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Original Article

# A Clinical Trial of Proton Pump Inhibitors to Treat Children with Chronic Otitis Media with Effusion

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**OBJECTIVE:** Gastroesophageal reflux (GER) is considered a cause of otitis media with effusion (OME). This study aimed to investigate whether OME can be effectively treated with a proton pump inhibitor (PPI), therefore implicating GER as a causative factor of OME.

**MATERIALS and METHODS:** A PPI or placebo was randomly administered to enrolled subjects for 4–8 weeks. To monitor effusion status, subjects underwent monthly pneumatic otoscopy and acoustic reflectometry. At enrollment and at completion of treatment, subjects underwent an audiogram and tympanogram for assessing changes in hearing due to altered fluid levels in the middle ear. After the treatment period, tympanostomy tube placement was recommended for subjects with unresolved effusion.

**RESULTS:** This study enrolled 16 patients with an average age of 5.17 years. Between the treatment and placebo groups, there was no significant difference in the need for tympanostomy tubes. At completion of this study, patients receiving Lansoprazole demonstrated a significant improvement in pure tone average ($p<0.01$) and speech recognition thresholds ($p=0.04$). Four patients (25%) from the cohort dropped out of the study. Eight patients (50%) from the cohort required tympanostomy tube placement.

**CONCLUSION:** Owing to difficulties with recruitment and small sample size, this study was unable to demonstrate the use of PPI in treating OME. A larger study is needed for further evaluation of this process.

**KEYWORDS:** Otitis media, effusion, proton pump inhibitor

## INTRODUCTION

Otitis media with effusion (OME) is a common childhood disorder, and its true incidence is difficult to ascertain because it is asymptomatic by definition. It is estimated that up to 25% of school-aged children have an effusion at some point [1]. Due to the frequency of episodes of acute otitis media during the early years of life, a young child may spend a significant portion of those years with effusion and associated hearing loss. OME is particularly important because hearing impairment associated with middle ear effusion over prolonged periods of time during the first few years of life may affect the development of speech and language. Children may receive decreased, distorted, or inconsistent auditory signals due to OME, which adversely affects the development of speech. In addition, impaired hearing can lead to the "tuning out" of sounds, later interpreted as inattentiveness and distractibility in the classroom [2]. In children, persistent middle ear effusion (>3 months) is the most common cause of hearing loss, and it is commonly treated with tympanostomy tube placement [3].

The three primary factors associated with the development of OME are upper respiratory tract infections, insufficient ciliary clearance, and poor drainage of the Eustachian tube [4]. The reflux of gastric contents, i.e., gastroesophageal reflux (GER), may contribute to the inflammation that is central to both the development and persistence of OME. GER, like OME, is common in children. GER has been shown to play a causative role in multiple upper respiratory tract complaints, most commonly intermittent vomiting and regurgitation in children. The most common extra-digestive symptoms are related to the respiratory tract, and they include bronchial hyperactivity, chronic cough, laryngitis, hoarseness, recurring pneumonia, otitis, and sinusitis [5]. In 2002, Tasker et al. [6] reported the presence of pepsin/pepsinogen in 90.8% of 65 middle ear effusion (MEE) samples obtained at the time of myringotomy in children. The pepsin–pepsinogen levels in these samples were 1000 times higher than those in the serum. Pepsin was noted to be active in 14.4% of 152 subjects who underwent tympanostomy tube placement [6]. Crapko et al. [7] identified pepsin activity in the mid-

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dle ear fluid of 60% of 20 subjects undergoing tympanostomy tube placement. These two studies suggest that GER plays a role in the development of OME. Esophageal pH monitoring with double probe confirmed that acid may pass the anatomical barrier of the upper esophageal sphincter and come into contact with the laryngeal and hypopharyngeal mucosa [8]. Contencin and Narcy have postulated that reflux material could also reach the nasopharynx. The angle of the pediatric Eustachian tube may allow the reflux of gastric contents into the nasopharynx to enter the middle ear. The putative mechanism of the development of OME in the setting of GER is through contact of the nasopharynx with reflux material [9]. Repeated exposure of the ciliated respiratory epithelium to pH 4 or less prevents ciliary movement and clearance. Hydrochloric acid and pepsin cause local inflammation, edema, and ulceration of the respiratory mucosa, leading to the loss of Eustachian tube ventilatory function.

