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Intranasal fluticasone associated with delayed tympanostomy tube placement in children with eustachian tube dysfunction

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ABSTRACT

Objectives: Pediatric patient caregivers may prefer to avoid a surgical intervention and request a medical management option for eustachian tube dysfunction (ETD). However, there are limited published data evaluating the efficacy of intranasal fluticasone in the medical management of ETD as an alternative to tympanostomy tube placement. The objectives of this study were to: 1) determine if intranasal fluticasone (INF) prevented tympanostomy tube placement in children with ETD, and 2) describe differences in patient response to INF related to cleft lip and/or palate (CLP) and Down syndrome.

Methods: Case series with planned chart review at a Tertiary academic hospital. We reviewed pediatric patients treated with INF for ETD. Inclusion criteria included ETD, no prior intranasal or oral steroid therapy, and no prior tympanostomy tube placement. Outcomes included time-to- tympanostomy tube placement with or without INF and therapy compliance. Kaplan-Meier survival analyses with log-rank tests and Fisher's exact tests were used to examine outcome variables.

Results: 676 fulfilled inclusion criteria. 393 (58.7%) were male, and 355 (52.5%) Caucasian with mean age of 27.1 months old. 92 (13.6%) had CLP and 46 (6.8%) had Down Syndrome. 266 (39.4%) received INF, and 202 (88.2%) were compliant at their next visit. 474 (70.1%) had tympanostomy tubes placed. Children treated with INF were less likely to have tympanostomy tubes placed than children not treated (52.6% vs. 81.5%; $p < 0.0001$). Using survival analyses, INF use was associated with significantly longer mean time-to-tympanostomy tube than no INF use (199.4 vs. 133.7 days; $p < 0.0001$). INF did not reduce time-to-tympanostomy tube in patients with CLP ($p = 0.05$) or Down Syndrome ($p = 0.27$).

Conclusion: INF significantly reduces the number of children requiring tympanostomy tube placement for ETD. The CLP and Down Syndrome anatomical variants may attenuate INF efficacy. Further *in vivo* characterization of INF action on eustachian tube tissues will help further substantiate these observations.

1. Introduction

Otitis media (OM) is one of the most common conditions of childhood and accounts for many pediatric office visits [1]. Acute otitis media (AOM) is characterized by rapid onset of inflammation of the middle ear space with a bulging tympanic membrane from purulent fluid [2]. Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear, without signs or symptoms of acute infection [2]. OME often develops during an upper respiratory infection (URI), because of poor eustachian tube function, or because of inflammation after an episode of AOM [3]. Intranasal inflammation in allergic rhinitis may also contribute to OME [4]. Both recurrent AOM and OME can result from underlying Eustachian tube dysfunction (ETD) preventing normal aeration of the middle ear space and creating a pressure inequality with the external auditory canal and middle ear.

ETD can arise from multiple etiologies. It can occur secondary to mucosal inflammation from infections or allergies. Inflamed or infected adjacent adenoid tissue can both contribute to inflammation of the Eustachian tube and may functionally impair the Eustachian tube which can in turn result in an otitis media. Younger children are at greater risk of ETD because their Eustachian tubes are shorter, less rigid and have a more horizontal position than adults and therefore may have less effective Eustachian tube

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function at baseline [5,6]. Persistent ETD may also lead to other conditions than OM such as tympanic membrane atelectasis, retraction pockets and cholesteatoma formation [7].

Recommended prevention measures for ETD and OM in children include exclusive breastfeeding for at least 6 months, vaccination with the pneumococcal conjugate vaccine and annual influenza vaccine as well as avoidance of tobacco smoke exposure [8]. Male sex, passive smoking exposure and daycare attendance are known risk factors [9]. AOM is treated with antibiotics as needed in certain cases. There are currently no specifically approved medical treatments recommended for recurrent AOM, OME or ETD [2]. Generally accepted management include only watchful waiting or surgical intervention with tympanostomy tube placement.

Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States [10]. The American Academy of Otolaryngology-Head and Neck Surgery Otitis Media with Effusion Guidelines outline that bilateral OME for 3 months or longer with documented hearing difficulties or recurrent AOM with current middle ear effusion are indications for tympanostomy tube placement [2,10]. Tympanostomy tubes can also be considered for children with OME for 3 months or longer and attributable symptoms such as vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life. The guidelines also recommend providers not use steroids, antibiotics, and anti-histamines for the purposes of treating OME. As of the writing of this manuscript, no formal guidelines have been published to address the medical or surgical management of ETD specifically. Moreover, the current tympanostomy tube guidelines addresses different types of OM but do not specifically discuss ETD in general [10].

