Comparison of Ofloxacin Otic Solution with Oral Amoxycillin Plus Chloramphenicol Ear Drop in Treatment of Chronic Suppurative Otitis Media with Acute Exacerbation

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Abstract

The efficacy and safety of 0.3 per cent Ofloxacin otic solution (OFLX) 6 drops twice daily was compared with those of oral Amoxycillin 500 mg three times daily plus 1 per cent Chloramphenicol ear drop at 3 drops three times daily (AMOX+CRP) in a two-week treatment of chronic suppurative otitis media (CSOM) with acute exacerbation. 80 adult patients were enrolled in a prospective, randomized, investigator-blind study at the outpatient ENT service of Chulalongkorn University Hospital.

The most common pathogens isolated at the pretreatment visit were Staphylococcus aureus (30.3%) and Pseudomonas aeruginosa (24.7%). The susceptibility of all the pathogenic isolates to ofloxacin, amoxycillin and chloramphenicol were 96.4, 57.1 and 51.8 per cent respectively.

The overall response expressed as an improvement or cure of otalgia, otorrhea and middle ear mucosal inflammation was recorded. It revealed that the improvement rate of the OFLX-treated patients was better than that of AMOX+CRP-treated, but was not statistically significant. However, the cure rate was significantly better in OFLX-treated than in AMOX+CRP-treated groups in terms of painless ($p=0.05$) and dry ($p<0.001$) ears.

Ototoxicity was assessed by an elevation in bone conduction threshold (BC) and/or speech reception threshold (SRT) of greater than 5 dB or a presence of high tone hearing loss resulting from treatments.

A significant decrease in BC and SRT was revealed in OFLX-treated ears ($p<0.0001$; $p=0.002$ respectively) but a significant elevation of BC was found in AMOX+CRP-treated ears ($p=0.007$). The ototoxic rate was significantly higher in AMOX + CRP-treated than in OFLX-treated ears whether assessed by BC ($p<0.001$) or SRT ($p=0.03$).

In conclusion, OFLX was more effective and safer than AMOX + CRP in the treatment of CSOM with acute exacerbation.

Key word : Chronic Otitis Media, Drug Therapy, Otic Solution, Ofloxacin, Amoxycillin, Chloramphenicol

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Chronic suppurative otitis media (CSOM) is a common disease with a 0.6 per cent incidence reported in the adult population[1]. An acute exacerbation usually results from bacterial invasion through the perforated eardrum or through the eustachian tube from the upper airway. The initial treatment of acute CSOM is medical therapy. The objectives are to eliminate the infection and thereby to decrease the aural symptoms viz. otalgia and discharge. Whenever the infection is controlled, elective tympanoplasty should be carried out to prevent reinfection and to create a normal hearing mechanism. Aural toilet and administration of antimicrobial agents are the main therapeutic approaches. Antibiotics are frequently used to eradicate pathogenic bacteria, but the most appropriate choice of antibiotic and the method of administration are still in question. Many otolaryngologists prescribe an oral antibiotic plus an otic solution. They believe that the infection should be controlled both systemically in the upper airway and locally in the middle ear. Sugiyama et al reported otic antibiotic drops to be more effective in reducing bacterial population than oral doses of antibiotic[2]. Choice of ototopical antibiotic should be relevant to the susceptibility of the common causative organisms i.e. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus* and *Klebsiella* species[3,4]. Popular antibiotics in ear drops include chloramphenicol, neomycin, polymyxin B and gentamycin. Caution must be exercised in the use of these ototopical antibiotics because of their ototoxic potential[5,6].

Ofloxacin is a fluoroquinolone antibiotic with a broad-spectrum bactericidal activity against aerobic gram positive and gram negative bacteria[7]. It has been shown not to produce histological or auditory functional damage when administered topically into the middle ear of animals[8-10]. Recently, many investigators have reported high clinical success in treating active CSOM with 0.3 per cent ofloxacin solution[3-4,11].

The objectives of the trial reported herein were to compare the efficacy and safety of 0.3 per cent ofloxacin otic solution (OFLX) with that of oral amoxycillin plus 1 per cent chloramphenicol ear drops (AMOX + CRP) as a treatment for CSOM with acute exacerbation in adult patients.