Current standards of treatment for GER include the use of a proton pump inhibitor (PPI) such as lansoprazole or omeprazole [10]. These medications have been shown to be safe for use in children as young as 2 years of age. Reflux reduction or the use of PPIs may have a role in the treatment of OME [11]. McCoul et al. [12] demonstrated in their 2011 before-and-after intervention study that following treatment with antireflux therapy, children with OME and GERD demonstrated an improved quality of life. Their study employed validated measures of disease burden of OME and GERD and demonstrated improvement with antireflux therapy. They concluded that a reduction in GER may play a role in the prevention of otitis media [12]. Thus, so far, the association between GER and OME has been difficult to establish because most children with GER or OME are asymptomatic. The purpose of the present investigation is to discern whether OME can be effectively treated with PPI, thus implicating the role of GER in the development and persistence of OME.

## MATERIALS and METHODS

This randomized double-blind placebo-controlled study was conducted at a tertiary-care pediatric otolaryngology practice. Institutional review board approval was provided by the Institutional Human Research Protection Office. After parental informed consent was obtained, children aged 2–12 years with a history of chronic OME who had met the indications for tympanostomy tube placement were recruited in the study. OME is defined as the presence of middle ear fluid on physical examination for at least 3 months, in at least one ear, and audiogram or hearing screening suggesting conductive hearing loss. Subjects were recruited from the clinical practice of a tertiary pediatric otolaryngology care center. Patients with a medical history or concurrent conditions known to increase the incidence of otitis media, OME, or GER, including cleft palate, neurologic delay, or Down syndrome, were excluded. In addition, patients with structural abnormalities of the tympanic membrane, including atelectasis, cholesteatoma, or deep retraction pockets, were also excluded. Randomization, which was performed by the research pharmacist who dispensed the study medications, was performed in blocks of six using a coin-flip to ensure equal numbers of patients in each group.

The treatment arm was given the PPI lansoprazole for 4–8 weeks, whereas the placebo arm was given placebo (sugar pill). Two dosages of lansoprazole were administered based on the weight of the patient. Patients weighing less than 30 kg were given 15 mg lansoprazole per day, whereas patients weighing more than 30 kg were given 30 mg per day. An investigational drug application was filed with the FDA, and exemption was subsequently granted. Each month, the patients returned to the clinic for an otologic examination to monitor the presence of fluid in the middle ear. The medication was administered for a minimum of 4 weeks, barring any change to the tympanic membrane necessitating urgent tympanostomy tube placement. The study included three clinic visits: an enrollment visit, followed by a visit after 4 weeks of treatment, and a third visit after 8 weeks of treatment. At any time along the experimental timeline, parents had the option of stopping drug treatment for tympanostomy tube placement. In addition, after 8 weeks of treatment with medication (either placebo or PPI), the parents were given the option to continue medication use for 4 more weeks, with one additional follow-up visit at 12 weeks. At the time of enrollment in the study, the patients underwent audiogram with tympanometry. These were repeated at the conclusion of the 3-month study period, if the effusions remained, to monitor changes in hearing due to altered fluid levels in the middle ear. At each clinic visit, the parents of the patient completed a validated questionnaire regarding the presence of symptoms associated with GER, the Gastroesophageal Reflux Questionnaire (I GERQ-9) [13]. At the conclusion of the treatment period, tympanostomy tube placement was recommended for patients with unresolved effusion.

The primary outcome of this study was to double the resolution rate of 20% in 3 months without intervention to 40% in 3 months with the use of PPI. Using a one-tailed alpha level of 0.05 to determine statistical significance, the minimum number of subjects that we had initially aimed to recruit was 64; in this calculation, a 10% drop-out rate was assumed.

Symptoms of GERD were monitored using the I GERQ-9. The I GERQ-9 is a validated questionnaire developed to improve history taking of infants and toddlers with suspected GER. The questions cover demographics, symptoms, and possible causes that are answered by the caregiver. The GER3-9P is used for older children. It is also a validated questionnaire for children aged 3–7 years that asks caregivers about current symptoms suggestive of GER.

Before the start of the treatment as well as at the end of the 2-month treatment period, tympanograms were performed for each patient. Tympanogram results from enrollment and study completion were compared and analyzed using a *t*-test. Audiograms were performed only for those patients for whom it was deemed clinically necessary.

