

## Role of Topical Application of Fosfomycin in Treatment of Chronic Suppurative Otitis Media

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### ABSTRACT

**Objective:** To find out the efficacy of topical application of 3% Fosfomycin in cases of Chronic Suppurative Otitis Media (CSOM).

**Methods:** This prospective study was conducted from January 2016 to December 2017 in the Department of ENT, Head & Neck Surgery, Dow University of Health Sciences & Dr. Ruth K.M. Pfau Civil Hospital Karachi, Pakistan. All patients had clinical diagnosis of CSOM. Fosfomycin 3% was given topical treatment in ear drop three times daily for one week. Amount given in each dose was 2 drops or 0.1 ml. A complete audiological assessment was conducted by an audiologist at day 7 and outcome of the treatment was noted as resolved (complete dry ear), Improved, Not-changed or Worsened.

**Results:** Out of 172 patients, 65 (37.8%) had pseudomonas Aeroginosa, 49 (28.5%) had Staphylococcus Aureus, 37 (21.5%) had Proteus Mirabilis, 6 (3.5%) had E Coli, 6 (3.5%) had Klebsiella Pneumoniae, 4 (2.3%) had Enterobacter species whereas 5 (2.9%) patients had miscellaneous organisms on culture of ear swab. The mean duration of discharge was  $7.23 \pm 5.78$  years. The outcome showed that majority of the patients 144 (83.7%) had completely dry ear after one week of treatment with 3% fosfomycin. Other 17 patients (9.9%) had improvement with decrease in amount of ear discharge. Nine patients (5.2%) had no change in ear discharge and in 2 cases (1.2%) amount of ear discharge increased.

**Conclusion:** The finding of this study depicted that topical application of 3% fosfomycin can be very beneficial in cases of CSOM. Overall response to treatment was good and no ototoxicity was noted.

**Key words:** Topical fosfomycin, Ear drops, Chronic suppurative otitis media.

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### INTRODUCTION

Chronic suppurative otitis media (CSOM) is an inflammatory condition of middle ear characterized by chronic ear discharge.<sup>1</sup> There

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is abnormality of pars tensa or pars flaccid. A permanent perforation is present in pars tensa while retraction pocket is usually seen in pars flaccid; it can be with or without cholesteatoma.<sup>2</sup> Disease with presence of cholesteatoma is called squamous disease while disease due to repeated infections of middle ear due to presence of perforation in pars tensa is called mucosal Disease.<sup>3</sup> The condition is called active when discharge is present and inactive when discharge is absent. Discharge in mucosal type of disease appears usually with entry of water in ear or with upper respiratory tract infection.<sup>4</sup>

Many topical preparations are available for treatment of ear discharge. Due to changing spectrums of resistance, many drugs now have reduced or no efficacy.<sup>5</sup> This demands change of prescription practice. This study was intended to evaluate role of fosfomycin in treatment of ear discharge due to CSOM. Fosfomycin was introduced in 1969. Mechanism of action involves the inhibition of UDP-N-acetylglucosamine enolpyruvyl transferase (MurA); an enzyme that catalyses the first step in bacterial cell-wall synthesis.<sup>6,7</sup> It has broad spectrum activity against several Gram-negative and Gram-positive aerobic bacteria.<sup>8</sup> Its most common clinical use over decades has been in treatment of uncomplicated urinary tract infections.<sup>9</sup> Use of oral and intravenous fosfomycin in treatment of ear discharge has been described in literature.<sup>10</sup> Use and safety of fosfomycin ear drops in animals showed no significant ototoxicities.<sup>11</sup> While other studies showed good results for the use of fosfomycin ear drops in humans.<sup>12</sup> Commercial preparation of fosfomycin ear drops with name of "Fosmicin-S Otic 3%" is available in Japan, Indonesia, Thailand and Vietnam.<sup>13</sup> No local study is found related to the use of these ear drops. The aim of this study was to evaluate effectiveness of fosfomycin ear drops in our local population for treatment of CSOM as injudicious use of many over the counter ear drops and growing resistance in bacteria has rendered many topical antibiotics ineffective for treatment of CSOM.