MATERIAL AND METHOD

This prospective randomized, investigator-blind clinical trial compared the efficacy and safety of 0.3 per cent ofloxacin otic solution (OFLX) with that of oral amoxycillin plus 1 per cent chloramphenicol ear drops (AMOX + CRP) in treatment of active chronic otitis media. Eighty adult and teenage patients were recruited between September 1996 and February 1998, in the outpatient service of the ENT Department, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok.

The inclusion criteria included an age greater than 15 years old, purulent or mucopurulent otorrhea, and central perforation of the tympanic membrane of greater than 21 days duration. Exclusion criteria were the presence of cholesteatoma or large aural polyp in the middle ear or mastoid, a history of ear surgery within the previous year, or therapy with systemic antibiotics or ototopical agents of any kind within two weeks. Pregnant and lactating females and patients allergic to either penicillin, chloramphenicol, or quinolone antibiotics were also excluded.

The nature of the study was clearly explained to all 80 eligible patients, and the parents or guardians of the teenagers. The patients were randomly divided into two groups. The patients in the first group (OFLX group) were treated with 0.3 per cent ofloxacin otic solution (6 drops twice daily) and oral placebo capsules (the same size and color as amoxycillin 500 mg capsule, three times daily) for two weeks. The patients in the second group (AMOX+CRP group) were treated with oral amoxycillin (500 mg three times daily) plus 1 per cent chloramphenicol ear drops (3 drops three times daily) for two weeks. Each patient was met at one-week intervals for two weeks (days 7 and 14).

On day 0 (first visit), the medical history was obtained from each patient, the inclusion and exclusion criteria were checked, and clinical evaluation was made. Microscopic examination was performed to measure the size of tympanic membrane perforation and to assess the aural discharge and middle ear inflammation. Otalgia, otorrhea and middle ear inflammation were scored from 0 to 3 according to severity (no symptoms/signs, 0; slight, 1; moderate, 2; severe or marked, 3). Before toileting, the middle ear discharge was collected with a fine cotton swab for standard bacteriological evaluations. Susceptibility tests to amoxycillin, chloramphenicol and ofloxacin were conducted by a disc diffusion method. Pretreatment pure tone and speech audiometry were evaluated by an authorized audiologist.

On days 7 and 14, clinical symptoms and signs were assessed by the patient (otalgia) and by the investigator (otorrhea and middle ear inflammation). Any side effects were also recorded. The patient was asked for the drug compliance, which was referred as a number of times the patient forgot to use the drug within 7 days. A good (0-3), moderate (4-7) and poor (>7) compliance were classified, and the good compliance was noted in more than 90 per cent of the patients in both groups. On day 14, each patient underwent post-treatment audiometric evaluations.

The patient's condition was considered improved if symptom/sign scores decreased at least one level, and cured if the symptoms of otalgia and middle ear inflammation disappeared and the ear became dry (score 0) without any complications at the end of the second week. The percentage of ears meeting these criteria (described as the "improvement rate" and "cure rate") from the two treatment groups were compared using the Chi square test.

Ototoxicity from otic solutions (OFLX and CRP) was determined by an elevation of bone conduction (BC) or speech reception threshold (SRT) from the pre-and post-treatment audiometric evaluation. The percentage of ears in which BC or SRT was elevated of greater than 5 dB or a high frequency hearing loss was detected with or without tinnitus was taken as the "ototoxic rate". The rates of the two groups were also compared using the Chi-Square test.

RESULT

A total of 80 patients were enrolled in the OFLX and AMOX+CRP groups. One patient from the OFLX group missed visits and was thus excluded from the study. The demographic characteristics of the 39 patients on OFLX and the 40 patients on AMOX+CRP are shown in Table 1. There were 25 males (31.64%) and 54 females (68.36%). The mean (± SD) ages of the patients by treatment group were 34.1±12.5 years and 32± 12.3 years for OFLX treated and AMOX+CRP treated subjects and the overall was 33±12.5 years. No significant differences in sex, age, laterality of infection, size, duration and cause of tympanic membrane perforation, or pathogenic organisms were noted between treatment groups at enrollment. The most common isolates were *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which comprised as much as 55 per cent in our study (Table 2). The susceptibility of the pathogenic isolates to the therapeutic agents (ofloxacin, amoxycillin and

Table 1. Demographic characteristics.

