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A RANDOMISED CONTROL TRIAL OF TREATMENT OF ACUTE DIFFUSE OTITIS EXTERNA WITH LOCAL ANTIBIOTIC EAR DROPS WITH AND WITHOUT ORAL ANTIBIOTICS

Dissertation submitted to

NATIONAL BOARD OF EXAMINATION IN

In partial fulfillment of the requirements

For the award of the degree of

DIPLOMATE OF NATIONAL BOARD OF EXAMINATIONS IN

OTORHINOLARYNGOLOGY

BY

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Under The Guidance of

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DISSERTATION SUBMITTED TO THE NATIONAL BOARD OF EXAMINATION IN PARTIAL FULFILMENT OF RULES AND REGULATIONS FOR THE AWARD OF

DIPLOMATE OF NATIONAL BOARD OF EXAMINATIONS IN OTORHINOLARYNGOLOGY

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DECLARATION

I hereby declare that the dissertation:

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CERTIFICATE

We hereby certify that this dissertation entitled:

A Randomized control trial of treatment of acute diffuse otitis externa with local antibiotic ear drops with and without oral antibiotics

is a bonafide work of Dr. FARHA A V during the period of 2015- 2017 in Manipal Hospital, Bangalore, under my guidance and supervision. This dissertation is done in partial fulfillment of the requirement of award of DNB in

Otorhinolaryngology

I have great pleasure in forwarding it to the National Board of Examination.

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Place: Dr Farha A V

Date:

LIST OF ABBREVIATIONS USED

AOE-acute otitis externa

PNH-polymyxin –B, neomycin, hydrocortisone ear drops

TM-tympanic membrane

EAC-External Auditory canal

IG wick-icthamol glycerin wick

NRS-Numerical Rating scale

VRS-Verbal Rating scale

GRS- Graphical Rating scale

VAS- visual analogue scale

EUM- Examination under Microscope

COE- chronic otitis externa

AMX- Amoxicillin

RCT-Randomized Control Trial

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INTRODUCTION

Otitis externa is a common external ear condition seen in both general practice and otolaryngology practice. Acute otitis externa (AOE) as discussed in this study is diffuse otitis externa, which may involve the external auditory canal, pinna and rarely the tympanic membrane. A diagnosis of diffuse AOE requires rapid onset (generally within 48 hours) in the past 3 weeks of symptoms and signs of ear canal inflammation. It is usually associated with tragal tenderness, otalgia and ear discharge.

The most common pathogens are *Pseudomonas aeruginosa* (20%-60% prevalence) and *Staphylococcus aureus* (10%-70% prevalence), often occurring as a polymicrobial infection. Other pathogens are principally gram-negative organisms (other than *P aeruginosa*), any one of which causes no more than 2% to 3% of cases in large clinical series.[1-8].Cerumen creates a slightly acidic pH that inhibits infection (especially by *P aeruginosa*) but can be altered by water exposure, aggressive cleaning, soapy deposits, or alkaline eardrops.[9,10] .Debris from dermatologic conditions may also encourage infections[5,12] as can local trauma from attempts at self-cleaning, irrigation, and wearing hearing aids.[13,14]

Failure to distinguish AOE from other causes of "the draining ear" (e.g., chronic external otitis, malignant otitis externa, middle ear disease, cholesteatoma) may prolong morbidity or cause serious complications [15, 16]**.** AOE is more common in regions with warmer climates, increased humidity, or increased water exposure from swimming[17, 18].

Otitis externa being a localized disease of external auditory canal, local treatment is adequate for the recovery from the condition. [1]. Topical antimicrobials are beneficial for AOE, but oral antibiotics have limited utility.[20] Nonetheless, about 20% to 40% of patients with AOE receive oral antibiotics, often in addition to topical therapy[21 22, 23]. Being a relatively common condition and the diversity of the intervention make it is necessary to follow evidence based treatment in OAE.

In this era of rising antibiotic resistance we should limit the use of systemic antibiotics where they are really not indicated or when local therapy is adequate for disease control.OAE is such a condition where many studies have been done to prove the efficacy of

the local antibiotics for the complete recovery .[24,25,26]. Nonetheless, about 20% to 40% of patients with AOE receive oral antibiotics, with or without concurrent topical therapy.[22,23] The oral antibiotics selected are usually inactive against P.aeruginosa and S aureus, may have undesirable side effects, and, because they are widely distributed throughout the body, serve to select out resistant organisms.[15]

It is a regular practice in our country to treat otitis externa with oral and local antibiotic. We have to take an effort to join our hands in reducing the systemic antibiotic usage, in view of preventing resistance, especially in pseudomonas sp. Therefore to follow a proper guidelines and evidences pertaining to the treatment of otitis externa is required in view of quality care with lesser exposure to antibiotics.

Prevention of AOE include removing obstructing cerumen; using acidifying ear drops, drying the ear canal with a hair dryer; using ear plugs while swimming; and avoiding trauma to the external auditory canal. Strategies to prevent AOE are aimed at limiting water accumulation and moisture retention in the external auditory canal and maintaining a healthy skin barrier. No randomized trials have compared the efficacy of different strategies to prevent AOE. Available reports include case series and expert opinion, which emphasize preventing moisture and water retention in the external auditory canal [19].

This study aims to provide a data for evidence based treatment of otitis externa in Indian population. Even though many studies have been conducted internationally and guidelines have been put forward, there is no study conducted in India comparing the efficacy of antibiotic ear drops to systemic and local antibiotics. In this study we wish to compare the efficacy of local antibiotics compared to local and systemic antibiotic for AOE, whether addition of systemic antibiotics hasten the recovery. As the international guidelines for treatment of otitis externa states that only local anti pseudomonal ear drops is indicated for its treatment, this study intends to compare the response in Indian population.[19] We also intend to compare the number of days taken for clinical recovery of the disease.

External ear

Development

External Auditory Meatus: The external auditory meatus develops from the dorsal portion of the first pharyngeal cleft. At the beginning of the third month, epithelial cells at the bottom of the meatus proliferate, forming a solid epithelial plate, the meatal plug. In the seventh month, this plug dissolves, and the epithelial lining of the floor of the meatus participates in formation of the definitive eardrum.

Auricle: The auricle develops from six mesenchymal proliferations at the dorsal ends of the first and second pharyngeal arches, surrounding the first pharyngeal cleft. These swellings, (auricular hillocks), three on each side of the external meatus, later fuse and form the definitive auricle. As fusion of the auricular hillocks is complicated, developmental abnormalities of the auricle are common. Initially, the external ears are in the lower neck region, but with development of the mandible, they ascend to the side of the head at the level of the eyes. [27]

Anatomy

The external auditory canal is a culde sac with tm at its blind end. The EAC is about 2.5 cm in length and comprises a lateral cartilaginous (membranous) portion and a medial bony portion.. The membranous portion accounts for the lateral third of the EAC, whereas the bony portion forms the medial two thirds. The skin that lines the membranous canal is thicker and more mobile, and it is endowed with sebaceous and apocrine (ceruminous) glands and hair follicles. Both sebaceous and apocrine ducts empty into a follicular canal that surrounds each hair follicle.[28,29]

The bony portion of the canal is lined by thin, immobile skin that lacks hair and glands and is continuous with the epithelium of the tympanic membrane. The bony-cartilaginous junction is the narrowest point, or isthmus, of the EAC; here a fibrous interface serves as a potential pathway for spread of malignant disease beyond the ear. The incomplete ossification of the anterior bony canal produces an opening into the infra temporal region, known as the foramen of Huschke, which may also serve as a means for extension of malignant tumors from the EAC to the deep lobe of the parotid gland. Naturally occurring defects in the cartilaginous portion of the EAC, known as the fissures of Santorini, also provide avenues of spread to the superficial lobe of the gland.

The anterior wall of the external meatus forms part of the temporomandibular joint. The superior wall is a part of the base of the skull. It separates the external acoustic meatus from the middle fossa of the skull. The inferior wall is contiguous with the parotid gland. The posterior wall of the external acoustic meatus is also the anterior wall of the mastoid process.

Epithelium of EAC

Skin of EAC is requires special mention. Unlike the rest of the body skin which normally grows directly from the basal layers towards the surface,. In EAC, there is outward, oblique growth of the epidermis of EAC and pars flaccida so that the surface layers effectively migrates towards the external opening of the canal. The normal rate of migration is about 0.1 mm/day,[30,31]although this range is hugely variable and in some conditions there is complete failure of migration with a consequent build-up of shed keratin in the ear canal.

Cerumen

The lining of the external ear canal is composed of keratinizing stratified squamous epithelium. The squamous epithelium of the lateral cartilaginous external ear canal also contains sebaceous and ceruminous glands. Cerumen (wax) is a mixture of secretions from the sebaceous and ceruminous glands along with desquamated keratin debris. Cerumen serves to protect the ear canal from moisture and maceration due to its high lipid content. In addition, the acidic pH of cerumen helps to inhibit microbial growth. Cerumen exerts a protective effect by maintaining an acidic milieu (pH of 5.2 - 7.0) in the external auditory canal whilst also lubricating the canal. It has also been shown to have significant antibacterial and antifungal properties.[32]

Water contamination and localized trauma may allow pathogenic bacteria to bypass these natural host defenses. Trauma to the external ear canal may be affected by means of instrumentation (such as with cotton-tipped applicators) or digital manipulation.[5,8]

Blood supply

The arterial supply of the external meatus is derived from branches of the external carotid. The auricular branches of the superficial temporal artery supply the roof and anterior portion of the canal. The deep auricular branch of the first part of the maxillary artery arises in the parotid gland behind the temporomandibular joint, pierces the cartilage or bone of the external meatus and supplies the anterior meatal wall skin and the epithelium of the outer

surface of the tympanic membrane. Finally, auricular branches of the posterior auricular artery pierce the cartilage of the auricle and supply the posterior portions of the canal. The veins drain into the external jugular vein, the maxillary veins and the pterygoid plexus. The lymphatic drainage follows that of the auricle [33]

The lymphatics of the auricle and external meatus drain interiorly into the pre-auricular (parotid) glands, inferiorly into the superficial cervical nodes along the external jugular vein, and posteriorly into the retroauricular (mastoid) glands.

Nerve supply

The auricle and external meatus are supplied by branches of Vth (auriculotemporal nerve), VIIth (temporal branches) and Xth (auricular branches) cranial nerves. The medial or posterior surface of the auricle is supplied by fibres of the great auricular nerve (C2 and C3) and the lesser occipital nerve (C2).

Otalgia

Otalgia can originate from pathologies inside the ear (primary otalgia) or can be a referred pain originating from outside the ear (referred otalgia) [34]. Since the ear sensory nerve supply originates from different nerves, pathologies of different head and neck structures can manifest themselves as otalgia, causing patients to seek medical help.

Otitis externa and otitis media usually presents with primary otalgia with or without associated ear discharge. Otalgia can be mild to severe, as in malignant otitis externa. The main symptom of otitis externa is ear pain or otalgia. It can vary from mild dull pain to severe excruciating pain. The skin of external ear is tightly attached to the underlying bone and cartilage. Edema occurring due to inflammation distracts the periosteal lining of bony canal cause extreme amount of pain.[35]

As the patient may well be unaware of any conditions outside his/her ear or of the fact that the cause may be outside the ear, otalgia is the chief complaint of the patient .Complaints of otalgia in the absence of swelling of the ear canal and without apparent middle ear disease should arouse suspicion of pathology outside the ear.

Perhaps the most common cause of referred otalgia is that of temporomandibular joint (TMJ) syndrome. These patients commonly complain of pain not only in the ear but also

radiating to the periauricular area, temple, or neck. There may be a history of gum chewing, bruxism, or recent dental procedure with subsequent malocclusion. On examination, they are tender over the affected TMJ and may have associated crepitus. On occasion; the only symptom of patients with upper aerodigestive tract cancer is that of otalgia. Older patients with a long history of tobacco and ethanol use, and more recently younger patients with human papilloma virus infection, suggest this possibility.[19]

A complete head and neck examination with visualization of the mucosal surfaces of the head and neck, assessment of any neck masses, and palpation of the tongue base is recommended. Other potential etiologies are dental pathologies (caries, impacted molars), tonsillitis, peritonsillar abscesses, retropharyngeal abscesses, carotidynia, styloid process elongation, angina, intrathoracic aneurysms, glossopharyngeal neuralgia, and geniculate neuralgia [19]

Normal flora of EAC

External auditory canal like our skin has a variety of normal flora in it. Both EAC and the cerumen has polymicrobial flora, but they vary in their composition of bacteriae. Coryneforms represented 22% of the bacteria in cerumen and 19% in the canal. Turicellaotitidis is the primary coryneform isolated from both the canal and the cerumen. Streptococci-like bacteria are 10% from the cerumen, 7% from the canal. In both cerumen and canal, Alloiococcusotitis is more than 95% of the streptococci-like bacteria. Fifteen gram-negative organisms are isolated from the canal and cerumen, including four Pseudomonas aeruginosa strains. Many of Staphylococcus epidermidis isolated also have a high-level resistance.[36]

Acute otitis externa

Otitis externa is a generalized condition of the skin of the external auditory canal that is characterized by general edema and erythema. It can present as diffuse or localized form of inflammation of external ear canal. It is the very common condition which is encountered in day to day outpatient services. Any condition or situation that disturbs the lipid/acid balance of the ear will predispose an individual to Otitis externa [37]

The otitis externa, an acute inflammatory condition of the skin of the external auditory canal is generally secondary to bacterial infection. This condition is often seen in primary care, with a reported prevalence of 1% within a 12 month period. Common symptoms associated with

AOE include otalgia, otorrhoea, pruritus, and hearing loss. In uncomplicated disease, clinical examination often shows oedema of the external auditory canal, with or without erythema and discharge, and a normal and intact tympanic membrane. A key clinical sign is tenderness over the tragus, with palpation producing sudden, intense, and severe pain, often out of proportion to otoscopic findings. In its severest form, acute otitis externa causes severe external auditory canal stenosis, perichondritis, and cellulitis of the pinna and surrounding skin.

As part of a comprehensive clinical assessment, risk factors should be identified. These include trauma to the canal (ear buds or scratching), water or moisture within the external auditory canal, foreign bodies (including hearing aids), eczema of the ear canal, and a compromised immune system (including patients with diabetes). Common causative organisms include *Pseudomonas aeruginosa* (20-60%) and *Staphylococcus aureus* (10-70%). Otomycosis is a rare but important cause of otitis externa and should be suspected in recurrent otitis externa after repeated or prolonged topical antimicrobial treatment.[38]

Epidemiology

Otitis externa is estimated to have a prevalence of 0.4 percent per year, affecting approximately 10 percent of the population during their lifetime.[29] AOE is more common in regions with warmer climates, increased humidity, or increased water exposure from swimming.[17,43]

Etiology

The etiology of AOE is multifactorial. Regular cleaning of the ear canal removes cerumen, which is an important barrier to moisture and infection.[41] Cerumen creates a slightly acidic pH that inhibits infection (especially by *P aeruginosa*) but can be altered by water exposure, aggressive cleaning, soapy deposits, or alkaline eardrops.[10,42] Debris from dermatologic conditions may also encourage infections,[7,12] as can local trauma from attempts at self-cleaning, irrigation,[43] and wearing hearing aids.[13,44] Other factors such as sweating, allergy, and stress have also been implicated in the pathogenesis of AOE.[17] AOE is more common in regions with warmer climates, increased humidity, or increased water exposure from swimming. [18,45] Most, but not all, studies have found an association with water quality (in terms of bacterial load) and the risk of AOE. The causative organisms are present in most swimming pools and hot tubs; however, even those that comply with water

quality standards may still contain AOE pathogens.[46,47,48] In addition, these organisms are present in the healthy external auditory canal, and thus the external auditory canal may be a source of AOE.[36]Some individuals appear more susceptible to AOE on a genetic basis (those with type A blood group).[49]

Pathophysiology

The clinical course of otitis externa has been divided into the following stages [29]

1. Pre-inflammatory;

2. Acute inflammatory (mild, moderate or severe);

3. Chronic inflammatory.

In the pre-inflammatory stage 1, the protective lipid/acid balance (normal pH 4-5) of the ear is lost and the stratum corneum becomes edematous, blocking off the sebaceous and apocrine glands producing aural fullness and itching. With further oedema and scratching, there is disruption of the epithelial layer and invasion of resident or introduced organisms. This results in the acute inflammatory stage 2, with a progressively thickening exudates, further oedema, obliteration of the lumen (mild, little or no obliteration; moderate, subtotal obliteration; severe, complete obliteration) and increasing pain. In the severe stages, auricular changes and cervical lymphadenopathy are often seen. Stage 3 otitis externa is characterized by thickening of the external canal skin and fibrous canal stenosis [54]

The *preinflammatory* stage consists of edema of the skin of the EAC. The *acute inflammatory* stage can be classified as mild, moderate, or severe. Mild acute inflammation is characterized by an erythema and edematous EAC with clear, odorless secretions. The inflammation becomes moderate with increasing oedema and pain and mucopurulent secretions. [52]most of the patient presenting with AOE is usually in this stage. Therefore they require only anti inflammatory treatment and prevention of the infection.