## METHODS

A prospective study was conducted in the department of Ear, Nose and Throats Dr. Ruth K. M. Pfau Civil Hospital Karachi, Pakistan. Study was done from January 2016 to December 2017. A total of 172 patients were included in this study through convenience sampling technique. All the patients presenting to OPD with chronic suppurative otitis media with clinical diagnosis of chronic suppurative otitis media, ear discharge for at least 6 months, who had not received any

topical or systemic antibiotic treatment for at least 1 month were included in this study. While patients with sensorineural hearing loss, with vertigo or positive fistula sign were not included. Moreover, patients with syndromic conditions, with craniofacial abnormalities and chronic medical conditions were also excluded from this study.

Patients from all age groups and genders were included. Written informed consent was obtained from all patients participating in this study. Demographic data and personal information's were recorded on purpose made performa. Results of ear swabs sensitivity and baseline pure tone audiometry was also recorded.

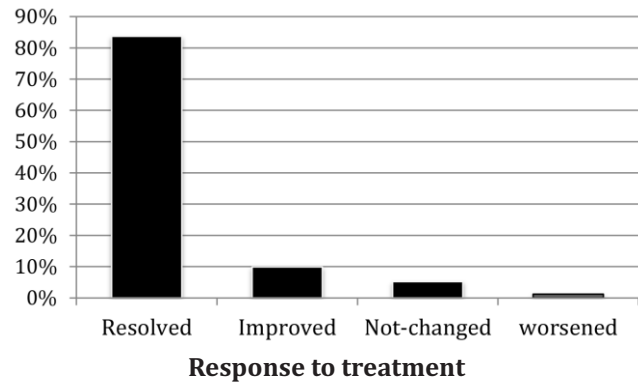
All the patients selected for this study had suction cleaning of ear done before start of therapy. Topical preparation of Fosfomycin was instilled in ear three times daily for one week. Amount given in each dose was 2 drops or 0.1 ml. Water precautions were advised and patients were called for follow up after one week. All patients had complete audiological assessment suited to their age and intellect by an audiologist at day 7. It was done to confirm hearing status of patient and monitor ototoxicity. Cases were followed up to 2 months. Response to treatment was categorized in four groups based on the clinical outcomes. Group 1 was labelled "Resolved"; it included patients with clinical outcome of cessation of ear discharge rendering ear dry. Group 2 was labelled "Improved"; it included patients with significant reduction of ear discharge with treatment as compared to amount of discharge at day 1 of presentation. Group 3 was labelled "Not-changed"; it included patients with no clinical sign of improvement or reduction of ear discharge after treatment. Group 4 was labelled "Worsened"; it included patients with increase in amount of ear discharge or clinically worsening of ear symptoms. All responses were judged by a single clinician to avoid inter-observation bias. Statistical Package for Social Sciences (SPSS) version 20 was used for statistical evaluation and results were expressed in percentages.

## RESULTS

Out of 172 patients, we had slight predominance of females 94 (54.7%) compared to males 78 (45.3%). Most common age group to be affected by CSOM was  $\leq 10$  years of age (n=61, 35.5%) followed by 11-20 years of age (n=49, 28.5%). (Table 1)

The mean duration of discharge was 7.23  $\pm$  5.78 years. The majority of the patients 107 (62.2%) were presented with  $\leq 7$  years of duration of discharge while 65 (37.8%) with  $>7$  years of duration of discharge. (Table 1)

Organisms on ear swab has showed that Pseudomonas Aeruginosa was observed in majority 65 (37.8%) patients followed by Staphylococcus Aureus 49 (28.5%), Proteus Mirabilis 37 (21.5%), E Coli 6 (3.5%), Klebsiella Pneumoniae 6 (3.5%), Enterobacter species 4 (2.3%) while 5 (2.9%) patients were presented with miscellaneous organisms on culture of ear swab. (Table 1)



**Figure 1: Results of treatment with 3% fosfo-mycin topical**

Response to treatment showed that "Resolved" had greatest proportion with 144 (83.7%) of patients coming back with cessation of ear discharge. These patients also reported symptomatic improvement after therapy. Seventeen patients (9.9%) fell in second group that was labelled "Improved" where as 9 (5.23%) and 2 (1.16%) patients fell in "Not-changed" and "worsened" respectively. (Fig: 1)