### Statistical Analysis

Statistical analysis was performed using Statistical Packages for the Social Sciences for Windows, version 21 (IBM Corp.; Armonk, NY, USA) and Microsoft Excel (Redmond, WA, USA). A two-sided binomial test was used to compare the presence and absence of effusions and hearing loss. Hearing loss was defined as a pure tone average (PTA)>25dB. Fisher's exact test or chi-square test was used to examine variables with discrete values associated with the outcome of interest, including demographic, family history, and comorbidity variables. Student's *t*-test was used to examine the association of continuous variables with the outcome.

## RESULTS

A total of 16 patients (10 males, 62.5%) met the inclusion criteria. The study aimed to recruit a minimum of 64 patients to establish significance allowing for a 10% drop-out rate. This unfortunately proved to be very difficult because this study was performed at a tertiary-care center and a majority of the patients encountered had other health problems leading to their exclusion. The study was closed after 2 years due to the inability to recruit subjects.

The mean (SD) age of the patients was 5.17 (1.72) years (Table 1). Fourteen children (88% of the cohort) had middle ear effusion at the time of enrollment. Similarly, 14 patients had at least one type B tympanogram at the time of enrollment. The most common GERD symptoms were halitosis, headache, coughing while lying down, difficulty breathing while sleeping, and itching of the ear [6 (37.5%)] (Table 2). The study participants belonged to households where the primary caregiver had an average educational level of an associate's degree and an average household income of $70,000–$79,999 per year. Additional characteristics are presented in Table 1.

Patients were randomly assigned to receive either Lansoprazole Solutabs or placebo. At the time of enrollment, the placebo group had significantly more exposure to second-hand smoke (p=0.02) and had significantly more pets at home (p=0.04) (Table 1.). Of those who completed the study, the placebo group had a significantly greater history of streptococcal infection (p=0.03) and continued to have a significantly greater exposure to second-hand smoke (p=0.01). Those in the placebo group were significantly more likely to have at least one otalgia per week (p=0.01). There was no significant difference in the need for tympanostomy tubes between the treatment group and the placebo group. At completion of the study, the patients receiving Lansoprazole demonstrated a significant reduction in diarrhea (p=0.03) and halitosis (p=0.03) and an improvement in hearing

**Table 1.** Baseline demographic characteristics of 16 study patients

| Characteristic | Cohort n=16 (%) | Placebo n=7 (%) | Lansoprazole n=9 (%) | p |
|---|---|---|---|---|
| Age, years, mean (sd) | 5.17 (1.7) | 5.53 (1.2) | 4.89 (2.0) | |
| Male | 10 (63) | 6 (85.6) | 4 (44.4) | |
| Premature | 2 (13) | 0 | 2 (22.2) | |
| Breast-fed | 11 (69) | 4 (57.1) | 7 (77.8) | |
| Needed PETs prior to the study | 11 (69) | 5 (71) | 6 (67) | |
| Chronic medical problem | 3 (19) | 1 (14.3) | 2 (22.2) | |
| Allergies | 2 (13) | 1 (14) | 1 (14) | |
| History of tonsillectomy and adenoidectomy | 2 (13) | 1 (14.3) | 1 (11.1) | |
| History of otitis media in the lifetime, years, mean (sd) | 1.81(0.75) | 2.1 (0.69) | 1.56 (0.73) | |
| Attends daycare | 9 (56) | 5 (71.4) | 4 (44.4) | |
| Attends school | 11 (69) | 4 (57.1) | 7 (77.8) | |
| Family history of otitis media | 8 (50) | 2 (28.6) | 6 (66.7) | |
| History of reflux | 2 (13) | 0 | 2 (22.2) | |
| Exposure to second-hand smoke | 6 (38) | 5 (71.4) | 1 (11.1) | 0.02 |
| Has pets at home | 12(75) | 7 (100) | 5 (55.6) | 0.04 |