Most common organism causing OAE

Bacterial infections account for over 90% of cases of AOE, and fungal infections account for the rest [39]. *Pseudomonas aeruginosa*, *Staphylococcus epidermidis, and S. aureus* represent the first, second, and third most common bacterial isolates from AOE,

respectively.[40] *Aspergillus* and *Candida* are the most commonly recovered fungal isolates, but they represent less than 2% of AOE cases.[40]. A susceptibility profile of S. aureus isolates has a lower frequency of high-level resistance. P.aeruginosa with high-level resistance to quinolones is very rare (0.1%).Likewise; resistance of P. aeruginosa to aminoglycosides is also rare.[38]

Pseudomonas – a gram negative bacilli:

Pseudomonas is a gram-negative rod that belongs to the family Pseudomonadaceae. More than half of all clinical isolates produce the blue-green pigment pyocyanin. *Pseudomonas* often has a characteristic sweet odor. These pathogens are widespread in nature, inhabiting soil, water, plants, and animals (including humans). *Pseudomonas aeruginosa* is a part of normal skin flora. It is also an important cause of infection, especially in patients with compromised host defense mechanisms. Bacterial infections of the external ear canal are most often caused by P. Aeruginosa aeruginosa. Its growth is inhibited in acidic of the medium.

The subspecies of *Pseudomonas* causing AOE may be different from those causing other *Pseudomonas* infections.[50,51] Pseudomonas aeruginosa in otitis externa displayed fewer of the usual biochemical features of the species than did the strains isolated from other infections. Some of these features, such as the production of pyocyanin, are influenced by nutritional factors; strains found in otitis externa probably represent the type of strains present in the natural habitat in water, as opposed to the strains that have adapted to the environment of other human infections. Increased knowledge of the characteristics of the strains found in otitis externa is important in understanding the pathogenesis of the disease and why P aeruginosa is the dominant infectious agent in otitis externa.[51]

The minimal nutritional requirements of *P. aeruginosa*, its tolerance of a wide variety of physical conditions, and its relative resistance to antimicrobial agents contribute to its ecologic success and to its role as an effective opportunistic pathogen. It rarely causes disease in healthy persons, although it is a common human saprophyte. In most cases the disease process begins with some alteration of normal host defenses, as in injury to the canal skin causing AOE. In addition to factors involved in the virulence of *P. aeruginosa*, its resistance to antimicrobials contributes to its role as an effective opportunistic pathogen. Resistance to antipseudomonal β-lactams has been well described, and resistance to recent-

generation cephalosporins, monobactams, and carbapenems is becoming a disturbing clinical problem.

P. aeruginosa shows a particular propensity for the development of resistance, and this situation is associated with increased rates of mortality and morbidity and higher costs. Ciprofloxacin, the most potent agent available in oral form for treatment of *P. aeruginosa* infections, is in particular jeopardy: in Europe, the United States, and Latin America, rates of susceptibility to the drug are between 60% and 75%. The eventual loss of this agent may mean that the treatment of all *Pseudomonas* infections will require injectable therapy and possibly hospitalization, a clear example of the increased costs associated with resistance [55]

Independent of the controversy that concerns the need for monotherapy versus combination therapy for *P. aeruginosa* infections, antimicrobial resistance of *P. aeruginosa* has reached a level in most regions of the world such that empirical therapy against this organism may require the initial use of 2 or more agents, until susceptibility testing results are known. Resistance levels will continue to increase unless measures are taken to curtail this rise. Combinations will suffice only for empirical therapy; they have not been shown to definitively reduce the development of resistance against modern β-lactams, and there is a risk that this approach could encourage resistance to both agents.[64] No new classes of antimicrobials active against *P. aeruginosa* will be available for therapy within the next 5–7 years. Most new quinolones in development are likely to show some degree of cross-resistance to ciprofloxacin [56].

Bacterial resistance is likely of far less concern with topical antimicrobials because the high local concentration of drug in the ear canal will generally eradicate all susceptible organisms plus those resistant to systemically administered antibiotics (which only achieve concentrations at the site of infection several magnitudes lower than when topically administered).[3]

Symptoms

Symptoms of AOE include otalgia (70%), itching (60%), or fullness (22%), with or without hearing loss (32%) or ear canal pain on chewing. A hallmark sign of diffuse AOE is tenderness of the tragus (when pushed), the pinna (when pulled), or both. The tenderness is often intense and disproportionate to what might be expected based on appearance of the ear canal on inspection.

Otoscopy will reveal diffuse ear canal edema, erythema, or both, with or without otorrhea or material in the ear canal. Regional lymphadenitis or cellulitis of the pinna and adjacent skin may be present in some patients [5,57]

Diagnosis

Diagnosis of AOE can typically be achieved through a careful history and physical examination. Predisposing factors, such as water contamination and instrumentation or manipulation of the ear canal should be sought. Patients with AOE will typically complain of acute onset (<48 h) of unilateral ear pain, itching, and a sense of aural fullness. The pain of AOE is exacerbated by manipulation of the tragus, pinna, or ear canal, and by opening and closing of the jaw. A history of diabetes or other immunocompromised states should be sought, as children with these conditions are predisposed to malignant external otitis. A history of tympanic membrane perforation or tympanostomy tube placement should also be sought, as this will impact the choice of therapy.

Physical examination will reveal erythema and edema of the canal, which may progress to complete occlusion of the canal and a resulting conductive hearing loss. In more severe cases, the infection may spread to the surrounding skin and regional lymphatics and present with cellulitis and regional lymphadenitis. Otoscopic evaluation will reveal moist ceruminous and exudative debris in the canal. Frequently, the discharge is associated with a pungent odor characteristic of *Pseudomonas* infection. Purulent discharge may be seen with acute otitis media with perforation or chronic otitis media. Therefore, inspection of the tympanic membrane is desirable, but may be precluded by patient discomfort or the degree of canal edema. Routine culture of the discharge from the ear is typically unnecessary and is not recommended.[54]

Treatment

Strategies to prevent AOE are directed toward preventing excess water contamination and avoiding trauma to the external canal. The use of alcohol drops or a hair dryer on a cool setting after water exposure are advocated by some experts as a means of drying the external ear canal. Otic drops containing acetic acid may be used either before or after water exposure to maintain the acidic pH of the ear canal. Direct comparisons of the efficacy of different preventative measures have not been performed. Recent clinical practice guidelines for the treatment of AOE emphasize the need for adequate assessment of pain and appropriate analgesic therapy [19] . It is not uncommon for the pain of AOE to be so severe as to require

narcotic analgesic therapy. In uncomplicated cases of AOE, treatment with ototopical drops for a 7–10-day course should be administered. Systemic therapy should be reserved for patients with diabetes, other immunosuppression, or extension of infection beyond the external ear canal [19] .

For ototopical therapy to be effective, aural toilet may be required to remove obstructing debris and allow access of the drops to the infected tissue. Wick placement should be performed if the canal edema is severe enough to prevent entry of the drops. Adequate delivery is enhanced by having someone other than the patient apply the drops . Specific instructions should be provided to caregivers regarding application of drops, including having the patient lie with the affected ear up during and for a period of 3 min following application, and for manipulation of the tragus to "pump" the drops into the more medial ear canal. Available ototopical medications for treatment of AOE share similar efficacy; therefore, choice of agent may be determined by clinician experience and patient preference. Table 1 provides a list of commonly used topical antimicrobial preparations in the treatment of otitis externa. Topical therapy in the setting of known or suspected tympanic membrane perforation or tympanostomy tube presence warrants additional consideration. Due to concerns over potential ototoxicity, topical therapy in this setting should be limited to drops without ototoxic potential. Currently, this limits therapy in the setting of a nonintact tympanic membrane to a topical fluoroquinolone. Clinical response to therapy is expected within 2–3 days. Failure of improvement over this time course should prompt medical reevaluation. Attention should be paid to factors which may be preventing adequate delivery of the medication, and to confirm the initial diagnostic impression. Contact sensitivity of the external ear canal should also be considered, a problem most commonly seen in ototopical preparations containing neomycin. During therapy, care should be taken to avoid water exposure, manipulation of the ear canal, or its occlusion (e.g., with headphones or hearing aids.[19,21]

Differential diagnosis

Although the physical examination for AOE is often revealing, several other processes may mimic AOE. Furunculosis of the EAC may present with pain, erythema of the canal, and possibly purulent otorrhea. The inflammation in furunculosis is commonly localized to one portion of the lateral canal, while that of AOE is circumferential. [19]

Otitis media with or without perforation of the TM may also mimic AOE, because the EAC may become inflamed, and purulent discharge from the middle ear may be

present. It is important to visualize as much of the TM as possible to evaluate for this possibility.[19]

Mastoiditis may also create a clinical picture similar to that of AOE. Precise localization of the tenderness to manipulation of the pinna versus the mastoid tip differentiates the two. Additionally, loss of the postauricular fold is more consistent with mastoiditis.[11]

Contact dermatitis of the ear canal may manifest with erythema and itching in or around the EAC. In patients who have had recurrent or prolonged treatment with topical medications, sensitization may occur that can result in a secondary contact otitis. Treatment involves the removal of the offending agent and application of topical steroids.[19]

Viral acute otitis externa is rare. Offending organisms include varicella, measles, or herpes virus. Ramsay Hunt syndrome (herpes zoster oticus) involves facial palsy associated with vesicles on the skin of the pinna or mouth.[19]

Prevention:

Prevention of AOE include removing obstructing cerumen; using acidifying ear drops shortly before swimming, after swimming, at bedtime, or all three; drying the ear canal with a hair dryer; using ear plugs while swimming; and avoiding trauma to the external auditory canal.[29,66,67,68]. Strategies to prevent AOE are aimed at limiting water accumulation and moisture retention in the external auditory canal and maintaining a healthy skin barrier. No randomized trials have compared the efficacy of different strategies to prevent AOE. Available reports include case series and expert opinion, which emphasize preventing moisture and water retention in the external auditory canal [19]

Complications

Otitis externa recovers fast and the complications are not so common. Few complications are cellulitis, perichondritis, and chondritis. In adults, the presence of these complications should prompt the administration of a systemic quinolone antibiotic. In children, in the case of a cellulitis, an oral antistaphylococcal drug may be initiated; however, if *Pseudomonas* is detected on ear culture, parenteral administration of antipseudomonal antibiotics is required.

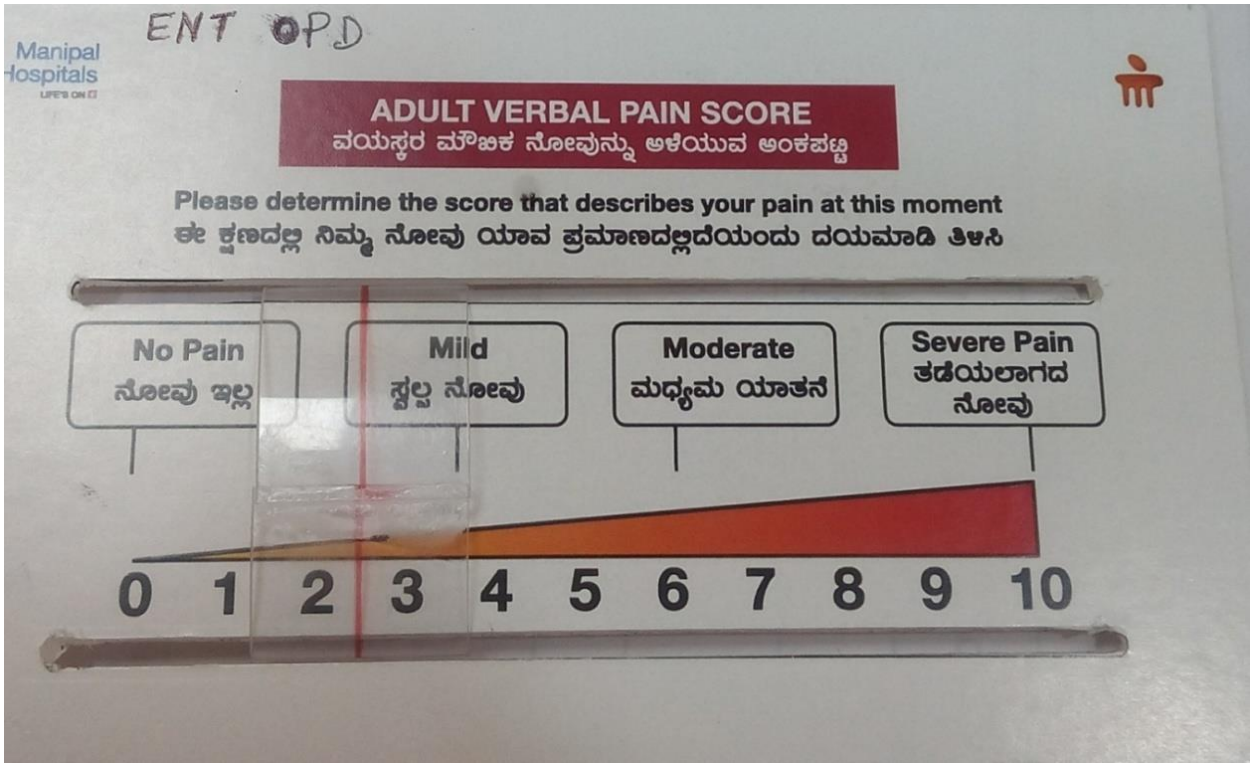
Complications of otitis externa usually are seen more common in diabetics and other immunocompromised conditions.in diabeties patients it can progress to malignant otitis externa or benign necrotizing otitis externa.

Numerical rating scale

In a Numerical Rating Scale (NRS), patients are asked to circle the number between 0 and 10, which fits best to their pain intensity. Zero usually represents 'no pain at all' whereas the upper limit represents 'the worst pain ever possible'. In contrast to the VAS/GRS, only the numbers themselves are valuable answers, meaning that there are only 11 possible answers in a 0–10, 21 in a 0–20 and 101 in a 0–100 point NRS[76].

There other different grading systems for assessment of pain. The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be'. The patient is asked to mark his pain level on the line between the two endpoints. The distance between 'no pain at all' and the mark then defines the subject's pain. If descriptive terms like 'mild', 'moderate', 'severe' or a numerical scale is added to the VAS,it is called a Graphic Rating Scale (GRS). In a Verbal Rating Scale (VRS) adjectives are used to describe different levels of pain. The respondent is asked to mark the adjective which fits best to the pain intensity. Sometimes due to the limited number of possible response categories, some patients may have problems in defining which answer fits best to their pain situation.

Numerical Rating Scales have shown high correlations with other pain-assessment tools in several studies. The feasibility and good compliance has also been proven. As it is easily possible to administer NRS verbally, it can be used in telephone interviews.[76]


ENT OPD
Manipal Hospitals
LIFE'S ON
ADULT VERBAL PAIN SCORE
ವಯಸ್ಕರ ಮೌಖಿಕ ನೋವನ್ನು ಅಳೆಯುವ ಅಂಕಪಟ್ಟಿ
Please determine the score that describes your pain at this moment
ಈ ಕ್ಷಣದಲ್ಲಿ ನಿಮ್ಮ ನೋವು ಯಾವ ಪ್ರಮಾಣದಲ್ಲಿದೆಯಂದು ದಯಮಾಡಿ ತಿಳಿಸಿ
No Pain
ನೋವು ಇಲ್ಲ
Mild
ಸ್ವಲ್ಪ ನೋವು
Moderate
ಮಧ್ಯಮ ಯಾತನೆ
Severe Pain
ತಡೆಯಲಾಗದ
ನೋವು
0 1 2 3 4 5 6 7 8 9 10

REVIEW OF LITERATURE

- **Hick s** [61] in 1983 studied a series of 26 patients with diagnosis of otitis externa, they were given treatment consisting of either drops only or aural toilet followed by aural drops. The efficacy in terms of resolution of symptoms and clinical signs were compared. In all but the most minor of cases, adequate curative treatment had to consist of complete aural toilet as well as aural drops. It was also shown that without aural toilet and visualization of the tympanum, more serious middle ear pathology could be missed. This study indicates that unless the patient is given the opportunity to have his ears properly cleaned, the general practitioner may not only be giving inadequate and ineffective treatment, but he may also be missing serious ear disease.