**Table 1: Comparison of response of treatment with baseline characteristics of the Patient (n=172)**

	Total	Resolved (n=144)	Improved (n=17)	Not Changed (n=9)	Worsened (n=2)
<b>Age, years</b>					
$\leq 10$	61	49 (34.0)	5 (29.4)	6 (66.7)	1 (50)
11-20	49	40 (27.8)	7 (41.2)	2 (22.2)	0 (0)
21-30	33	28 (19.4)	4 (23.5)	0 (0)	1 (50)
$>30$	29	27 (18.8)	1 (5.9)	1 (11.1)	0 (0)
<b>Gender</b>					
Male	78	66 (45.8)	8 (47.1)	3 (33.3)	1 (50)
Female	94	78 (54.2)	9 (52.9)	6 (66.7)	1 (50)
<b>Duration of ear discharge, years</b>					
$\leq 7$	107	86 (59.7)	13 (76.5)	7 (77.8)	1 (50)
$>7$	65	58 (40.3)	4 (23.5)	2 (22.2)	1 (50)
<b>Organisms on ear swab</b>					
Pseudomonas Aeruginosa	65	55 (38.2)	6 (35.3)	3 (33.3)	1 (50)
S. Aureus	49	43 (29.9)	3 (17.6)	3 (33.3)	0 (0)
Proteus Mirabilis	37	31 (21.5)	5 (29.4)	1 (11.1)	0 (0)
E Coli	6	5 (3.5)	0 (0)	0 (0)	1 (50)
Klebsiella Pneumoniae	6	3 (2.1)	2 (11.8)	1 (11.1)	0 (0)
Enterobacter	4	4 (2.8)	0 (0)	0 (0)	0 (0)
Others	5	3 (2.1)	1 (5.9)	1 (11.1)	0 (0)

All data presented as number (%)

## DISCUSSION

CSOM represents one of the major health burden in developing countries like Pakistan.<sup>14</sup> If left untreated it can lead to dire complications.<sup>15</sup> In our study most common age group to be affected was up to 10 years of age followed by 11 to 20 years. This is in parallel with other studies done in our region as well as other under developed countries such as Uganda and Ethiopia.<sup>16</sup> This indicates major load of this disease falls upon young populations.

One of the previous studies describes *Pseudomonas Aeruginosa* as the most common pathogen isolated by the ear swabs in cases of CSOM.<sup>17</sup> Commonality of this pathogen as most frequent has been observed by other researchers in Pakistan, India and Singapore.<sup>18-20</sup> Ciprofloxacin ear drops are commonly prescribed for treatment of CSOM. In last decade, ciprofloxacin resistant strains of *Pseudomonas* have emerged.<sup>21</sup> It was found in the study that Ciprofloxacin is now only sensitive in 63% of the cases caused by *Pseudomonas* and only 50% sensitive in cases caused by *Staphylococcus aureus*.<sup>22</sup> Good sensitivity to Gentamicin is being reported but its ototoxicity has limited its use.<sup>23</sup> Intravenous antibiotics such as Piperacillin/tazobactam and Imipenem, are also being used increasingly for resistant cases.<sup>24</sup> High cost of this treatment is a major hurdle.

Fosfomycin has been around for nearly past 5 decades<sup>6</sup>. It was found to be effective in treatment of gram-negative bacteria. It has not been widely used for cases of CSOM.<sup>25</sup> Many researchers have used fosfomycin ear drops in animal models. One particular study of note was done which shows no significant ototoxicity in albino guinea pigs with application of 3% solution of fosfomycin.<sup>11</sup>

Formulation of 3% Fosfomycin solution and its brand Fosmicin-S Otic is available for sale in Japan and Vietnam.<sup>13</sup> In our study we have found that application of 3% Fosfomycin solution was helpful in controlling the discharge in 83.7% of the cases while 9.9% of the cases were reported as improved. No

hearing impairment was found with audiological follow up during and after study. This denotes that Fosfomycin can very well serve as a good inclusion in current otologic practices of management of ear discharge. Feasibility of its topical application with good results and limited or none ototoxicity makes it a good drug for treatment. Larger studies are needed in this regard to better appreciate its role and to establish newer prescribing guidelines.

## CONCLUSION

With changing spectra of bacteria and growing resistance, role of fosfomycin needs to be explored in greater depths. Fosfomycin provides a very good alternative to traditional treatment regimens. It can be employed in chronically discharging ear that is not responding to other topical medications before moving to systemic antibiotics. More studies are needed to better understand the role of fosfomycin in the treatment of CSOM and to establish or eliminate concerns regarding its safety in topical ear drops.

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