PETs: Tympanostomy tubes

**Table 2.** Physical examination and symptoms of study participants at the time of enrollment

| Physical Examination Finding/Symptom | Cohort n=16 (%) | Placebo n=7 (%) | Lansoprazole n=9 (%) |
|---|---|---|---|
| Physical Examination Finding | | | |
| Abnormal pneumatic otoscopy right | 1 (6) | 1 (14) | 0 |
| Abnormal pneumatic otoscopy left | 1 (6) | 0 | 1 (13) |
| Abnormal TM mobility right | 14 (88) | 7 (100) | 7 (78) |
| Abnormal TM mobility left | 14 (88) | 6 (86) | 8 (100) |
| Abnormal TM appearance right | 11 (69) | 6 (86) | 5 (63) |
| Abnormal TM appearance left | 10 (63) | 5 (71) | 5 (71) |
| Abnormal TM position right | 4 (25) | 3 (43) | 1 (13) |
| Abnormal TM position left | 9 (56) | 4 (57) | 5 (56) |
| Other abnormal middle ear condition | 3 (19) | 1 (14) | 2 (22) |
| Other abnormal middle ear condition | 3 (19) | 0 | 3 (33) |
| Right middle ear effusion | 14 (88) | 7 (100) | 7 (78) |
| Left middle ear effusion | 15 (94) | 6 (86) | 9 (100) |
| Abnormal right tympanogram | 13 (81) | 7 (100) | 6 (100) |
| Abnormal left tympanogram | 12 (74) | 6 (86) | 6 (100) |
| Symptoms (at least once weekly) | | | |
| Heart burn | 0 | 0 | 0 |
| Chest pain | 0 | 0 | 0 |
| Sour taste in mouth | 2 (13) | 0 | 2 (25) |
| Coughing while supine | 6 (38) | 4 (57) | 2 (25) |
| Increased salivation | 3 (19) | 1 (17) | 2 (25) |
| Difficulty sleeping after eating | 3 (19) | 0 | 3 (38) |
| Difficulty breathing while sleeping | 6 (38) | 2 (29) | 4 (50) |
| Earache | 8 (50) | 5 (71) | 3 (38) |
| Itching of the ear | 6 (38) | 3 (43) | 3 (38) |
| Drainage from ears | 2 (13) | 1 (14) | 1 (13) |
| Difficulty hearing | 8 (50) | 4 (57) | 4 (50) |
| Ringing in the ears | 5 (31) | 4 (57) | 1 (14) |
| Headache | 6 (38) | 4 (57) | 2 (29) |
| Diarrhea | 4 (25) | 0 | 4 (50) |
| Bad breath | 6 (38) | 2 (29) | 4 (50) |
| Syncopal episode | 1 (6) | 0 | 1 (13) |
| Bloating | 3 (19) | 1 (14) | 2 (25) |
| Vomiting | 0 | 0 | 0 |

TM: tympanic membrane

**Table 3.** Audiometric characteristics of study participants at the time of enrollment and at completion of the study

| | Placebo | | Lansoprazole | | |
|---|---|---|---|---|---|
| | Enrollment dB HL | Completion dB HL | Enrollment dB HL | Completion dB HL | p |
| Right pure tone average | 26.2 | 30.8 | 26.4 | 36.7 | |
| Left pure tone average | 23.1 | 12.5 | 26.7 | 8.3 | 0.00 |
| Right speech recognition threshold | 26.7 | 15 | 26.4 | 20 | |
| Left speech recognition threshold | 21.7 | 20 | 27.9 | 7.5 | 0.04 |

dB HL: decibels hearing level

as demonstrated by PTA (p=0.00) and speech recognition threshold (SRT) (p=0.04) (Table 3).

Eight (66%) of the twelve patients who completed the study required tympanostomy tubes. Those who required tubes were significantly more likely to have a family history of otitis media (p=0.01). The educational level of the primary caregiver was significantly lower for patients who required tympanostomy tube placement (p=0.03).

Four (25%) patients dropped out, failing to return for the second visit. All patients who had withdrawn had been assigned to the Lansoprazole group. They were significantly different from those who completed the study in two ways: those who had withdrawn were significantly less likely to have an abnormal position of the tympanic membrane (p=0.03) and were less likely to have tinnitus (p=0.01).

## DISCUSSION

In developed nations, chronic OME is the most common cause of pediatric hearing loss [14]. Gastroesophageal reflux disease (GERS) is a common physiologic occurrence in infants, and it decreases in frequency in the first year of life [15]. Pediatric middle ear disease is most common in the early years of life, and it often coexists with GERD. The size and shape of the immature Eustachian tube may contribute to an increase in reflux of nasopharyngeal contents into the middle ear [12]. Tasker et al. [6] and Lieu et al. [11] reported the presence of pepsin in the middle ear fluid in children with OME. This suggests that gastric refluxate can enter the middle ear and thus contribute to the development of OME.