- Pistorious et al,[6] In a prospective, multicenter, randomized trial, in 1999 the efficacy and safety of a 1-week treatment regimen of ciprofloxacin otic drops (0.2%), with or without hydrocortisone, or polymyxin B-neomycin-hydrocortisone otic suspension (PNH) were compared in patients with acute diffuse otitis externa of less than 3 weeks' duration. Of 703 patients valid for efficacy analysis they conclude that Ciprofloxacin otic drops, with or without hydrocortisone, were as effective as PNH in the treatment of acute otitis externa. The addition of hydrocortisone to ciprofloxacin resulted in a statistically significant reduction in the time-to-end of ear pain when compared with ciprofloxacin alone.

- Another study aiming to compare the clinical outcome of patients receiving topical ciprofloxacin 0.3%/dexamethasone 0.1% (CD) otic suspension with that of those receiving polymyxin B/neomycin/ hydrocortisone (PNH) otic suspension for the treatment of acute otitis externa (AOE) was done by **Rahman et al** [64]. Data from 2 institutional review board-approved, multicenter, observer-masked, parallel-group, randomized, non-inferiority clinical trials conducted at 76 institutions across the United States between April 1998 and July 1999 were pooled together for this analysis. Patients > or =1 year of age diagnosed with AOE were considered for inclusion in the studies. Patients were randomly assigned to receive CD or PNH for 7 days. CD was administered as 3 drops in children and 4 drops in patients > or =12 years of age BID. PNH was administered as 3 drops in children and 4 drops in patients > or =12 years of age TID. The clinical investigators were blinded to treatment assignment. Otic inflammation, tenderness, edema, and discharge were

clinically assessed on days 3, 8, and 18 of the studies. Otic inflammation and edema were evaluated using a 4-point scale (none = 0; mild = 1; moderate = 2; and severe = 3). Otic tenderness and discharge were rated on a binomial scale (absent = 0 and present = 1). The clinical assessments were aggregated into a 9-point composite clinical scale (range, 0-8) to compare baseline severity between groups.Data from 1072 patients (1242 ears) were included in the analysis (CD, 537 patients; PNH, 535 patients). Both groups were similar with respect to sex, with 50.7% and 53.5% females in the CD and PNH groups, respectively.. The log-rank test revealed a significant difference in the AOE cure curves between the CD and PNH groups (P = 0.038). The proportions cured in the AOE at-risk groups at the day-3, -8, and -18 assessments in the CD and PNH treatment groups were 0.14 and 0.10, 0.75 and 0.72, and 0.98 and 0.97, respectively. The Kaplan-Meier summary statistics indicated that the mean time to cure was 0.6 day less with CD compared with PNH (9.7 vs 10.3 days). Treatment-related adverse event rates were similar between the 2 groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%).

- **Sam Rowland et al** [21] in 2001 conducted an epidemiological data survey,to define the descriptive epidemiology of otitis externa in the general population, to describe the first-line drug treatment used by UK GPs, and to determine factors related to second disease episodes. All cases of otitis externa occurring in 1997 in practices contributing data to the UK General Practice Research Database.the results showed the diagnosis of otitis externa common in all age groups and, except in the elderly, was more common in females than males with an increase in disease episodes at the end of the summer in all age groups except the 60 years and over group. In the majority of cases GPs prescribed ear drops (85%), but a significant proportion of patients were also prescribed oral antibiotics (21%). Referral to secondary care was uncommon (3%). Among patients prescribed ear-drop formulations, those containing both steroid and antibiotic or steroid alone were used most commonly and were associated with the lower rates of disease persistence but not recurrence. Among patients prescribed antibiotics, penicillins were prescribed most commonly. Disease persistence rates, and to a lesser extent disease recurrence rates, were higher in patients prescribed oral antibiotics. Patients prescribed steroid or steroid/antibiotic

combination ear drops have fewer subsequent consultations for otitis externa over the following 28 days.

- In a randomised trial on 213 patients in primary care, **Van Balen et al** [62] in 2003 analysed the treatment of acute otitis externa with three different types of ear drops. The use of drops containing corticosteroid resulted in a shorter duration of symptoms, lower rate of recurrence, and higher rate of cures than those that contained acetic acid alone. s Ear drops containing corticosteroids are more effective than acetic acid ear drops in the treatment of acute otitis externa in primary care. Steroid and acetic acid or steroid and antibiotic ear drops were equally effective.

- As there is growing concern over the use of systemic antibiotics and the development of bacterial resistance. **Weber et al** [63] performed an evidence-based review to answer the following clinical question, "Do antibiotic ototopical medications induce antibiotic resistant organisms?"They performed a MEDLINE search of the published literature from 1966 to the 2004.these articles were reviewed and graded according to the evidence quality. After an initial screening of over 2,500 articles, 38 articles were analyzed further; of these, 11 were determined to warrant extensive review. Eight articles evaluated chronic suppurative otitis media; 2, otitis externa; and 1, post-tympanostomy tube otorrhea, whereas 3 others studied systemic absorption. Of the 8 chronic suppurative otitis media studies, there were thought to be 5 grade 2B studies, 1 grade 1B study, and 1 grade 2C study. These studies did not demonstrate a propensity for the development of resistant organisms. No study answered the question as to whether resistance to systemic antibiotics might occur in otitis externa. Overall grade B evidence seems to indicate that no significant antibiotic resistance develops from the use of ototopical antibiotic treatment.

- In 2006 **Rosenfeld et al** [11] put forward a guideline with evidence-based recommendations to manage diffuse acute otitis externa (AOE). The primary purpose was to promote appropriate use of oral and topical antimicrobials and to highlight the need for adequate pain relief. The guideline was created with the use of an explicit, a prioritized , evidence-based protocol. The group made a *strong recommendation* that management of AOE should include an assessment of pain, and the clinician should recommend analgesic treatment based on the severity of pain. The group made *recommendations* that clinicians should: 1) distinguish diffuse AOE from other causes

of otalgia, otorrhea, and inflammation of the ear canal; 2) assess the patient with diffuse AOE for factors that modify management (nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, prior radiotherapy); and 3) use topical preparations for initial therapy of diffuse, uncomplicated AOE; systemic antimicrobial therapy should not be used unless there is extension outside of the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. The group made *additional recommendations* that: 4) the choice of topical antimicrobial therapy of diffuse AOE should be based on efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost; 5) clinicians should inform patients how to administer topical drops, and when the ear canal is obstructed. This was the first, explicit, evidence-based clinical practice guideline on acute otitis externa, and the first clinical practice guideline produced independently by the AAO-HNSF. © 2006 American Academy of Otolaryngology-Head and Neck Surgery Foundation.

- **Roland et al**[65] conducted an RCT to demonstrate clinical equivalence (statistical no inferiority) of topical ciprofloxacin and hydrocortisone (CHC, Cipro HC) and topical neomycin/polymyxin b/hydrocortisone (NPH, Cortisporin) with systemic amoxicillin (AMX, Amoxil), for treatment of acute otitis externa (AOE). It was conducted in 2008 as randomized, active-control, observer-blind, multicenter trial. Altogether, 206 patients were enrolled (CHC, 106; NPH + AMX, 100). Patients were > or =1 year of age, had AOE >2 days with at least mild symptoms, and gave informed consent. All were evaluable for safety, and 151 were evaluable for efficacy. Ciprofloxacin and hydrocortisone 3 drops twice daily for 7 days (adults and children) or NPH 4 drops (adults) or 2 drops (children) with AMX 250 mg (adults and children) 3 times daily for 10 days, were prescribed as directed in approved product labeling. The primary efficacy variable was taken as response to therapy 7 days after treatment ended (test of cure). Secondary variables included time to end of pain, symptom scores (otalgia and tenderness) and microbiological eradication. Noninferiority was declared if the lower confidence limit around the measurement difference was above -10 (nearer zero).Response to therapy was higher for CHC (95.71% vs 89.83%) but was statistically noninferior (lower confidence limit, -4.98) to NPH + AMX. Median time to end of pain was 6 days for both groups. Noninferiority was declared for symptom scores at all measurement periods and for microbiological eradication. No serious

adverse events related to treatment were reported. This study concluded that Ciprofloxacin and hydrocortisone is clinically equivalent to NPH + AMX for the treatment of AOE in adults and children. However, low systemic exposure, absence of ototoxicity, and less frequent dosing clearly favor Cipro HC..

- **Hajioff et al** [66] conducted a systematic review in 2010 and aimed to find out the effects of empirical and prophylactic treatments for otitis externa. The search was done in all important online databases up to October 2007 .They found nine systematic reviews, RCTs, or observational studies those meeting inclusion criteria. The results were Combining topical antibacterial agents and corticosteroids (methylprednisolone–neomycin drops) is likely to be more effective than placebo in reducing signs and symptoms of otitis externa over 28 days. There was clinically important results from RCTs about whether oral antibiotics are better than no active treatment or topical anti-infective agents in people with otitis externa.

- **Shresta et al**[37] conducted a prospective RCT compare the efficacy of treatment between steroid–antibiotic and 10% Ichthammol glycerine packs (IG packs) in acute otitis externa. It was conducted in Kathmandu University Hospital, Dhulikhel from July 2009 to December 2009 on 82 patients. Painand edema was compare as the final outcome. The mean age was 23.5 years. out of which 51.2% were females and 48.8% were males. Average number of visits in 10% IG pack group was 5.4 days while in steroid–antibiotic group it was 3.5 days. There was statistically significant decrease in the number of visits in steroid group ($P < 0.05$). Similarly, decrease in pain score in second visit was statistically significant ($P = 0.02$) in steroid–antibiotic group as compared to 10% IG pack, while the edema score in second visit while comparing steroid–antibiotic group with 10% IG pack was statistically not significant ($P = 0.07$), whereas it was statistically highly significant on fourth visit ($P = 0.001$). in their study the control of pain and edema was more and hence the number of visits is significantly less in steroid–antibiotic packing group, so it was recommended to use steroid–antibiotic pack for effective treatment of acute otitis externa

- **Collier et al** [67] conducted an analysis to describe pre- and postguideline prescribing patterns by clinician specialty and antimicrobial type and assess trends over time. It was a Retrospective longitudinal analysis of a large insurance database of outpatient visits in 2004 to 2010 for AOE in United States. —The analysis included 907,261

initial outpatient visits. Use of systemic antimicrobials declined by 4.9% from 36.5% of initial visits in 2004 to 32.1% in 2010. Use of systemic antimicrobials varied by specialty. Systemic antimicrobials were prescribed in 47.1% of 2010 emergency department (ED) visits, 25.9% of otolaryngologist visits, and 20.4% of pediatrician visits. Penicillins were prescribed most frequently, followed by cephalosporins, erythromycin/macrolides and quinolones. Opioids were prescribed in 26.4% of ED visits and 9% of outpatient visits. The study concluded that the frequency of systemic antimicrobial prescriptions showed a decline from 2004 to 2010 within each clinical specialty studied. However, declines were modest (−4.4% overall [95% CI −5.0, −3.8], from 36.5% to 32.1%), and one-third of visits in 2010 resulted in prescriptions for systemic antimicrobials, despite exclusion of repeat visits and visits with complicating factors. The use of systemic antimicrobials varied by specialty. Otolaryngologists and pediatricians had the lowest rate of systemic antimicrobial use overall, while ED physicians were most likely to prescribe systemic antimicrobials.

- In 2010 **Kaushik et al's**[25] Cochrane review was a meta analysis of RCT s related to AOE with a total number of 3382 patients. Aim was To assess the effectiveness of interventions for acute otitis externa. The date of the most recent search was 6 January 2009.from the result they included only Randomized controlled trials evaluating ear cleaning, topical medication or systemic therapy in the treatment of acute otitis externa were eligible. They excluded complicated acute otitis externa; otitis externa secondary to otitis media or chronic suppurative otitis media; chronic otitis externa; fungal otitis externa (otomycosis); eczematous otitis externa; viral otitis externa and furunculosis.The result showed topical antibiotics to be more effective than placebo on treatment of AOE. There was no statistical significant variation in the results comparing different antibiotic ear drops. They concluded that "topical treatment alone as distinct from systemic ones is effective for uncomplicated acute otitis externa". The overall quality of studies was low. No clinically meaningful differences were noted in clinical cure rates between the various topical interventions reviewed. One notable exception involved a trial of high quality which showed that acetic acid was significantly less effective when compared with antibiotic/steroid drops in terms of cure rate at two and three weeks .One trial of low quality comparing quinolone with non-quinolone antibiotics did not find any difference in clinical cure rate. No trials evaluated the effectiveness of ear cleaning. Only two trials evaluated steroid-only

drops. One trial of low quality suggested no significant difference between steroid and antibiotic/steroid but did not report the magnitude or precision of the result. Another trial of moderate quality comparing an oral antihistamine with topical steroid against topical steroid alone found that cure rates in both groups were high and comparable (100% (15/15) and 94% (14/15) respectively at three.

- **Moseges et al** [26] in 2011 conducted a electronic database meta-analysis of RCT on otitis externa comparing the efficacy of treatment of ciprofloxacin local and oral treatment .This systematic review compares the efficacy of treatment using a ciprofloxacin 0.2% solution with other therapeutic options. The number of studies was 14: six studies using a ciprofloxacin 0.2% solution, and eight studies using both 0.2% and 0.3% solutions. The studies included in the review demonstrate the statistical equivalence between the ciprofloxacin solution (0.2%) and the reference products PNH (a combination of polymyxin B, neomycin sulfate and hydrocortisone), auriculum powder, and ciprofloxacin foam with respect to the cure rate. The research groups consistently observed high in vitro activity of ciprofloxacin against *Pseudomonas aeruginosa*. They concluded that "the clinical success" consistently shows higher rates in patients treated with fluroquinolones, than in the control group. They also noticed the absence of ototoxicity and low systemic exposure caused by local ciprofloxacin ear drops; and hence confirmed the non-inferiority of ciprofloxacin ear drops over other treatment modalities

- **Pabla et al** [67] conducted a prospective observational study on the management of otitis externa in consecutive patients referred to an ENT emergency clinic was undertaken. Data were collected and analyzed on symptoms, initial management by general practitioners, findings and treatment in the ENT clinic. A total of 106 patients were studied. The mean duration of symptoms before presentation to clinic was 13 days; 42% of patients received no treatment by their GP prior to referral to the ENT emergency clinic. Only 14% of patients received topical antibiotics alone, whilst 44% received oral antibiotics, either alone or in conjunction with topical antibiotics by their GP. Of the 106 patients, 86% received topical antibiotics in the ENT emergency clinic and oral antibiotics were reserved for those presenting with complicated acute otitis externa. Topical antibiotics are associated with a decrease in disease persistence, whilst oral antibiotics are associated with an increase. However, general practitioners were prescribing oral antibiotics more often than required. There are few regional

guidelines and no explicit national guidelines on the management of acute otitis externa for GPs to refer to. We suggest the implementation of national guidelines to aid clinical practice

- **Mittal et al** [68] conducted a prospective interventional trial in 2014 comparing the pH of external auditory canal (EAC) in normal individuals and patients with acute otitis externa (AOE), its variation with change of temperature and humidity, different symptoms and number of symptoms at presentation (Day 0) and various stages of treatment in 100 normal ears and forearms and 50 ears having AOE. The mean pH of normal EAC was 3.950 ± 1.199 while that of forearm was 4.775 ± 0.910. There was increase in pH with increase in relative humidity, however, the change in the pH of EAC was statistically not significant ($p > 0.05$). the pH of the AOE group was far more alkaline than the normal ear. Significant fall in pH was observed at 1 and 2 weeks of treatment. The normal EAC pH is relatively more acidic as compared to that of forearm skin and it became more alkaline in cases of AOE with reversion back to acidic pH after treatment. Acidification of the EAC is the only treatment required in most cases. No significant change in pH of ears was observed with changes of temperatures and humidity.

- **Sanders et al** [69] conducted a retrospective data analysis on AOE patients in wellington hospital over a period of 4 years from2007 to 2011 to identify the microorganism responsible for AOE. 144 cases were included in the study. *Pseudomonas aeruginosa* (*P. aeruginosa*) was the most common organism (46.5 per cent), while *Staphylococcus aureus* (S. *aureus)* was the second most common (31.9 per cent). Most patients received appropriate topical treatment. However, a significant number were treated with systemic antibiotics alone without adverse outcomes .their recommendations were broad-spectrum topical antimicrobial therapy in all patients with uncomplicated AOE and culture-sensitive topical treatment with consideration of systemic antimicrobials for severe AOE requiring hospital admission.