	OFLX	AMOX + CRP	Overall
Total patients	**39**	**40**	**79**
Male	13 (33.3%)	12 (30%)	25 (31.6%)
Female	26 (66.7%)	28 (70%)	54 (68.4%)
Age (yrs)			
range	16 - 68	15 - 78	15 - 78
mean (± SD)	34.1 ± 12.5	32 ± 12.3	33 ± 12.5
Total ears	**44**	**45**	**89**
Cause of perforation			
Unknown	28 (63.6%)	28 (62.2%)	56 (62.9%)
Infection	14 (31.8%)	16 (35.6%)	30 (33.7%)
Trauma	2 (4.4%)	1 (2.2%)	3 (3.4%)
Duration of perforation (yrs)			
Range	1/12 - 50	2/12 - 40	1/12 - 50
Mean (± SD)	8.5 ± 10.7	10.4 ± 12	9.1 ± 11.3
Side of perforation			
Right	18 (46.2%)	19 (47.5%)	37 (46.8%)
Left	16 (41%)	16 (40%)	32 (40.5%)
Bilateral	5 (12.8%)	5 (12.5%)	10 (12.7%)
Size of perforation (mm)			
Range	1-8	1-7	1-8
Mean (±SD)	4.2 ± 1.8	4.1 ± 1.7	4.1 ± 1.8

Table 2. Types of isolated pathogens from 89 ears.

	OFLX (44 ears)	AMOX + CRP (45 ears)	Overall (89 ears)
Staphylococcus aureus	13 (29.5%)	14 (31.1%)	27 (30.3%)
Pseudomonas aeruginosa	11 (25%)	11 (24.4%)	22 (24.7%)
Pseudomonas species	4 (9.1%)	3 (6.7%)	7 (7.9%)
Klebsiella species	3 (6.8%)	4 (8.9%)	7 (7.9%)
Acinetobacter species	2 (4.5%)	3 (6.7%)	5 (5.6%)
Enterobacter species	2 (4.5%)	1 (2.2%)	3 (3.4%)
Proteus mirabilis	2 (4.5%)	2 (4.4%)	4 (4.5%)
Other gram negative bacteria	2 (4.5%)	1 (2.2%)	3 (3.4%)
Contamination	5 (11.3%)	4 (8.9%)	9 (10.1%)
No Growth	4 (9.1%)	5 (11.1%)	9 (10.1%)

