduction of ciprofloxacin, a quinolone antibiotic effective in covering Staphylococcal and Pseudomonal species without the ototoxic properties of older aminoglycoside antibiotics. (12) Recent studies have suggested the antibiotic properties of topical ciprofloxacin are not necessary in reducing postoperative complications, and simple diluents such as normal saline can be used to reduce incidence of otorrhea and obstruction. (10)

# Objectives:

In this study, two treatment arms, an intraoperative only topical ciprofloxacin [IO] and an extended postoperative topical ciprofloxacin [PO] are compared against a non-treatment control group to determine the efficacy of topical ciprofloxacin drops in preventing postoperative otorrhea and ventilation tube obstruction. We hypothesise that the use of IO and PO ciprofloxacin drops will be superior to control in preventing both postoperative otorrhea and ventilation tube obstruction.

# Methods:

The study was a single centre, double-blinded, 3-arm parallel-group randomized controlled trial with equal allocation [1:1:1] conducted in *“Blinded for review”.* The study took place at two sites within *“Blinded for review”.*, a large tertiary health network in *“Blinded for review”*. Human research ethics (HRE) approval was granted by the HRE committee at *“Blinded for review”.*, and the trial was prospectively registered on the *“Blinded for review”* clinical trials registry prior to commencement. Randomisation was unchanged throughout the trial. Eligible participants were pediatric patients aged 17 or under who were undergoing bilateral MEVT insertion with or without concurrent upper airway surgery (tonsillectomy and/or adenoidectomy) for a diagnosis of rAOM or cOME. Exclusion criteria included allergy to quinolone antibiotic, intraoperative finding of purulent middle ear effusion or significant middle ear pathology requiring intervention and insertion of long-term MEVTs (T-tube or Paparella tube).

All recruited patients had Reuter-Bobbins ventilation tubes inserted using a standardised technique under general anaesthesia by otolaryngology trainees, fellows or surgeons with intraoperative findings documented. Patients allocated to IO group received 5 drops of topical ciprofloxacin (Ciloxan 0.3% Ear Drops) into each ear following insertion of MEVTs. Patients allocated to PO group received 5 drops of topical ciprofloxacin into each ear during surgery as well as twice a day for 5 days postoperatively. Following instilling drops during surgery, surgeons were instructed to perform tragal pressure to ensure penetrance of the drops into the middle ear cleft. Patients allocated to the control group did not receive any topical ciprofloxacin. Cotton wool balls were inserted into both ears at the end of surgery to ensure patient blinding.

The primary endpoint was the presence of postoperative otorrhea and ventilation tube obstruction during otoscopy and tympanometry assessment at 6 weeks postoperatively. Direct otoscopic examination and clinical history were used to assess for otorrhea, whilst direct otoscopic examination as well as a finding other than a Jerger Type B(hi) tympanogram was used to assess ventilation tube obstruction.

Our anticipated sample size was 360 participants. To detect a reduction from 11% to 4% in the incidence of our primary outcomes with a two-sided significance of 5% and a power of 80%, we calculated 240 ears per group was required, given an estimated attrition rate of 7.5%. An interim analysis was conducted once 150 patients were recruited. There were no statistically significant findings or significant adverse events at the interim analysis.

Simple randomisation of sealed opaque envelopes was used to generate our randomisation sequence given our anticipated 360 participants. These were prepared by a party separate to the research team. The allocation sequence was not known to the researcher enrolling participants, as they were detailed on a card within sequentially numbered sealed opaque envelopes located in a secure location within the operating theatre. The envelopes were also lined with additional paper to prevent visualisation of the allocation card. Randomisation took place at the start of surgery and patient details and envelope number were recorded on the allocation card by theatre staff. These allocation cards were moved at the end of each week to a secure location chosen by the data monitoring committee.

Patients allocated to either intraoperative drop or control groups were blinded of their treatment allocation, while the postoperative drops group were not blinded of their treatment allocation. Outcome assessors and data analysts were blinded of the treatment allocation for all groups until completion of the study.

Analysis was conducted on a by-ear basis, each participant ear was treated as an individual data point. Chi-square tests were used to calculate relative risk and two-tailed p-values for each of the following pairings: IO vs Control and PO vs Control, for postoperative otorrhea and ventilation tube otorrhea. The Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement will be used to report the findings.

# Results:

Recruitment commenced in May 2018 and concluded in March 2020, with last follow-up complete in June of 2020. A total of 296 participants were randomized and losses and exclusions are detailed in Figure 1. The most common reason for exclusion was “presence of purulent middle ear effusion” (n=18). Trial recruitment was impacted by the COVID-19 pandemic in March 2020 along with nationwide directives to halt elective surgeries. A per-protocol analysis was performed as “presence of purulent effusion” could only be determined at time of surgery and would require immediate and extended treatment with antibiotic drops and an intention-to-treat analysis would not be appropriate in establishing the effect of antibiotic drop exposure on the non-purulent ear.

Two-hundred and fifty-six pediatric patients completed the study for a total of 512 ears. Eighty-nine participants were randomized to control, 87 to the intraoperative group and 80 to the postoperative group. Baseline demographic data for each group is summarised in Table 1. The median participant age was 4.02 years, with a range of 0.72 years to 13.1 years. Most participants were male (59.7%), were receiving their first set of MEVTs (77.3%) and have not had a previous tonsillectomy or adenoidectomy (88.3%). The most common indication for surgery was chronic otitis media with effusion (66.0%). Most operated ears had presence of middle ear effusion (58.6%), with mucoid effusions being the most common type of effusion. A relatively small percentage of operated ears had tympanic membrane bleeding (8.4%). The median time to review was 6.71 weeks. There was no statistically significant heterogeneity between the three allocation groups in terms of demographic characteristics (p>0.05).