- **Musa et al** [70] conducted a prospective study of 13,328 cases of ear diseases seen within January 2009 and March 2013, in Nigeria. 133 cases were diagnosed with otitis externa across all age groups. Hospital prevalence stands at 1.0%. There were 81(60.9%) males and 52(39.1%) females in ratio 1.5:1. Children age 0-15 constitute

55(41.3%) while young adults and adults were 78(58.6%). The minimum age at presentation was one year, while maximum age was 64 years. Mean age was 24 years with a standard deviation of ± 1.12 Years. Ear pain as only presenting symptom was the major complain found in this study accounting for 68(51.1%). Acute diffuse otitis externa was the commonest diagnosis accounting for 101(75.9%) and associated clinical findings ranging from tragal tenderness, hyperaemia and oedema of ear canal in 57 (54.9%). Ear swab was not routinely done and only 6(15.8%) of the discharging ears had microscopy done and the organisms were PSEUDOMONAS spp and klebsiella. Empirical treatment was the commonest treatment modality and about 91% of the patients had complete symptom resolution by second visit. Complication was observed in only one case of necrotizing otitis externa who was retro-viral positive.

- **Prassanna et al** [71] conducted a prospective cross sectional study of 100 participants to assess the aerobic bacterial flora of normal human EAC. the result of the study showed monomicrobial and polymicrobial flora mainly staphylococcus *epidermidis* (88%), staph. *aureus* (23%).diphthiroids (7%), e.*col*i (5%), pseudomonas (3%).this study pointed out to the fact that the causative organism of otitis .externa (staph *aureus*, pseudomonas *aeuroginosa*) are normal inhabitants of EAC. the conditions of EAC which alter the physiology or the continuity of the skin leads to development of AOE.

- **Rishi bhatta et al** [72] conducted a prospective randomised clinical trial comparing IG wick packing and steroid antibiotic packing for relief of pain in case of AOE. It says AOE to be common in young adults and children. In their study right ear was more affected ,which could be attributed to right-handedness.the result showed lesser no: visits for steroid packing group, indicating faster control of pain

- **Margaret et al** [73] conducted a multicenter evaluator blinded RCT comparing the efficacy of 2 antibiotic ear drops: ciprofloxacin 0.2%otic solution and PNH on treatment of otitis externa. The outcome showed non-inferiority of ciprofloxacin 0.2% over PNH in clinical cure rate and bacteriological eradication.

- **Gurov et al** [74] studied the efficacy and tolerability of oral ciprofloxacin in treatment of AOE .It was a multinational multicentric trial. It demonstrated oral ciprofloxacin as a good alternative in the treatment of AOE and chronic otitis externa where the topical drug delivery cannot be ensured. The treatment ensured significant clinical and

bacteriological cure rates in their efficacy analysis. In their study the most common organism was staph aureus followed by pseudomonas species.

- **Rosenfeld et al** [19] in 201 published a clinical practice guideline,which is an update and replacement for an earlier guideline published in 2006 by the American Academy of Otolaryngology-Head and Neck Surgery Foundation. This update provides evidence-based recommendations to manage acute otitis externa. The primary outcome considered in this guideline is clinical resolution of AOE.

  The purpose of the original guideline was to promote appropriate use of oral and topical antimicrobials for AOE and to highlight the need for adequate pain relief. The development group made strong recommendations that (1) clinicians should assess patients with AOE for pain and recommend analgesic treatment based on the severity of pain and (2) clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated AOE unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. The development group made recommendations that (1) clinicians should distinguish diffuse AOE from other causes of otalgia, otorrhea, and inflammation of the external ear canal; (2) clinicians should assess the patient with diffuse AOE for factors that modify management (nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, prior radiotherapy); (3) clinicians should prescribe topical preparations for initial therapy of diffuse, uncomplicated AOE; (4) clinicians should enhance the delivery of topical drops by informing the patient how to administer topical drops and by performing aural toilet, placing a wick, or both, when the ear canal is obstructed; (5) clinicians should prescribe a non-ototoxic preparation when the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube; and (6) clinicians should reassess the patient who fails to respond to the initial therapeutic option within 48 to 72 hours to confirm the diagnosis of diffuse AOE and to exclude other causes of illness.

Part II

AIM AND OBJECTIVES OF STUDY

AIM

1. **To assess the time taken for the ear to get back to normal and symptomatic relief with local antibiotics vs. local antibiotic and oral antibiotic.**

As the treatment of otitis externa does not have a standard protocol, patients are treated with ear drops alone and at times with oral antibiotics also. As both the treatments are effective, here we are comparing the time taken for the ear to get back to normal, clinically and symptomatically, in each group

2. **To evaluate if oral antibiotic offers any additional benefit in treatment of acute otitis externa, over local drops alone**

Addition of an oral antibiotic along with the ear drops in an uncomplicated AOE, is it really required? Does it really change the outcome of the disease? Does it prevent any complications?

OBJECTIVES OF THE STUDY

1) To compare the duration of recovery from the symptoms in treatment of acute otitis externa between local antibiotic alone against local and oral antibiotic.

2) To investigate if treatment with only local ear drops gives similar results as combination therapy of local and oral antibiotic.

3) To compare course of events during both treatment category.

4) To assess any development of complications during the course of treatment

MATERIAL AND METHODS

A prospective, non blinded randomized, comparative study of local ear drops alone vs. local with oral antibiotic in patients with acute otitis externa coming to ENT OPD, Manipal hospital, Bangalore

STUDY AREA

The study was conducted in the Department of Otorhinolaryngology, Manipal Hospital, Old Airport Road Bangalore. This is a 650 bedded multispecialty hospital comprising of intensive care units, outpatient departments, adult and paediatric emergency units. Approximately 100-150 patients visit the ENT OPD every day. The patients included in the study were assessed in the ENT OPD on the day of presentation. They were reviewed in OPD on day 3 and day 7 days and then telephonically on day 14.

STUDY DESIGN

Prospective non-blinded randomized comparative trial

STUDY PERIOD

December 2015 to march 2017

STUDY POPULATION

The study population comprised of adults between 18-60 years of age, with otitis externa who presented to the department of Otorhinolaryngology, Manipal Hospital, Bangalore.

SAMPLE SIZE WITH JUSTIFICATION

Based on previous literature survey findings for outcome variables such as pain scores, or time taken for symptomatic relief, with 90% statistical power at 5 % level of significance, a of total of 72 patients were studied , with 37 patients in the study group and 35 patients in control group.

Null hypothesis: There is no significant improvement in the recovery period of otitis externa by adding oral antibiotics with local ear drops.

Alternative hypothesis: There is significant benefit in terms of recovery period by adding oral antibiotics with ear drops for treatment of otitis externa.

Type 1 error rate α:

The probability of committing a type I error (rejecting the null hypothesis when it is actually true) is called α (alpha) [75.] In a two-sided test it is usually set at 0.05. In this study also we predefined a statistical significance level of α =0.05.

Power of the study: (1-type2 error)/β

The alternative hypothesis is associated with type II error, when we are not able to reject the null hypothesis. This is given by the power of the research (1- type II error/β): the probability of rejecting the null hypothesis when it is false. Conventionally, the power is set at 0.80, for higher the power, the more sample is required[75]

In our study also we have taken power as 0.80

Δ: (clinically permissible margin of non equivalence):

It has been set as 0.5 with a significance of 95%

Sample size calculation

The sample size was calculated based on the equivalence study design formula

$$N = 2 \times \left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta_0} \right)^2 \times p \times (1-p)$$

Prevalence of otitis externa is 1% as of previous studies [21]

N=number of patient required in each arm

P=prevalence of the disease, which is taken as 1%.

The adequate sample size for an equivalence study is 30.15 which can be rounded off to 31.Total number of patient in each group of our study is 37 in only local ear drops treatment group and 35 in group with oral and local antibiotic.

Randomization

Patients were allocated into two groups based on random table generated by Randomization.com.

SAMPLE TECHNIQUE

Source of Data

Data for the study were collected from patients coming to ENT OPD aged between 18 to 60 years diagnosed with acute diffuse otitis externa of less than 3 week duration. Eligible patients had symptoms of otitis externa within 2 days of study entry, including oedema of the ear canal, erythema, tragal tenderness and or otalgia. Patients with any of the exclusion criteria were removed from the study.

Those patients who were treated with local ear drops alone (ciprofloxacin-D), was compared with those treated with ear drops (ciprofloxacin-D) and oral antibiotic (quinolone). Acetaminophen 650 mg was prescribed as and when required

INCLUSION CRITERIA

- Patients with ear pain and ear discharge
- Duration less than 3 weeks
- Age between 15 -60 years.
- Duration of disease less than 3 weeks

EXCLUSION CRITERIA

- Patient with diabetes, HIV, immunocompromised
- Patients with perforated TM
- History of chronic otitis media
- Invasive malignant otitis externa
- Patient with skin lesions-dermatitis of the surrounding area
- Patient with allergy to topical drugs and surrounding cellulites
- Those who have already taken medications for otitis externa
- Fungal otitis externa
- Previous episode of otitis externa in last 30 days
- Pregnancy and lactating mothers.
- Allergy to oral quinolones

DATA COLLECTION TECHNIQUE AND TOOLS

The data was collected by interviewing and examining the patient on the day of presentation (day 1), then on day 3 and day 7.they were telephoned on 14th day and enquired about the symptomatic relief and need for analgesia if any. In case of persisting symptoms, they were requested for OPD review. Examination of the patient included both otoscopic and microscopic examination.

Numerical rating scale:

In a Numerical Rating Scale (NRS), patients are asked to circle the number between 0 and 10, which fits best to their pain intensity. The score give by the patient was recorded in the proforma on each visit.

External auditory canal wall edema

Otic inflammation and edema was measured by taking the five point grading scale for the occlusion of EAC

Grade 0: normal EAC

Grade 1: minimal edema with no occlusion, more than 75% of TM visualized

Grade2: mild edema, 50-75% of TM visualized

Grade 3: severe edema: less than 50% of TM visualized

Grade 4: complete occlusion of EAC, TM not visualized

Ear discharge

The discharge in the EAC was quantified as nil, scanty, moderate and copious.

Nil-no ear discharge/debris in canal

Scanty-few clumps of debris in canal, not requiring cleaning

Moderate-canal mostly filled with discharge but not pouring out

Copious-discharge coming out of EAC

The findings were recorded with a hand held otoscope on each visit.

EAC is examined under microscope on the first visit and if any discharge is cleared. Patients were treated with ivalon otowick or IG wick in case of severe edema. The choice of the wick was not standardized.

Method of collection of Data:

Sampling procedure:

Patients were allocated to two different groups by using closed block random number generated table, by randomisation.com

A predesigned proforma was used to record the relevant information (patient's data, and clinical findings,) from the individual patient selected with inclusion and exclusion criteria. They are requested to report back to the OPD for follow-up on day 3, ie after 48 hours of starting of treatment. The clinical findings on this day are also entered in the table. Then he/she is advised to report back 48 hours later and 7 days later. On day 14 a telephonic communication was done with the patients and the data is filled

Statistical analysis:

The outcome in two groups: group A; local antibiotics only and group B; local antibiotic with oral antibiotics (in form of success rate, pain relief, and number of analgesics taken) were compared.

- Data was expressed as percentage and mean ± S.D.
- Kolmogorove-Smirnove analysis was performed for checking linearity of the data
- Fischer's exact test or Chi square test was used to analyze the significance of difference between frequency distribution of the data.
- Student's unpaired t test was used to assess the significance of difference between two study groups for various parametes.
- P value <0.05 was considered as statistically significant.
- SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

METHODOLOGY

The patients when presented to ENT OPD with complaints of ear pain between 18 to 60 years of age were interviewed. They were again filtered according to the predefined criteria for inclusion and exclusion. The patient was explained about the study and the treatment options available. The patient was given full authority to opt in or opt out from the trial. After signing the informed consent form the choice of treatment was taken from the random number table. Each patient was given the next treatment in continuity given by the random number table.

The day of commencement of treatment was taken as day 1. Pain score and symptoms were recorded after interviewing the patient. NRS was used to rate the pain. Presence or absence of itching of EAC was noted. The patient was then examined with a hand held otoscope for ear discharge and canal wall edema. The scoring for canal wall edema and the quantity of the discharge if any was documented. Aural toileting when required was performed under microscope. In case of obstructing edema of EAC, IG wick or IVALON otowick were inserted to enhance the drug delivery. The subjects were counseled about the requirement of reassessment and aural toileting in the treatment of acute otitis externa, and the review was fixed after48 hours of treatment on day 3.

On day 3 visit, the pain score, itching and the number of analgesics taken were recorded by interviewing the patient. Otoscopic examination was performed and the respective findings documented. In case of persisting discharge EUM and aural toileting was done. The treatment patient was continued regardless of the findings. The patient was reassured and requested to report back on day 7.

On day 7 visit, all the study parameters were assessed and documented. If the patient was asymptomatic at that point of time, the last day he was symptomatic was recorded as the days taken for recovery. The total number of analgesics taken by the patient was also noted. No treatment was continued after this day.

On day 14 the patient was reached telephonically and enquired about the symptoms and the response recorded. If the patient was asymptomatic at that point ,the last day he had symptoms was taken as the day of recovery. Number of analgesics taken were also noted

The data was tabulated separately in two similar charts for both treatment groups. Statistical analysis was done comparing the data between the charts.

PROCEDURE

Otoscopic examination: Welch Allyn otoscope was used. Visualization of TM was noted, as it helps in the differential diagnosis of AOE and grading of the canal wall edema

EUM and aural toilet: proper toileting of the EAC was done in cases with moderate and copious ear discharge. Otowick or icthamol glycerin packing was done in indicated cases.

RESULTS

The total patient profile of 73 patients was studied from December 2015 onwards to march 2017

Study design: A non blinded prospective randomized controlled study

Table: Age distribution in study subjects

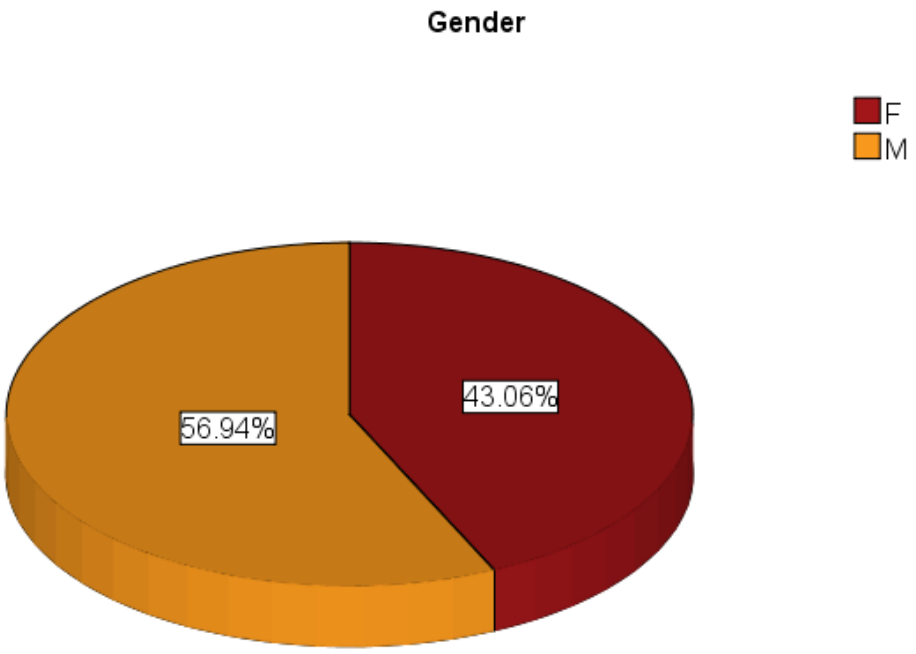
	Age (Years)	Frequency	Percent
Valid	</=30	20	27.8
	31-40	21	29.2
	41-50	15	20.8
	51-60	16	22.2
	Total	72	100.0

Our study group was aged between 18 to 60 years of age. In total of 72 patients studied 20 were between 18 to 30years of age. 21 patients were in the age group of 30 to 40 years. 15 patients were in the age group of 41-50 years and 16 in the age group of 51 to 60 years.

Table: Gender distribution in study subjects

Gender distribution in the study

	Gender	Frequency	Percent
Valid	F	31	43.1
	M	41	56.9
	Total	72	100.0



Out of 72 subjects studied, 31 patients were females and 41 were male.

There is a significant predominance of males for the otitis externa in this study

The stratified sex distribution shows predominance in males in the mid-agegroups,ie between 30 to 50.