In some instances, pediatric patient caregivers may prefer to avoid a surgical intervention and request a medical management option for ETD. Although small, the risks of tympanostomy tube placement are enough to create an undesirable risk-benefit ratio for some caregivers. These include tube retention, tympanic membrane perforation, chronic otorrhea and tympanosclerosis, There is also concern about the potential negative neurocognitive effects of general anesthesia exposure in young children [11,12]. Additionally, in some cases the indications for tympanostomy tube placement have not yet been completely met, but the child appears to be on a trajectory to meet them. In these situations, a medical treatment option would be ideal. There is evidence to suggest that patients with adenoidal hypertrophy may also have an increased likelihood of improvement in OME or AOM with intranasal steroids through published randomized control trials [13–15]. As of the writing of this manuscript, there are no published data evaluating the efficacy of intranasal fluticasone (INF) in the medical management of ETD as an alternative to tympanostomy tube placement. The objective of this case series was to determine if INF was associated with decreased need for tympanostomy tube placement in children with ETD. We also sought to describe differences in patient response to INF related to cleft lip and/or palate (CLP) and Down Syndrome diagnoses.

2. Methods

This study protocol was reviewed and approved by the Duke University Medical Center Institutional Review Board (IRB; protocol Pro00059173).

2.1. Study design

The study was designed as a retrospective case series with chart review of pediatric patients that were treated with INF for ETD. The study population consisted of 676 patients who were treated with INF from 1997 to 2011. INF was investigated at our institution primarily because it is covered by all insurance including Medicaid and therefore consistently used as the first-line intranasal steroid. The standard initial dose recommend to patients was one spray per nostril of 50-mcg dose-metered fluticasone, for a total of 100-mcg daily. Eligible patients were identified by querying our medical record for pediatric patients who presented with ETD using ICD-9 codes (381.81 & 381.9). This also captured patients with OME and recurrent AOM. Specific inclusion criteria included age less than eighteen years old, presence of ETD (defined below), no prior intranasal or oral steroid therapy, no prior tympanostomy tube placement or otologic surgery, and no prior tonsillectomy or adenoidectomy. All charts were reviewed and patients not satisfying these criteria were excluded, as well as patients treated with an intranasal steroid other than fluticasone. Extending the adult definition of ETD to a pediatric setting, ETD was defined as clinical evidence and symptoms consistent with pressure dysregulation of the middle ear [16]. In the case of evaluating our pediatric patients, the diagnosis of ETD was rendered by clinical history of middle ear fluid, hearing loss or recurrent acute otitis media with the assistance of the patients' guardian, with or without otoscopic insufflation by an otolaryngology physician or physician assistant and/or tympanometry by a dedicated pediatric audiologist (normative range of values for tympanometry pressures −150 to +25 daPa). Findings for ETD had to be present in at least one ear. On otoscopy, ETD was diagnosed if the tympanic membrane appeared retracted with or without a middle ear effusion, and/or if mobility was impaired with application of otoscopic insufflation. ETD was diagnosed on tympanometry if a 'Type B or C' tympanograms were observed. There are no universally accepted measures to determine Eustachian tube function efficacy [16]. With respect to decisions made for tympanostomy tube placement, our providers' intent and general approach was to follow the published guidelines for tympanostomy tube placement [10]. For the patients in this study, the decision for tympanostomy tube placement was individualized in a shared decision with the patient's caregiver and generally occurred after complications related to ETD developed such as chronic OME with or without conductive hearing loss, or recurrent AOM. In general, the minimal time interval between INF initiation and the next clinic visit was set at 3 months (90 days) by routine.

Demographic variables collected included gender, date of birth, age at clinic visits, diagnosis, presence of Down Syndrome, CLP, or other major co-morbid diagnoses. To assess socioeconomic factors for each patient, each patient's zip code was cross-referenced against their zip codes' corresponding percent of population below poverty line, percent of population unemployed, and zip codes' socioeconomic status indices.

2.2. Outcomes

Outcomes include time-to- tympanostomy tube placement from the first encounter with an otolaryngology provider with or without INF, time-to-last visit, and therapy compliance. Tympanostomy tubes were typically offered if there was a lack of clinical improvement. Clinical improvement was noted by normalization of tympanic membrane position on otoscopy, normalization of tympanic membrane mobility on tympanometry or resolution of recurrent OM (i.e. no episodes within the time interval of observation). Patients were grouped into the "INF" group for subsequent analyses if they received INF at the initial clinical visit. Patients who did not receive INF at the initial clinical visit, were included in the "no INF" group. Therapy compliance was assessed by asking the caregivers if the patient had been receiving INF as prescribed at the