The primary outcomes are shown in Table 2. The overall rate of otorrhea at 6-weeks was 9.0%. The number of ears that developed otorrhea is summarised in Figure 2. Otorrhoea developed in 8 of 174 (4.6%) ears in the intraoperative group, 14 of 160 (8.8%) ears in the postoperative group, and 24 of 178 (13.5%) ears in the control group. Patients receiving intraoperative antibiotics were less likely to develop otorrhea compared to the control group (RR=0.341, 95%CI 0.158–0.738, NNT= 11.25, p=0.006). The use of intraoperative topical antibiotic drops resulted in an 8.89% absolute risk reduction for developing postoperative otorrhea. There were no statistically significant differences in otorrhea between the other groups (p>0.05). Ventilation tube obstruction occurred in 7.8% of ears. The number of ears that developed obstruction is summarised in Figure 3. Ventilation tube obstruction developed in 11 of 174 (6.3%) ears in the intraoperative arm, 8 of 160 (5.0%) ears in the postoperative arm and 21 of 178 (11.8%) ears in the control arm. Patients receiving postoperative antibiotics were less likely to develop ventilation tube obstruction compared to the control group (RR=0.424, 95%CI 0.193 to 0.930, NNT=14.7, p=0.032). No adverse side effects were reported during the study.

# Discussion:

Ventilation tube otorrhea and obstruction occur in a small proportion of patients, as such the effects of antibiotic prophylaxis may not be seen in study designs that are insufficiently powered. Prior well-designed studies that were at low risk of bias may have potentially discounted the effectiveness of antibiotic prophylaxis through their study designs. (10, 13-16)

Although new formulations of antibiotic prophylaxis such as thermosensitive intratympanic ciprofloxacin polymer (12) have shown efficacy for preventing otorrhea, these formulations are often cost-prohibitive and not widely available. Topical antibiotic drops remain the prophylactic agent of choice for postoperative complications of ventilation small tube insertion in clinical practice, due to its ease of use and low cost. (17)

As with most research, this trial has its limitations. The anticipated sample size was not met by approximately 12% owing to the uncontrollable cessation of the trial due to the COVID-19 pandemic. This slight reduction in statistical power from an anticipated 80% to an actual 71.5%, may lead to increased type II statistical errors. Indeed, some groups seem to benefit from antibiotic prophylaxis, but statistically significant differences were not detected. Larger studies or meta-analysis of well-designed studies are required to clarify the efficacy of postoperative topical drops for preventing postoperative otorrhea and intraoperative topical antibiotic drops for preventing ventilation tube obstruction. The study did not account for variances in parental and child adherence to behavioural modifications such as avoidance of water and waterproofing whilst bathing, as well as antibiotic drop application technique. Although appropriate instructions and directional materials were provided to all participants to explain expected behaviours, future research should assess and control for variances in adherence to behavioural modifications and antibiotic drop administration. Furthermore, parental reporting was relied on for detection of early otorrhea in the first 6 weeks prior to outpatient follow-up where otoscopic examination and tympanometry were performed by a blinded assessor. This may contribute to under-reporting of cases across all groups, potentially limiting identified cases to those that were clinically significant or severe.

In this large 3-arm single-blind randomized controlled trial, we demonstrated statistically significant differences between a single application of topical ciprofloxacin and no antibiotic prophylaxis in reducing ventilation tube otorrhea at 6 weeks postoperatively and found a prolonged application of ciprofloxacin drops to be superior to no prophylaxis in reducing the incidence of ventilation tube obstruction at 6 weeks. The broad inclusion criteria of this study make it generalisable to all pediatric patients undergoing insertion of ventilation tubes in most developed nations with access to modern medical and surgical therapies.

This study supports current evidence supporting the use of a single application of topical antibiotic drops. Our study had a control arm otorrhea rate of 13.5% and obstruction rate of 10.9%. This is in keeping with the ranges quoted in previous systematic reviews of 9% to 54% for otorrhea and 10% to 14% for obstruction (18, 19). Our treatment groups had an otorrhea rate of 4.6% and 8.8%, and an obstruction rate of 6.3% and 5.1% for the intraoperative and postoperative groups respectively. This is also in keeping with the ranges quoted in prior studies of between 1% and 17% for otorrhea and 2% to 7% for obstruction. (18-20)

# Conclusions:

A single intraoperative application of topical ciprofloxacin was effective in reducing the incidence of postoperative otorrhea by 65% when compared to control. A prolonged course of topical ciprofloxacin following intraoperative application was effective in reducing the incidence of ventilation tube obstruction by 54% when compared to control. We recommend a single application of topical ciprofloxacin in patients who are at higher risk of developing otorrhea, while a prolonged application is recommended in patients at higher risk of developing ventilation tube obstruction. Future studies on this topic should seek to clarify whether particular subgroups of patients benefit more from prophylactic topical antibiotics and model for cost-effectiveness.

The authors have no conflict of interests to declare.

A copy of the trial protocol can be found online and is available at: *“Blinded for review”.*

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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