Table: Age and gender distribution in study subjects

			Gender		Total
			F	M	
Age (Years)	</=30	Count	13	7	20
		% within Gender	41.9%	17.1%	27.8%
	31-40	Count	10	11	21
		% within Gender	32.3%	26.8%	29.2%
	41-50	Count	1	14	15
		% within Gender	3.2%	34.1%	20.8%
	51-60	Count	7	9	16
		% within Gender	22.6%	22.0%	22.2%
Total		Count	31	41	72
		% within Gender	100.0%	100.0%	100.0%

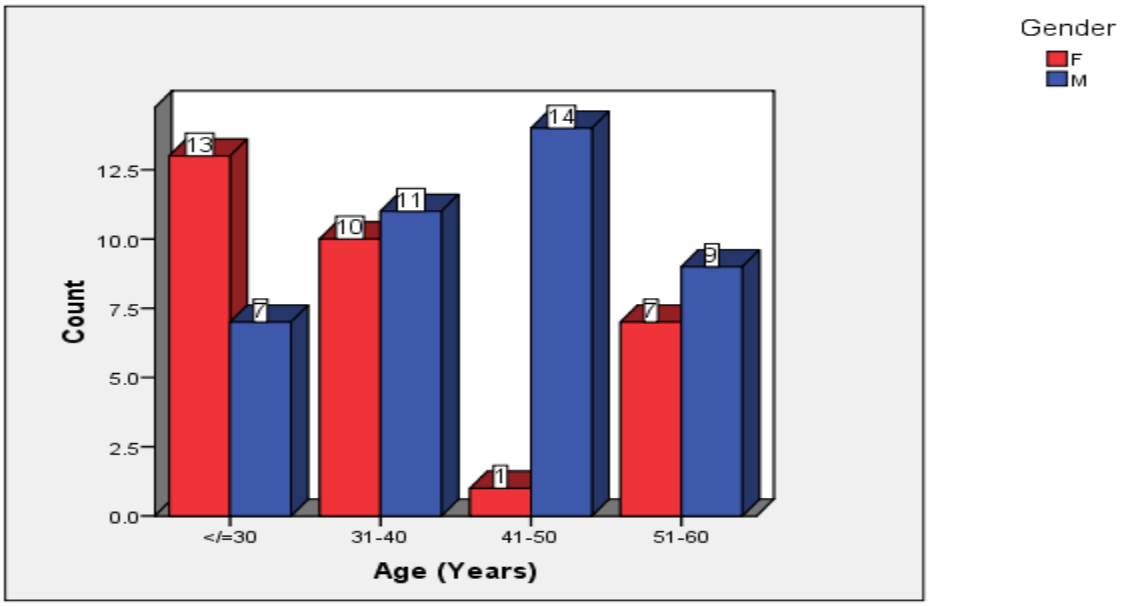


Table: Comparison of distribution of side of ears in study groups

Side of Treatment group Cross tabulation

			Treatment group			P value
			Ear drop only	Ear drop + antibiotic	Total	
Side	Left	Count	16	19	35	0.24
		% within Treatment group	43.2%	54.3%	48.6%	
	Right	Count	21	16	37	
		% within Treatment group	56.8%	45.7%	51.4%	
Total		Count	37	35	72	
		% within Treatment group	100.0%	100.0%	100.0%	

In the ear drop only group left was affected for 16 patients and right in 21 patient.

In the combination treatment group 19 patients had left ear disease and 16 had right ear affected.

Comparison of distribution of side of ears in study groups was performed using Chi-square test. Both groups were found to be matched for distribution of side of ears.

Left side and right side had a similar incidence in this study with a p value of 0.24

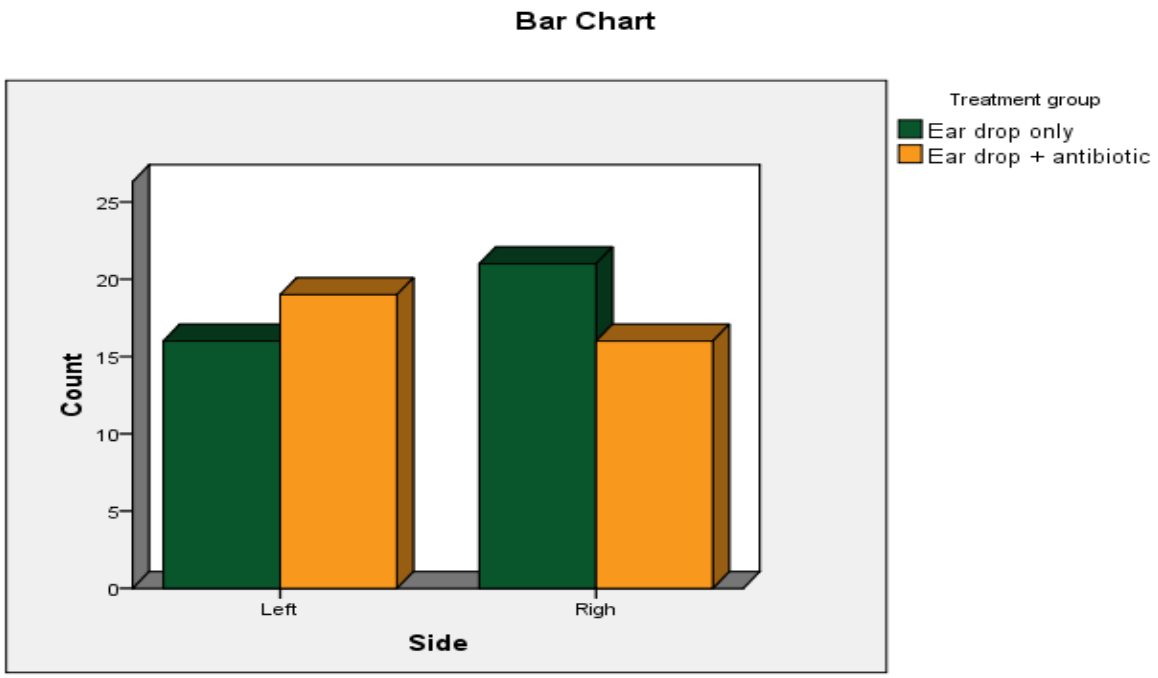
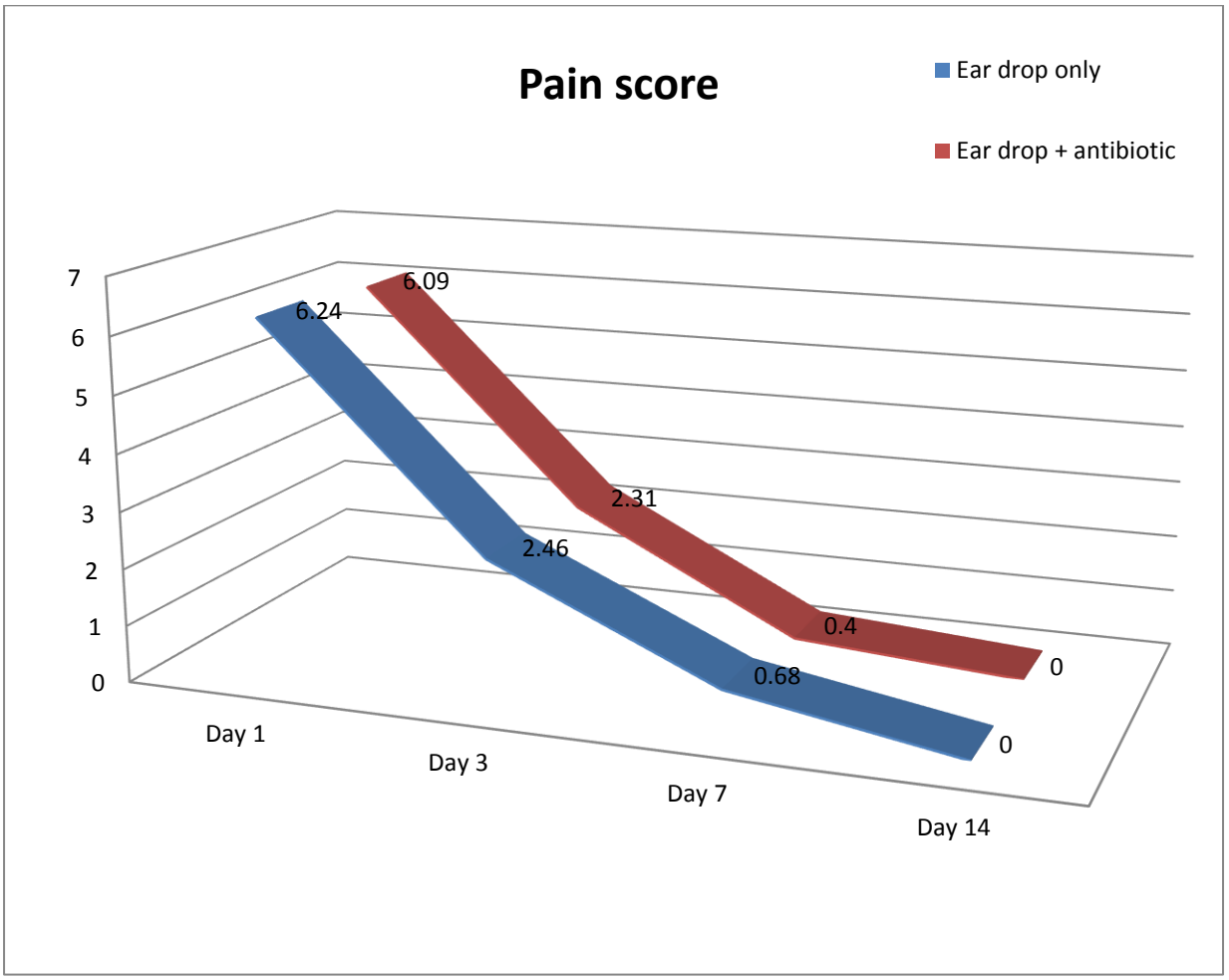


Table: Comparison of pain scores on follow-up between two groups.

	Treatment group	N	Mean	Std. Deviation	Std. Error Mean	t	p value
Pain score day1	Ear drop only	37	6.24	1.53	0.25	0.44	0.66
	Ear drop + antibiotic	35	6.09	1.48	0.25	0.44	
Pain score day3	Ear drop only	37	2.46	1.12	0.18	0.60	
	Ear drop + antibiotic	35	2.31	0.93	0.16	0.60	0.55
Pain score day7	Ear drop only	37	0.68	0.53	0.09	3.00	
	Ear drop + antibiotic	35	0.4	0.57	0.08	3.00	
Pain score day14	Ear drop only	37	0.00	.00[a]	0.00	-	-
	Ear drop + antibiotic	35	0.00	.00[a]	0.00		

Comparison of pain scores on follow-up between two groups were carried out using student's unpaired t test. No significant difference was detected between pain scores of two groups at day 1 and day 3 and day 7. Pain score reached 0 in both groups at day 14.



Itching in EAC

Itching of EAC was found in 15 patients out of the 72 subjects. regardless of the treatment started, none of them complained of itching on follow ups

Table: Comparison of itching in ear in different treatment group in follow up

Statistics

Treatment group		Itching in the ear day 1	Itching in the ear day 3	Itching in the ear day 7	Itching in the ear day 14
Ear drop only	N	9	0	0	0
	%	24.3	0	0	0
Ear drop + antibiotic	N	8	0	0	0
	%	22.9	0	0	0

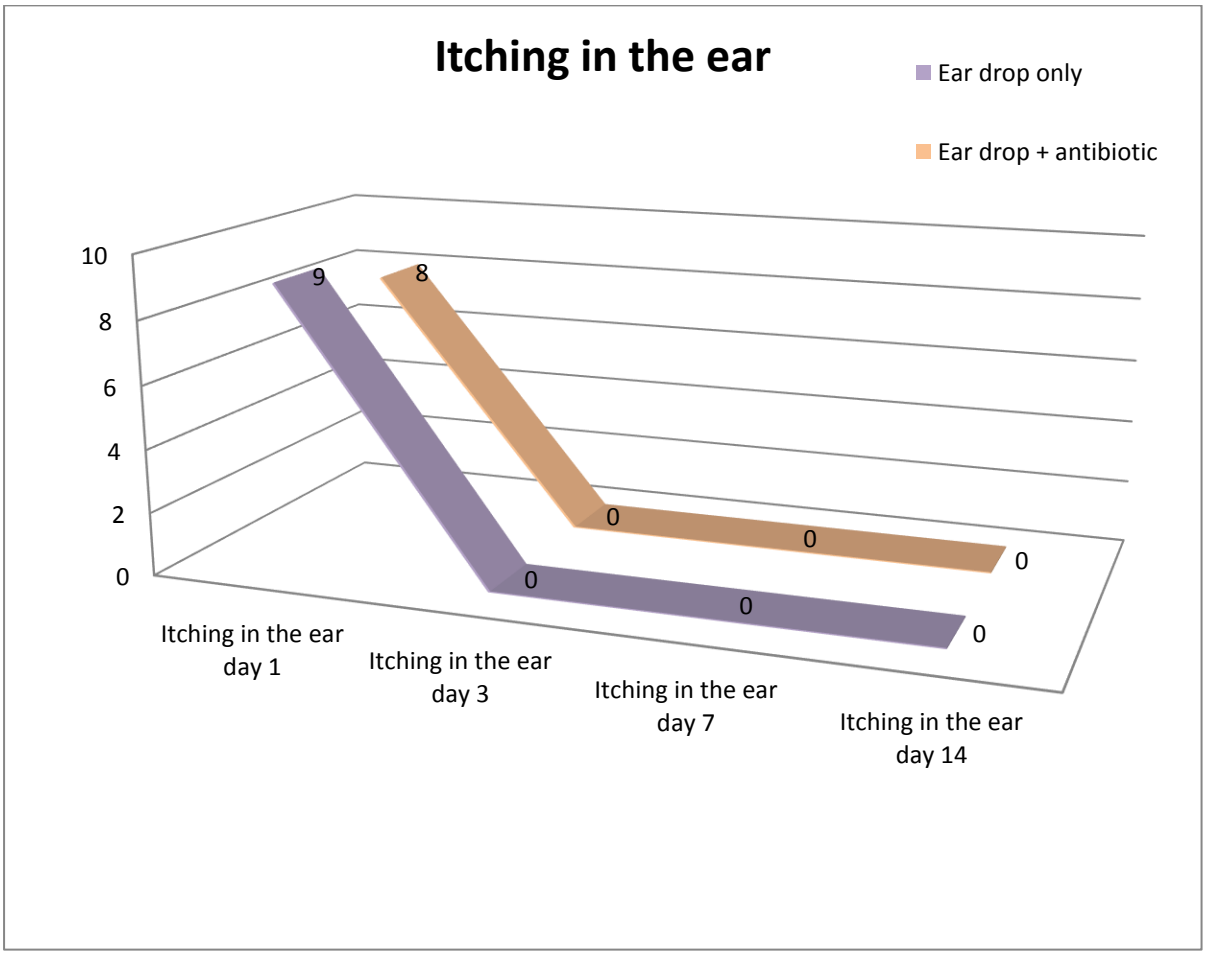


Table: Discharge in follow up in study group

Ear Discharge

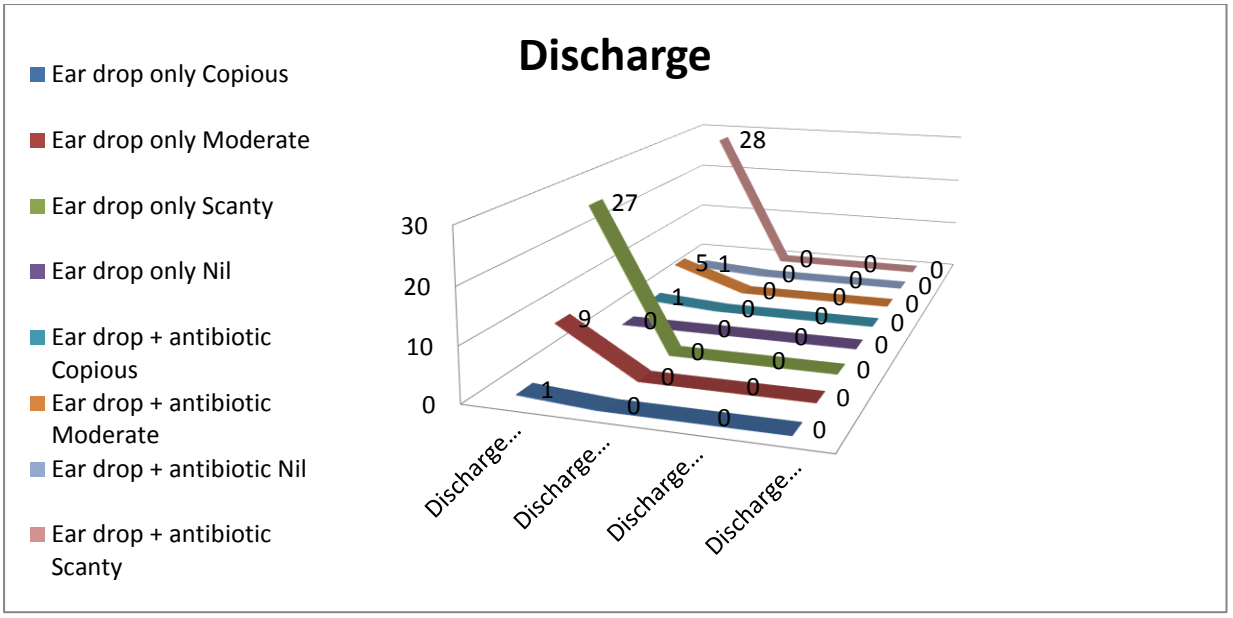
Treatment group		day 1	day 3	day 7	day 14
Ear drop only	Copious	1	0	0	0
	Moderate	9	0	0	0
	Scanty	27	0	0	0
	Nil	0	0	0	0
	Total	37	0	0	0
Ear drop + oral antibiotic	Copious	1	0	0	0
	Moderate	5	0	0	0
	Scanty	28	0	0	0
	Nil	1	0	0	0
	Total	35	0	0	0

Ear discharge was noted to be copious only in 2 patients in the study group.