GER is considered a cause of OME. In pediatric sinusitis, improvement with empiric antireflux therapy has been demonstrated in up to 85% of children studied [16]. This has led to a decrease in the number of surgical procedures required for treating pediatric sinusitis [17]. We hypothesize that there is a similar pathogenesis relating OME with GER. However, current data measuring the concentration of pepsin and pepsinogen in middle ear fluid report conflicting results, and the association between GER and OME remains inconclusive. Recent literature indicates that pepsin present in middle ear effusions is almost certainly due to reflux of gastric contents and that there may in fact be a role of antireflux therapy for treating OME.

The present study intended to demonstrate whether OME can be effectively treated with PPIs, the current accepted treatment for GER, therefore implicating GER as a causative factor of OME. However, owing to difficulty with patient recruitment and small sample size, this could not be accomplished. Patients treated with PPI did show improvements in hearing over the 3-month period. However, there were no significant differences in the need for tympanostomy tubes at the end of the trial period. This is likely attributable to the small sample size. The number of subjects who completed the study was less than 20% of the initial intended number to establish significance. With greater enrollment, the administration of a PPI may lead to significantly improved hearing and reduction in the need for tympanostomy tubes. At the study conclusion, 66% of the participants required tympanostomy tubes. A total of 33% of our subjects achieved resolution of their effusion by the end of the 3-month study period. Rosenfeld et al. [18] reported a 28% spontaneous resolution rate of effusion at the end of 3 months (95% CI: 14%–41%), with respect to effusion of unknown duration, if left untreated. This suggests that the treatment of our participants, whether with placebo or Lansoprazole, made no significant difference in the course of disease as the resolution rate was nearly the same as that for untreated patients.

The small number of subjects may account for the statistically significant differences between the placebo arm and the treatment arm. The placebo group both at the time of enrollment and at the study conclusion was noted to have a significantly greater exposure to second-hand smoke in comparison to the treatment group. Paradise et al. noted in their 1997 study that exposure to second-hand smoke is a risk factor for the development of OME. This may have attributed to the persistence of the effusion beyond the 3-month treatment period of the present study. In addition, Paradise et al. [19] also cited a lower socioeconomic status as well as family history of OM as risk factors for the development of OME. In our study, patients with a family history of OME and those with a primary caregiver who had a lower educational level were significantly more likely to require tympanostomy tube placement at the study conclusion. This is in concordance with current literature on the topic.

As expected, the administration of PPIs led to reduction in gastrointestinal symptoms, including diarrhea and halitosis. Shashidhar et al. [20] demonstrated in their 2000 study that administration of PPIs significantly decreased the incidence of gastrointestinal symptoms, including vomiting, abdominal pain, diarrhea, anorexia, and halitosis. We would expect this result to reflect in our study cohort [20].

It was difficult not only to recruit patients who met the inclusion criteria but also to maintain study involvement. A total of 25% of recruited patients dropped out. All of them were in the placebo group. They were significantly less likely to have an abnormal position of the tympanic membrane as well as tinnitus at the time of enrollment. Although we cannot say definitively, this implies that patients who had withdrawn were less symptomatic in comparison to those who remained in the study. Those who had withdrawn possibly did not have

OME as severely as those who remained in the study. Undoubtedly, this would have an implication for study outcomes as the withdrawal of patients who were less severely affected would result in a higher than expected rate of tympanostomy tube placement at the study conclusion. If repeated, this study should be conducted in a community setting rather than a tertiary-care setting. It was very difficult to recruit patients without any other comorbidity from a tertiary-care setting.

Those who received PPI at the study conclusion had significantly improved PTA and SRT. Although our study was a small-scale study and could not prove significance in the rate of tympanostomy tube placement between the two groups, the improvement in audiological outcomes in those receiving PPIs implies that some reduction of effusion occurred. However, we cannot determine if this is the impact of the PPI or the natural healing process that occurs in OME resolution. This study should be repeated in a community-based otolaryngology practice with larger number of participants. In a large-scale study, effusions may be sufficiently reduced by the administration of PPIs to demonstrate a difference in tympanostomy tube requirement after 3 months.

**Ethics Committee Approval:** Ethics committee approval was received for this study from Washington University IRB was provided by the Institutional Human Research Protection Office in August 2007.

**Informed Consent:** Written informed consent was obtained from parents' of the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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