27 out of 37 patients in group A had only scanty ear discharge, which on subsequent follow up was cleared.9 patients had moderate amount of discharge in treatment group A.

28 patient from treatment group B presented with scanty ear discharge, which subsequently cleared up with treatment.5 patients in group B had moderate amount of discharge.

Regardless of the treatment and the amount of the discharge, it seemed to reduce on commencement of treatment.

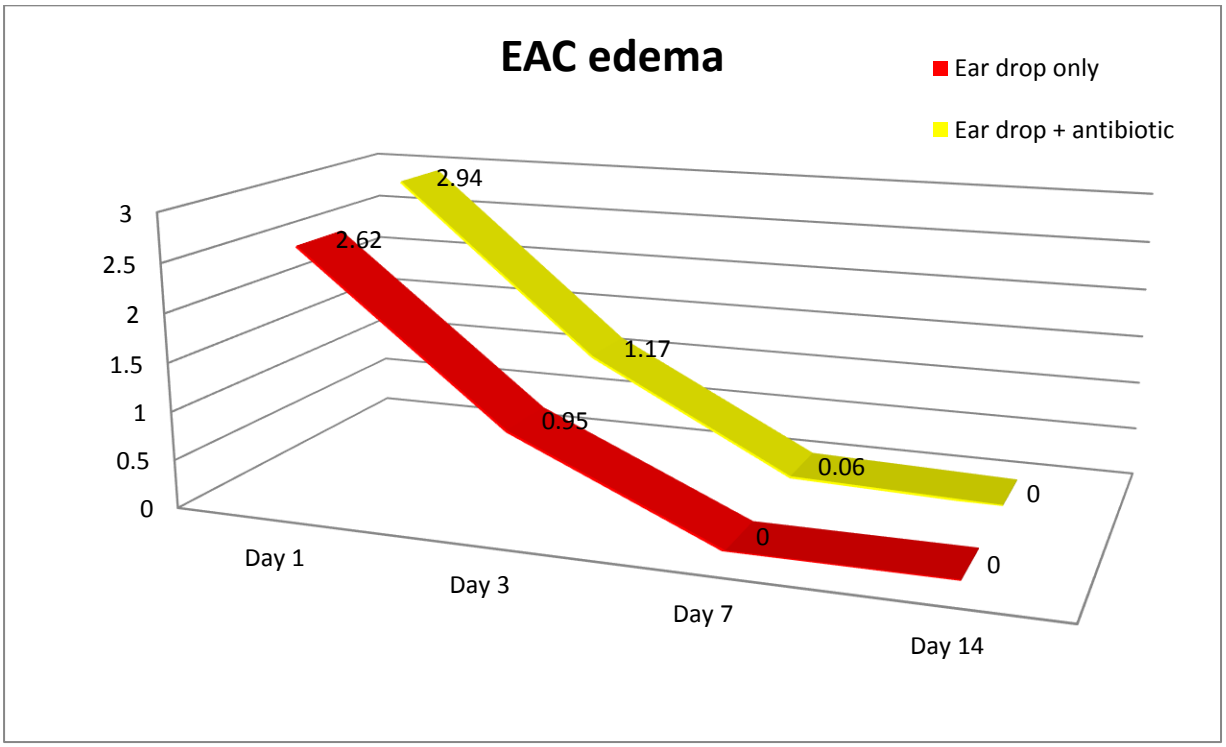


Out of total 72 patients studied 55(76.38%) patients presented with scanty amount of discharge. Only 2 of them had copious or pouring ear discharge.

Table: Comparison of EAC edema in study groups over follow up period

	Treatment group	N	Mean	Std. Deviation	Std. Error Mean	t	P value
EAC edema day1	Ear drop only	37	2.62	0.83	0.14	-1.79	0.08
	Ear drop + antibiotic	35	2.94	0.68	0.12		
EAC edema day3	Ear drop only	37	0.95	0.74	0.12		
	Ear drop + antibiotic	35	1.17	0.45	0.08	-1.56	0.12
EAC edema day 7	Ear drop only	37	0.00	0.00	0.00		
	Ear drop + antibiotic	35	0.06	0.24	0.04	-1.44	0.16
EAC edema day14	Ear drop only	37	0.00	.00000[a]	0.00	-	
	Ear drop + antibiotic	35	0.00	.00000[a]	0.00		-

Comparison of EAC edema in study groups over follow up period was performed using student's unpaired t test. No significant difference was noted on any day of follow up between the two treatment groups



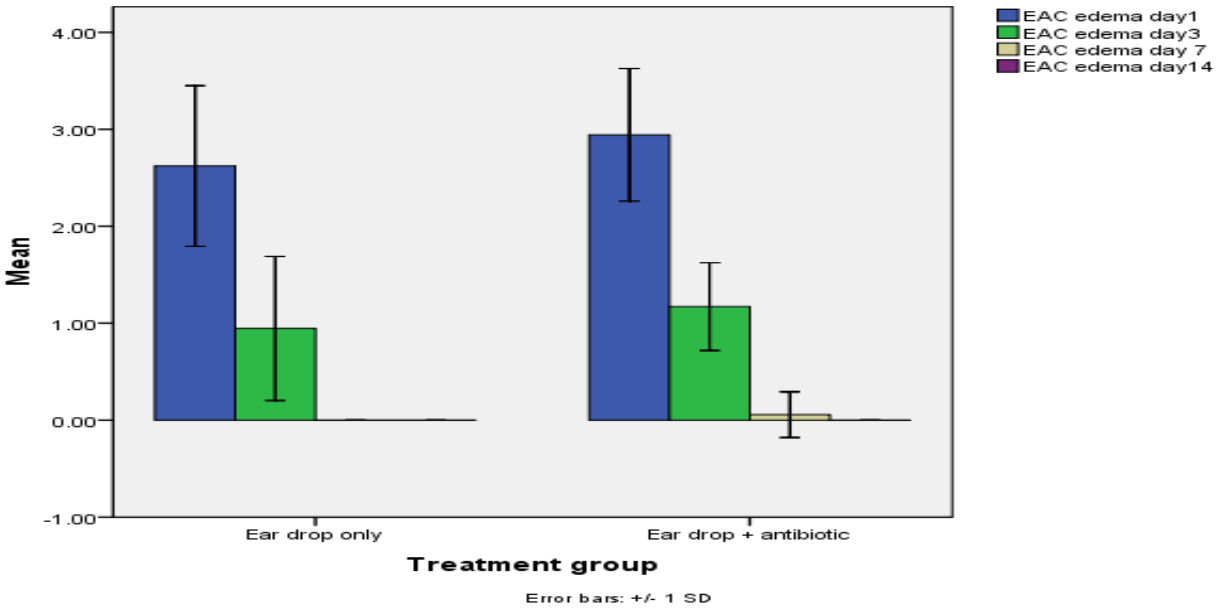


Table: Comparison of duration of recovery between study groups.

Group Statistics

	Treatment group	N	Mean	Std. Deviation	Std. Error Mean	t	P value
Duration of recovery (days)	Ear drop only	37	3.7568	1.23391	.20285	-.925	.358
	Ear drop + antibiotic	35	4.0571	1.51352	.25583		
Analgesic	Ear drop only	37	4.9459	2.14665	.35291		
	Ear drop + antibiotic	35	5.0857	2.03458	.34391	-.284	.778

Comparison of duration of recovery between study groups was performed using students unpaired t test. No significant difference was noted indicating that both treatment methods require similar duration for complete recovery.

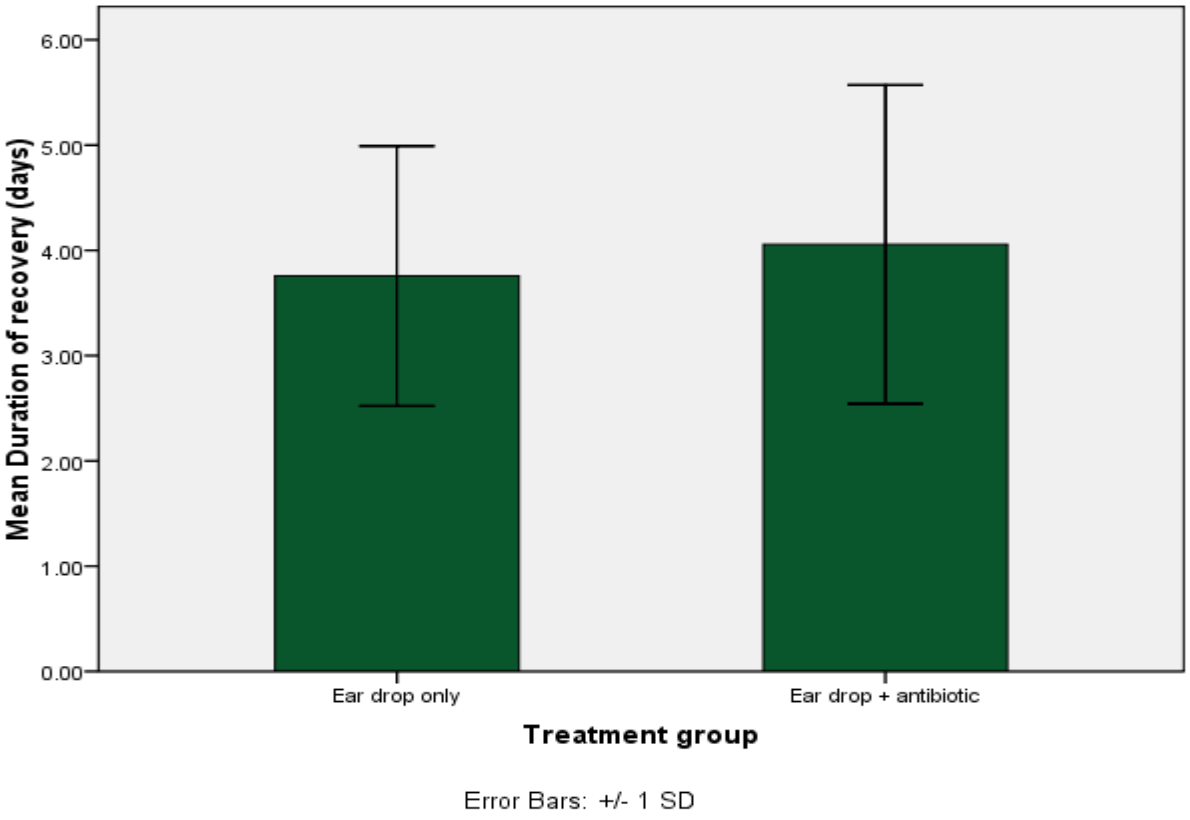


Table: Comparison analgesics used between study groups.

Group Statistics

	Treatment group	N	Mean	Std. Deviation	Std. Error Mean	t	P value
Analgesic	Ear drop only	37	4.9459	2.14665	.35291		
	Ear drop + antibiotic	35	5.0857	2.03458	.34391	-.284	.778

Comparison analgesics used between study groups was performed using students unpaired t test. No significant difference was noted indicating that both treatment methods require similar analgesia.

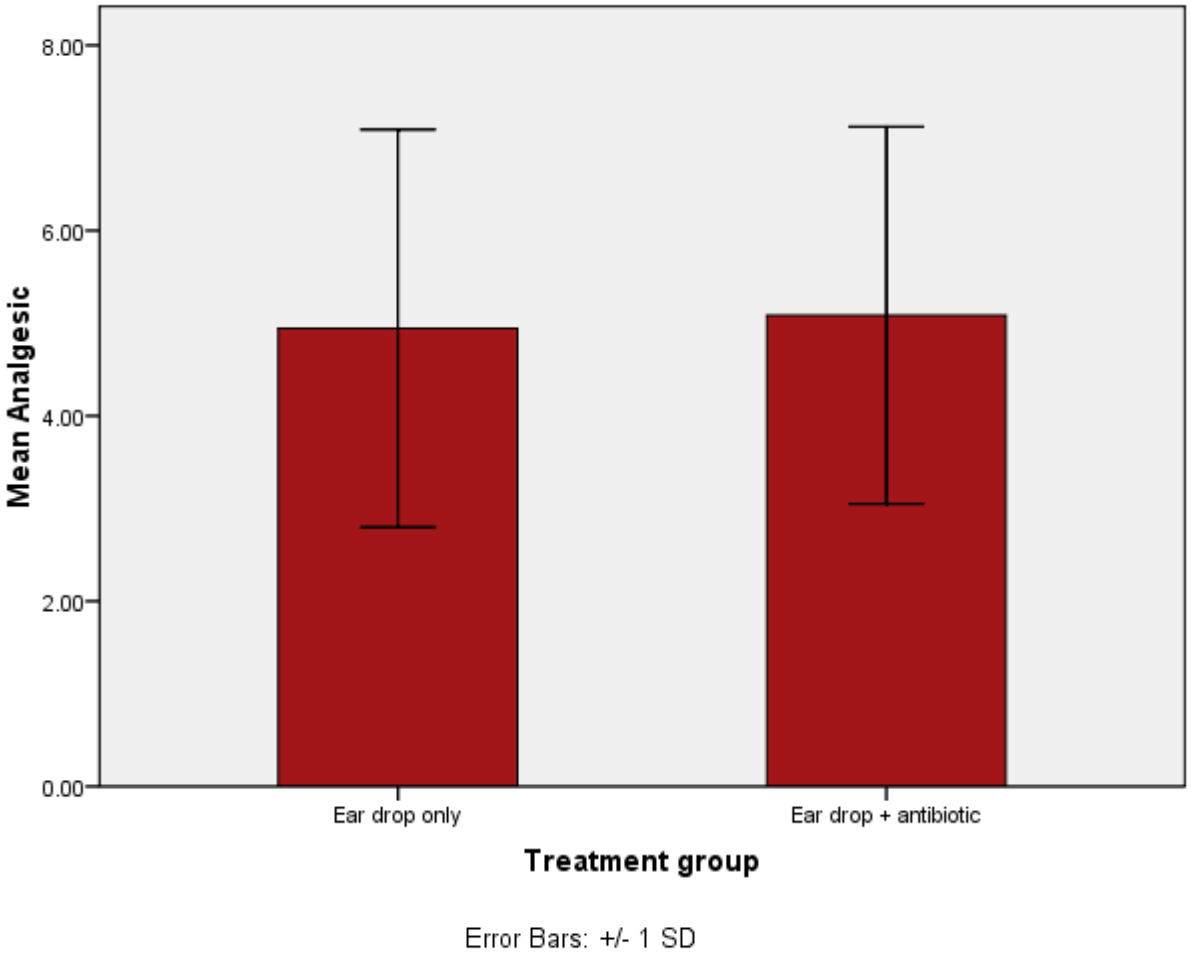
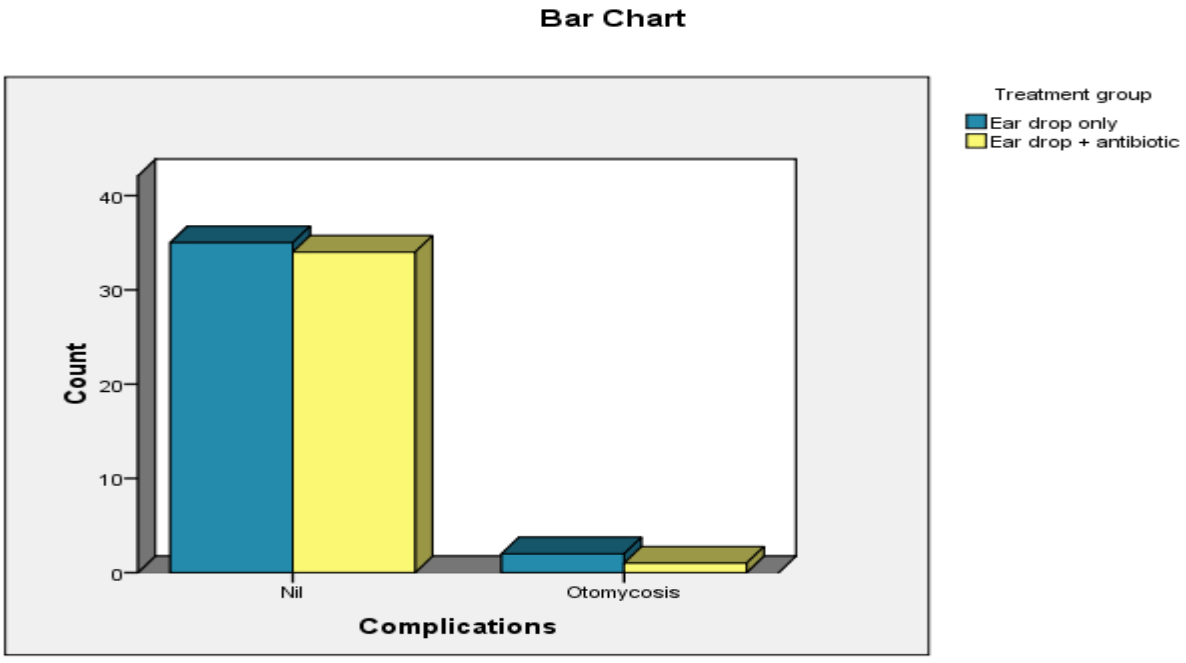


Table comparison of complications between study groups

			Treatment group			P value
			Ear drop only	Ear drop + antibiotic	Total	
Complications	Nil	Count	35	34	69	0.521
		% within Treatment group	94.6%	97.1%	95.8%	
	Otomycosis	Count	2	1	3	
		% within Treatment group	5.4%	2.9%	4.2%	
Total		Count	37	35	72	
		% within Treatment group	100.0%	100.0%	100.0%	

Comparison of complications between study groups was performed using Fischer's exact test. No significant difference was noted between two groups indicating no association of any treatment modality with complications.



Only 3 patients out of 72 treated had otomycosis.2 patients were from the local antibiotic group and 1 in the combination treatment group. There is no significant difference in development of otomycosis in both the groups.No other complications of AOE were noted in either treatment groups.

DISCUSSION

Otitis externa is a common condition, and most cases are treated by family physicians and general practitioners. The most common complaint is earache. Other symptoms, such as discharge, reduced hearing and itching occur less frequently. Although otitis externa is a common, there are different methods of treatment, ranging from aural toileting alone to a combination of local and systemic antibiotics. According to literature 40 percent of patients who received both topical and systemic medication which are not active against Staphylococcus aureus or Pseudomonas aeruginosa, which are the most common bacterial pathogens in otitis externa [22]

The prevalence of otitis externa varies from region to region with a yearly rate of four per 1,000 in the US, 10 per 1,000 in the UK, and 12 per 1,000 in Netherlands [21]. It is seen in all age groups and is five times more common in swimmers [25]. There were no studies conducted to determine the prevalence of the disease in India.

P. aeruginosa and *S. aureus has been* identified as the causative organism of AOE in literature. [77] *P. aeruginosa* was found in 46.5 per cent of patients, while *S. aureus* was found in 31.9 per cent. They were found concurrently in 8.4 per cent of cases, and again, this proves consistent with information published [77]. In many studies the same organism has also been identified among the normal flora of EAC. It points out to the fact that not only the presence of the organism in EAC causes AOE, other factors like continuity of the lining, humidity, pH and the presence of cerumen also decides the development of AOE.

The treatment of external ear infections can range from simple ear wax removal, use of acidified preparations, local antibiotic/ steroid drops, systemic antibiotics alone with or without drops, local ointment packing and icthamol glycerin wicks. Various studies has been conducted comparing their efficacy.[36,72] In India, the choice of first-line treatment depends on clinician preference and experience, financial considerations of the patient, and previous patient resistance to antibiotics. Most primary care clinicians will treat otitis externa without microbiology results as most will resolve with the regular treatments. It is difficult to determine which patients will be refractory to topical treatment. However, it seems logical that patients requiring assessment and management in the hospital setting should all have microbiology swabs obtained as these cases are at higher risk of complication and antibiotic resistance.

There are multiple international reviews on treatment of otitis externa, very little is published in India. The meta-analysis conducted worldwide [19, 25] propose only local antibiotics for the treatment of uncomplicated otitis externa. Many studies have been conducted comparing the efficacy of different preparations of ear drops. In the Cochrane review no specific combination was found superior to other, except for the delayed recovery in case of acetic acid treatment.

Pseudomonas and Staph.aureus being identified as the most common pathogenic organism for AOE, it is prudent to start the patient on antibiotic ear drops rather than any other drops like acetic acid or H_2O_2. The addition of steroid to the antibiotic ear drops has shown significant improvement in the recovery of the disease. [26]. In our study all the patients were given a baseline treatment of ciprofloxacin 0.2% in combination with dexamethasone (ciplox-D) ear drops. The control groups were also given oral ciprofloxacin 500 mg twice daily in addition to the local drops. As the concentration attained by the drug in EAC is much higher (100 times), when used locally it gives added benefit compared to systemic treatment. Regardless of the antibiotic sensitivity many a times the ear drops give betterment of the symptoms. [19].

Many studies have reviewed the use of oral antibiotics in AOE [11, 64, 74, 7] depicting the effectiveness of local antibiotic treatment. In AOE the factors which prompt us on starting systemic therapy should be those patients susceptible for progression to malignant otitis externa, or a combination of otitis media along with AOE. [19]Regardless of all these evidences, the common practice for treatment of AOE is usually a prescription of both local ear drops and oral antibiotics. This tendency may be because of the severity of the pain presented by the patient or the signs. An uncomplicated AOE has been put under trial for the efficacy of multiple modalities of treatment across the world with all the studies showing resolution with local treatment. There is a paucity of trials in this topic in India as mentioned earlier. In this era of rising antibiotic resistance, the systemic antibiotic should be used judiciously. As we know pseudomonas which is a common causative of AOE has the capability to develop resistance against many of the antibiotics, use of higher group of antibiotics should be reserved for other complicated conditions rather than AOE which can be controlled with topical medications.

The age group with the highest incidence of AOE includes 5 to 10 years. However, over half of the cases seen are in adults over 20 years of age, and a decline in incidence is apparent for those older than 50 years [79,80] The Baseline AOE severity and demographic characteristics was similar between the 2 treatment groups in our study. The

mean patient age was 37.5 and 41.4 years in the Group A and group B, respectively. But the sex ratio between the groups was not similar with 35.1% and 55.1% females in the A and B groups, respectively. The age group up to 18 and above 60 was excluded from this study, in view of potential immunocompromised status and ethical issues. So the demography of the diseases does not reflect the literature where there is an equal gender ratio [11].

Side of the infection in this study showed no difference in the side preponderance. In some studies [72] they have demonstrated an increase in number of right otitis externa compared to left, this has been substantiated by the theory that people tend to use ear buds and other material in the right ear than the left due to the right-handedness.[37].

Itching of EAC is the lowest in sequence in the spectrum of symptoms of AOE. Patients complain of itching only in the first few days. [68] Early AOE may include pruritus and erythema with scanty clear discharge. Itching of the EAC was not a significant finding during the episode of AOE in our study. But retrospectively in the history many of them gave a positive history of itching which then led to manipulation of the EAC. Persistence of itching in the EAC should prompt us the differential diagnosis of otomycosis in a setting of acute otitis externa resistant to treatment. In our subjects even though some of them had itching in EAC, on commencement of the treatment it was no more an issue to them. So we can consider this more as a discomfort in the ear perceived as itching by the patient, may be because of developing edema. Development of itching as a new symptom during the course of treatment should be considered as either allergic reaction to the local antibiotic or development of otomycosis.

The comparison of pain score in the groups showed no variation in the final outcome. On the 1st follow up both group patients had significant improvement. In the result of our study there was no significant difference in the mean pain score between the two treatment groups on the follow up visits. The analgesia given to the patients was oral paracetamol tablets on demand. The 2014 guideline by Rosenfeld et al has emphasized the requirement of adequate pain management in treatment of AOE. It has been recommended to use a regular dose of analgesic rather than on demand. This is to break or prevent the pain cycle. As in our study they have also emphasized on the ongoing assessment of the pain, for early detection of development of complications. Adding a topical steroid to topical antimicrobial drops has been shown to hasten pain relief in some randomized trials [61]. We used a combination of ciprofloxacin and dexamethasone local ear drops in both the treatment groups. Another randomized multicenter trial showed no differences in pain duration or

bacteriologic efficacy between topical ciprofloxacin/hydrocortisone (Cipro HC) and combination therapy with oral amoxicillin and topical neomycin/polymyxin b/hydrocortisone.[78]

Ear discharge is the second presenting complaint to the pain, in AOE, and many a time only a clinical finding. It gives little information about the course of the disease or the progress. In our study most of the patients had scanty ear discharge only. The color of the ear discharge may indicate the causative organism. Ideally in tertiary care setup it is advisable to take a smear of it and send for a culture and sensitivity, if we expect a delayed resolution, may it be because of the co morbidities or the history.

The ear canal should be cleared of inflammatory debris, obstructing cerumen, or any foreign object for effective treatment of AOE. There are no randomized studies of the use of aural toilet in AOE, but some investigators have proposed that aural toilet by itself (without antimicrobials) is therapeutic.[81] Aural toilet is performed by the clinician with a gentle lavage using body temperature water, saline solution, or hydrogen peroxide. Alternative methods of aural toilet include physically removing the obstructing debris with suction or dry mop Adequate visualization for suctioning may be facilitated by using a binocular otologic microscope. The drug delivery to EAC has to be assured by proper aural toilette and in case of edematous external auditory canal by placement of IG wick or otowick.

The skin that lines the membranous canal is thicker and more mobile, and it is endowed with sebaceous and apocrine (ceruminous) glands and hair follicles. Both sebaceous and apocrine ducts empty into a follicular canal that surrounds each hair follicle.[82,83] The bony portion of the canal is lined by thin, immobile skin that lacks hair and glands and is continuous with the epithelium of the tympanic membrane. The cartilaginous portion contains hair follicles and sebaceous and apocrine glands beneath a squamous epithelial surface layer.so when the EAC is infected and edema of the skin occurs it gives rise to severe pain. The increase in the edema of canal may lead to occlusion of EAC and temporary conductive hearing loss.[84]

Cerumen is found in the external portion of the canal and is a hydrophobic, slightly acidic (pH 6.0 to 6.5) substance formed by glandular secretions and sloughed epithelium. The ear canal possesses a unique self-cleansing mechanism. The sloughed keratinous layer of the TM migrates in a centrifugal fashion toward the annulus and subsequently to the cartilaginous canal, where it is combined with glandular secretions and extruded as cerumen.. A relatively acidic pH and hydrophobic

nature account for its bacteriostatic properties.[84] Fabricant [85] in 1957, was the first otolaryngologist who proposed AOE is related to a loss of acidity. However, he couldn't prove it. Martinez-Devesa et al. [6] showed a very close correlation between the severity grade of chronic otitis externa (COE) and the pH of the EAC. In a study conducted in New Delhi by Mittal et al [68]. It was observed that the pH of the normal EAC was acidic as compared to that of the body and it became more alkaline in acute otitis externa. It was also noted that the pH of EAC in AOE at presentation was highest in cases with otorrhea followed by cases with aural fullness and decreased hearing. Moreover, the pH of the EAC became relatively more alkaline when the number of symptoms at presentation increased. They could also establish that the treatment of the condition was associated with restoration of pH of EAC back to normalcy. In our study there was no assessment done on the pH of the EAC. The ear drop used (ciplox-D) is acidic with 4.3 pH.

A warm, moist environment favors bacterial growth, and is responsible for the increased incidence of acute otitis externa during summer months and in tropical regions. During the summer in temperate climates and particularly during the monsoon in India more cases of otitis externa are seen more often. There is an increase in the incidence of AOE in swimmers also. In our study it was noticed that more number of patients were collected during the summer, with a significantly less number in the other seasons. Many cases were outside the inclusion criteria, either because of the age or due to the co morbidities.

The no: of days taken for ear to get back to normal was the primary outcome measured and it showed no significant difference in the addition of oral antibiotic group over the only local ear drops treatment. The mean number of analgesics taken by the patients also did not vary in the groups. As the guidelines put forward by the AAO-HNS in 2014.treatment of an uncomplicated otitis externa should be local antibiotic drops after a thorough ear toilette. The patient are to be followed up for reassessment and modification of the treatment if required.

Efficacy of topical therapy can be summarized using meta-analysis of randomized controlled trials and review to articles [11] [25] *[26]* Although these 3 meta-analyses differ in study design, trial selection, and methods of statistical pooling, they all concluded that topical therapy is highly effective first-line therapy for diffuse AOE. They did not find any meaningful differences in clinical outcomes on different permutations of the drug chosen. There is a paucity of studies on treatment of acute otitis externa from India. Being a very populated country and AOE as a common disease in warmer climate, the prevalence of disease may vary from the existing international data. In one study they have quoted the relation of pH with AOE [68] and a few studies has been on the causative organism of AOE.

Topical preparations are recommended as initial therapy for diffuse, uncomplicated AOE because of safety, efficacy over placebo in randomized trials, and excellent clinical and bacteriologic outcomes in comparative studies. The recent Cochrane review affirms this recommendation and states, "Topical treatments alone, as distinct from systemic ones, are effective for uncomplicated AOE." [19]

Rosenfeld and colleagues [11] found no significant differences in clinical outcomes of AOE for antiseptic versus antimicrobial, quinolone antibiotic versus nonquinolone antibiotic or steroid-antimicrobial versus antimicrobial alone. Regardless of topical agent used, about majority of patients had clinical resolution within 7 to 10 days. It shows that AOE is essentially a self limiting condition which requires proper analgesia and strict follow-up only. But having in mind the microbial flora responsible for AOE, it won't be justified not to add an antibiotic ear drops for the treatment. Kaushik and coworkers [25] also reached the same conclusion in their Cochrane review. In contrast, M̨sges and colleagues [26] found superior clinical cure rates for topical quinolone over other antibiotic-steroid combination drugs Two meta-analyses have compared a quinolone drop versus neomycin–polymyxin B–hydrocortisone drop for diffuse AOE, with no significant difference in adverse events individually or when combined.[11,25]

The lack of differences in efficacy among most topical antimicrobial and steroid preparations suggests that patient preference and clinician experience are important aspects in selecting therapy. The most common problems on topical therapy *are* pruritus and site reaction, rash, discomfort, otalgia, dizziness, vertigo, superinfection, and *rarely* reduced hearing. None of the randomized trials reported otomycosis after topical antibiotics, although otomycosis has been described anecdotally following topical ofloxacin therapy for AOE.[87] Contact dermatitis is a potential sequel of topical antimicrobial or steroid therapy but is rare after a single course of therapy for diffuse AOE.

The optimal duration of therapy has not been determined and varies from a few days up to several weeks. Recent trials recommend 7 to 10 days of topical therapy. Three randomized trials have compared topical antimicrobial versus placebo for treating diffuse AOE.[88,89,90].Another trial reported significantly less edema and itching 3 days after initiating therapy and less edema, itching, redness, scaling, and weeping 7 days after initiating therapy.

There are no data on the efficacy of systemic therapy using appropriate antibacterials and stratified by severity of the infection. Moreover, orally administered antibiotics have significant adverse effects that include rashes, vomiting, diarrhea, allergic

reactions, altered nasopharyngeal flora, and development of bacterial resistance.[10,91,92,93]. Community consequences include direct transmission of resistant bacterial pathogens in homes and child care centers. Despite the well demonstrated safety and efficacy of topical preparations for treating AOE, about 20% to 40% of subjects with AOE nonetheless receive oral antibiotics, often in addition to topical antimicrobials.[94]. In our study there was no statistically significant improvement of the disease due to addition of oral antibiotics. In practice most of the oral antibiotics selected are inactive against *P aeruginosa* and *S aureus*, the most common pathogen of AOE. Further, treatment with penicillins, macrolides, or cephalosporins increases disease persistence and treatment with cephalosporins also increases recurrence.[95]. In a study where patients were randomized to topical ointment plus oral antibiotic (trimethoprim-sulfamethoxazole) versus topical ointment plus placebo, there was no significant difference in cure rates at 2 to 4 days [91] which is similar to our results.

An argument against the use of oral antibiotics for diffuse AOE limited to the ear canal is the efficacy of topical treatments that do not include antibiotics. Effective topical treatments include acetic acid, boric acid, aluminum acetate, silver nitrate and an endogenous antiseptic N-chlorotaurine. Topical steroids are also effective as a single agent or in combination with acetic acid or an antifungal preparation. Considering the success of these nonantibiotic therapies, it is likely that for cases of uncomplicated AOE, oral antibiotics, particularly those with no activity against *P aeruginosa* or *S aureus*, are unnecessary. [19]

The advantage of topical therapy is the very high concentration of antimicrobial that can be delivered to infected tissue, often 100 to 1000 times higher than can be achieved with systemic therapy. For example, a 0.2% solution of antibiotic each dose of 3 to 5 drops contains about 0.5 to 1.5 mg of antibiotic. Topical therapy also helps in avoiding prolonged exposure of bacteria to sub therapeutic concentrations of antibiotic and may it is less likely than systemic therapy to result in selective pressure for resistant organisms.[1] . Avoiding antibiotic exposure of host bacteria resident outside the ear canal provides a further advantage to reducing the selection of resistant microorganisms. Restrictive use of oral antibiotics for AOE is important because of increasing resistance among common pathogens, especially *S aureus* and *P aeruginosa*.

As per the latest recommendation of AAO-HNS the initial topical therapy applies to the otherwise healthy patient with diffuse AOE that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection. Topical therapy should be supplemented by systemic antibiotics if the affected individual has a condition, especially

diabetes, that is associated with markedly increased morbidity, or HIV infection/AIDS with immune deficiency, that could impair host defenses; if the infection has spread beyond the confines of the ear canal into the pinna, skin of the neck or face, or into deeper tissues such as occurs with malignant external otitis; or if there is good reason to believe that topical therapy cannot be delivered effectively [19] Systemic antibiotics, if indicated, should include coverage for common AOE pathogens, including *P aeruginosa* and *S aureus.*

The number of analgesics taken by the patient is an indirect indicator of the symptomatic relief of the disease. It was 4.9 numbers in the local antibiotic group and 5.1 in the combination treatment group, with a p value of 0.778, showing no statistical significance. The no: of analgesics were compared as a treatment outcome in one other study which showed similar outcome. As the 2014 guidelines [19] the prescription of analgesic should be to prevent the pain rather than a PRN prescription. This will prevent the pain cycle. Mild to moderate pain usually responds to acetaminophen or non steroidal anti-inflammatory drugs given alone or in fixed combination. Administering a non steroidal anti-inflammatory drug during the acute phase of diffuse AOE significantly reduces pain compared with placebo.[96] Local analgesic ear drops is not recommended for analgesia in AOE. It can mask the development of complications and has not found to be superior to any other treatment. There is no specific indication for using topical anesthetic drops in treating AOE, and using them may mask progression of underlying disease while pain is being suppressed. If a topical anesthetic drop is prescribed for temporary pain relief, the patient should be re-examined within 48 hours to ensure that AOE has responded appropriately to primary therapy.

The development of complication or progression to a malignant otitis externa is very rare in a primary uncomplicated case of AOE, especially if the patient doesn't have any co morbidities. In our study only 3 patients, 2 in the local antibiotic only group and 1 in the combination treatment group developed otomycosis. Otomycosis per se is not a complication of AOE; rather it can be a coexisting condition or a side effect of antibiotic exposure. There are no other studies where they could substantiate this finding. Other complications of otitis externa is documented nowhere is any other studies or literature following a simple AOE.

In our study the p value showed no significant difference between any of the outcomes in the disease between the two treatment groups. Therefore the chances of rejecting the null hypothesis are low, which means both the treatment groups are equivalent in its

outcome. There is no benefit on addition of oral antibiotic in treatment of acute otitis externa. Moreover the patient need not be exposed to a systemic therapy if it is equally curable by topical therapy.

This study is restricted in some aspects, namely the pediatric age group were not included. The time span in which the study conducted in a single tertiary hospital should have been more or a multicentre study involving more primary care setups. As AOE usually presents to the primary care most of the time and the treatment are curative. So they don't attend a tertiary care as often as the primary setup. As the hospital where our study was conducted is a multispeciatity hospital, it may not be reflecting the actual percentage of disease prevalence and distribution. Moreover most of the patient attending our clinic with AOE had the exclusion criteria, indicating that the study group should have included some of them, say non complicated diabetics etc. More studies on otitis externa have to be done and awareness about the effectiveness of local antibiotic for the cure of AOE should be done among the primary care physicians and in otolaryngologist. By avoiding unwanted use of antibiotics we can join our hands for the next generation to inherit the range of antibiotic sensitivity.

LIMITATIONS

- The number of subject was very limited. Even though the prevalence of the disease is expected to be 1%.being a tertiary level hospital and AOE being a disease presented to primary care doctor the proportion of AOE presenting to our study setup is significantly lesser than the actual prevalence of the disease.
- As the diabetics and the pediatric population are major percentage of AOE patients, they were not included in our study.
- This study did not evaluate the recurrence of the disease.
- The sex ratio in each groups were not similar.

RECOMMENDATIONS

- The treatment of uncomplicated AOE without any other co morbidities should be local antibiotic ear drops along with steroid drops.
- The use of systemic antibiotics should be restricted to patients with immunocompromised status or suspecting complication.

- The study comparing the efficacy of these two treatment groups has to be done as a multicentric trial in more primary care setup.
- The treatment guideline for acute otitis externa has to be more popularized among the primary care physicians and the otolaryngologist.
- Once the treatment has been started, improvement is expected in 48 hours with complete resolution within 7 days. Any prolongation or increase in the symptom during the course of treatment should prompt us on looking beyond AOE, as it will resolve in this prescribed time.

SUMMARY:

This was a prospective, non blinded randomized, comparative study conducted by Dr. Farha AV on treatment of acute otitis externa comparing local ear drops alone vs. a combination of local with oral antibiotic for acute otitis externa on a total of 73 patients coming to ENT OPD, Manipal hospital, Bangalore under the guidance of DR.SHALINA RAY. The period of study was December 2015 to April 2017.

AIM OF THE STUDY

1. To assess the time taken for the ear to get back to normal and symptomatic relief with local antibiotics vs. a combination therapy of local antibiotic and oral antibiotic
2. To evaluate if oral antibiotic offers any additional benefit in treatment of acute otitis externa, over local drops alone.

OBJECTIVES OF THE STUDY

1) To compare the duration of recovery from the symptoms in treatment of acute otitis externa between local antibiotic alone against local and oral antibiotic.

2) To investigate if treatment with only local ear drops gives similar result as combination therapy of local and oral antibiotic.

3) To compare course of events during both treatment category.

4) To assess any development of complications during the course of treatment

MATERIALS AND METHODS:

- A time bound non blinded prospective, randomized comparative study design was conducted on 73 patients diagnosed to have acute otitis externa. Patient aged between 18-60 years with complaints of ear ache and/or ear discharge for the last 48 hours was enrolled in the study unless they met the exclusion criteria.
- After approval of institutional ethical committee, data was collected over 26 months from Dec'15 to March'17.
- Patient's details were incorporated on basis of the proforma thereby including history, clinical examination.
- Data was expressed as percentage and mean ± S.D. Kolmogorove-Smirnove analysis was performed for checking linearity of the data. Fischer's exact test or Chi square test was used to analyze the significance of difference between frequency distribution of the data. Student's unpaired t test was used to assess the significance of difference between two study groups for various parameters. P value <0.05 was considered as statistically significant.

OBSERVATION AND RESULTS:

- A total of 72 patients were studied, 20 patients were between 18 to 30years of age. 21 patients from 30 to 40 years. 15 patients in the 41-50 years group and 16 in the age group of 51 to 60 years.
- Out of 72 subjects studied, 31 patients were females and 41 were male. There was a significant predominance of males for the otitis externa in this study. The stratified sex distribution shows predominance in males in the mid-age groups, i.e.30 to 50 years
- In the ear drop only treatment group, left ear was affected for 16 patients and right in 21 patients. In the combination treatment group 19 patients had left ear disease and 16 had right ear affected. Comparison of distribution of side of ears in study groups was performed using Chi-square test. Both groups were found to be matched for distribution of side of ears. Left side and right side had a similar incidence in this study with a p value of 0.24
- Comparison of pain scores on follow-up between two groups were carried out using student's unpaired t test. No significant difference was detected between pain scores

of two groups at day 1 and day 3 and day 7. Pain score reached 0 in both groups at day 14.

- Itching of EAC was found in 15 out of the 72 subjects. Regardless of the treatment started, none of them complained of itching on follow ups
- Ear discharge was noted to be copious only in 2 patients in the study group. 27 out of 37 patients in group A: local antibiotic group had only scanty ear discharge, which on subsequent follow up was cleared. Nine patients had moderate amount of discharge in same group. 28 patient from treatment group B; combination treatment had presented with scanty ear discharge, which subsequently cleared up with treatment. 5 patients in same had moderate amount of discharge. Regardless of the treatment and the amount of the discharge, it seemed to reduce on commencement of treatment.
- EAC edema was seen in all of the patients with varying degrees. Both treatments showed statistically similar pattern of recovery.
- Comparison of duration of recovery between study groups was performed using students unpaired t test. No significant difference was noted indicating that both treatment methods require similar duration for complete recovery.
- Comparison of analgesics used between study groups was performed using students unpaired t test. No significant difference was noted indicating that both treatment methods require similar analgesia. This was taken as an indirect indicator of efficacy of treatment.
- Only 3 patients out of 72 treated had otomycosis.2 patients were from the local antibiotic group and 1 in the combination treatment group. There is no significant difference in development of otomycosis in both the groups.
- No other complications were noted in either of the groups during the study.

CONCLUSIONS

Otitis externa is a much localized ear disease, caused by mainly pseudomonas aeruginosa. In this study where we compared the clinical outcome of two method of treatments comparing only local ciprofloxacin with dexamethasone ear drops against a combination of same ear drops along with oral ciprofloxacin. The results were showing no significant difference in the outcome in terms of time taken for recovery and improvement in symptoms. We noticed that the patients in both the study groups recovered by 5 days from

start of treatment. Only two patients developed complication of treatment. The mean numbers of analgesics taken by the patients were also similar in both groups. On statistical analysis we could not prove superiority of one group over the other. So both the treatments have equivalent outcome. Therefore addition of a systemic antibiotic can be avoided without any reduction in the quality of care. Topical antibiotic and steroid drops alone is as effective as a combination of local and oral antibiotic.

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ANNEXURE A

STUDY PROFORMA

Randomized control trial of treatment of acute diffuse otitis externa with local antibiotic ear drops with and without oral antibiotics

NAME:

AGE: --------- YRS

SEX: MALE FEMALE

HOSP NO

CONTACT NO:

PRESENTING COMPLAINTS:

Ear pain

YES NO

Ear discharge:

Side: duration:

History of trauma YES NO

Duration: pain score: 1-2-3-4-5-6-7-8-9-10

Itching : present /absent

Past history: yes / no

TREATMENT GIVEN:

Local antibiotic: Ciplox-D YES NO

Oral antibiotic: Quinolones YES NO

	At diagnosis (day1)	1st follow up(day 3)	2nd follow up(day7)	3rd follow up(day14)
Pain score (0-10)				
Itching (0-1)				
Eac edema (0-4)				
Ear discharge (nil,scanty,moderate,copious)				
Number of analgesics taken				
Total number of days				
Complications (if any)				

Patient information sheet

Study title: Randomized control trial of treatment of acute diffuse otitis externa with local antibiotic ear drops with and without oral antibiotics

Purpose, background and reason of study

I am approaching you on behalf of Dr. SHALINA RAY, under whose guidance I, Dr. Farha .A.V, DNB resident in ENT, Manipal Hospital is doing a study: Randomized control trial of treatment of acute diffuse otitis externa with local antibiotic ear drops with and without oral antibiotics

Otitis externa is a common disease which affects the outer part of the ear. It is more commonly seen in swimmers and those who use ear buds. This condition tends to be more during humid seasons. Otitis externa is usually treated in two different ways-only with local ear drops and with oral medicines.

I am going to give you information and invite you to be a part of this research. There may be words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

PROCEDURE

This facility is being offered to all patients who attend ENT OPD at Manipal Hospital, Bangalore, and diagnosed with otitis externa which come under the inclusion criterias.You will be put on to one of the two groups-group A: only with local ear drops, group B: ear drops and oral antibiotic. We'll request you to come for regular follow up 3 days post treatment and weekly till you are symptomatically better. The patients are put into each group alternatively according to the serial number.

You will be asked to provide your personal details. And you will be requested to give your feedback on each visit how your symptoms are we will be filling a simple form with all your symptoms and the findings we notice. The standards of care u receive won't change.if any increase in pain or swelling of the affected ear please do report immidiatly back us.

RISKS AND BENEFITS

Risks

There are no risks involved. Similar studies comparing local ear drops vs oral antibiotics has been conducted in other countries, with a result of local antibiotic ear drop as the standard of care.

Benefits

The benefit of this study is to measure the necessity of oral antibiotics in treatment of otitis externa. In this era of rising antibiotic resistance, thus study will help us to guide the requirement of systemic treatment in otitis externa. Unwanted exposure to the systemic antibiotic also can be avoided.

VOLUNTARY PARTICIPATION

Your participation in this research is entirely voluntary. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this clinic/hospital. You may change your mind later and stop participating even if you agreed earlier.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the hospital. Details regarding your treatment and follow up will not be recorded for study purpose.

PRIVACY, CONFIDENTIALITY AND DISCLOSURE OF INFORMATION

Confidentiality

Complete confidentiality will be maintained in all steps during the study.your personal dat or your treatment dat wont be shared with anybody.

In case of any queries ,feedback kindly get back to us.

Old airport road, Bangalore

CONTACT DETAILS

WHOM TO CONTACT

1)Investigator:

Dr. FARHA A V

DNB Trainee

Dept of Otolaryngology

Manipal hospital,

2)Guide:

Dr SHALINA RAY

Senior consultant

Manipal hospital

Old airport road ,Bangalore

Ph: 9741127651

3)Ethical committee:

Dr. Vishwanath Siddini

Member Secretary

Ethics Committee of Manipal Hospital

Bangalore – 17

Contact No. 9845174866

ANNEXURE B

SUBJECT INFORMED CONSENT FORM

STUDY TITLE : Randomized control trial of treatment of acute diffuse otitis externa with local antibiotic ear drops with and without oral antibiotics

SUBJECTS'S HOSPITAL NO:_____

SUBJECT'S NAME:_____

DATE OF BIRTH / AGE: _____

		SUBJECT INITIAL BOX
1	The content of the above consent form and the procedure has been explained to me in a language _____ known to me and I have understood the same.	
2	I understood that my participation in the study is voluntary and that I am free to withdraw any time, without my medical care or legal rights being affected.	
3	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	
4	I agree to take part in the above study	
5	I have received a copy of the signed and dated informed Consent Form.	

Informed Consent Signatures

Subject's Signature _____ Date / Time _____

Or Thumb impression. (Person signing to complete)

Printed name of subject _____

(Person Signing to complete)

Signature of _____ Date / Time _____

The Investigator (Person signing to complete)

Printed name of Investigator _____

(Person signing to complete)

Witness signature

ANNEXURE C

MASTER CHART.

ANNEXURE D

Random number table

1. BOTH_____
2. BOTH_____
3. DROPS_____
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73. BOTH_____

74. DROPS_____

75. DROPS_____

76 subjects randomized into blocks of 4 4 2 6 4 4 4 4 2 8 2 6 6 8 4 2 6

To reproduce this plan, use the seed 22201 along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels as entered originally.

Randomization plan created on 6//2015, 6:18:52 PM

The randomization scheme was generated by using the Web site Randomization.com (http://www.randomization.com).

Randomization.com. [http://www.randomization.com/]

ANNEXURE E

SCIENTIFIC COMMITTEE APPROVAL

ANNEXURE F

ETHICAL COMMITTEE APPROVAL