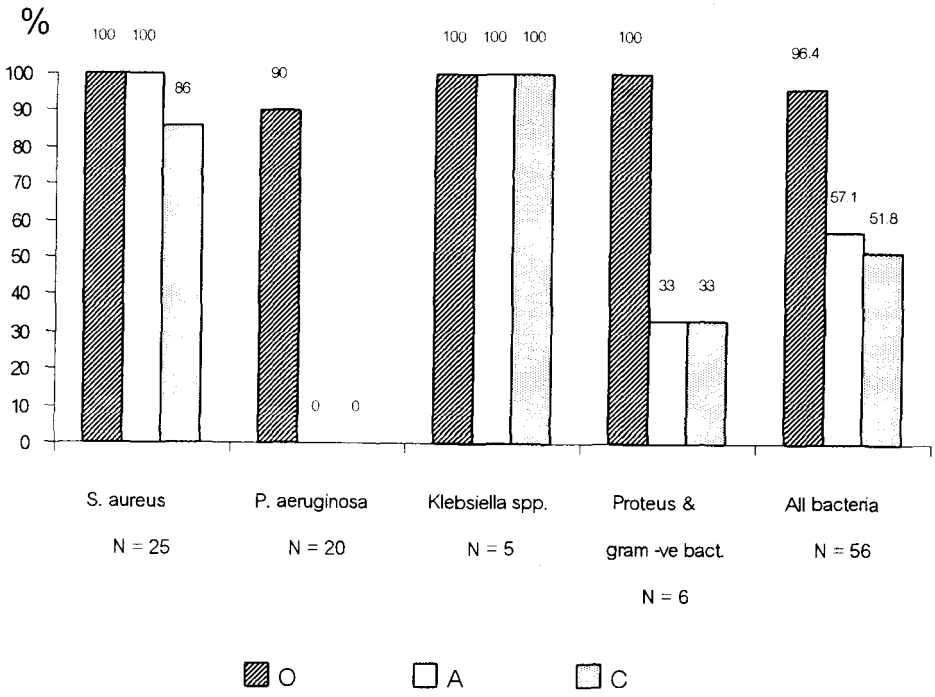

Fig. 1. Histograms of susceptibility of pathogenic isolates to the therapeutic agents (Ofloxacin, O; Amoxycillin, A; Chloramphenicol, C).

chloramphenicol) was assessed by a disc diffusion method. One hundred per cent of *Staphylococcus aureus*, 90 per cent of *Pseudomonas aeruginosa* and 96.4 per cent of all bacterial isolates were sensitive to ofloxacin. Only 57.1 and 51.8 per cent of all pathogenic isolates were sensitive to amoxycillin and chloramohenicol, respectively, (Fig. 1).

A significant decrease in severity score of otalgia, otorrhea and middle ear mucosal inflammation was obtained post-therapeutically in both groups (Table 3). Responses to the treatment were documented as the percentage of ears that had improved (improvement rate) or were cured (cure rate) according to the above criteria. Improvement

Table 3 Pre and Post treatment symptom/sign scores (A), and response rate after the 2-week treatment. (B)

Symptoms /signs	A. Severity scores				B. Response rate			
	OFLX		AMOX+CRP		Improved		Cured	
	Pre-	Post-	Pre-	Post-	OFLX	AMOX+CRP	OFLX	AMOX+CRP
Otalgia	1.5 (0.71)	0.25 (0.52)	1.43 (0.56)	0.5 (0.56)	87.5%	80%	79.2%	53.3%
	(P < 0.001)*		(P< 0.001)*		(P = 0.462)**		(P = 0.05)**	
Otorrhea	1.85 (0.83)	0.36 (0.73)	1.91 (0.76)	0.74 (0.65)	92.3%	86%	76.9%	37%
	(P < 0.001)*		(P < 0.001)*		(P = 0.365)**		(P < 0.001)**	
Middle ear inflammation	1.76 (0.67)	0.42 (0.59)	1.5 (0.59)	0.55 (0.66)	89.5%	83.8%	63.2%	54.8%
	(P< 0.001)*		(P < 0.001)*		(P = 0.426)*		(P = 0.664)**	

* paired *t* test
** Chi square test

Table 4. Pre and post-treatment audiometry (A) and ototoxic rate (B) between two treatment groups.

	A. Pre and Post treatment audiometry				B. Ototoxic rate	
	OFLX		AMOX+CRP		OFLX	AMOX+CRP
	Pre-	Post-	Pre-	Post-		
BC (dB)	23.4(9.7)	21.2(8.5)	22.8(10.4)	24.8 (10.4)	5.3%	45%
	(P < 0.001)*		(P= 0.007)*		(P < 0.001)**	
SRT(dB)	44.6(15.8)	41.2(16.6)	40.6(18.1)	40.9(11.7)	10.5%	30%
	(P = 0.002)*		(P = 0.81)*		(P = 0.033)**	

* paired *t* test
** Chi square test

rates of otalgia, otorrhea and mucosal inflammation of above 80 per cent in all parameters were obtained in both OFLX and AMOX+CRP treated patients, but these were no statistically significant difference. A significant difference for cure rate was established in otalgia (P=0.05), and otorrhea (P<0.001), but not in mucosal inflammation (P=0.664) (Table 3).

In an attempt to verify the ototoxic potential of OFLX and CRP, the pre and post treatment audiometric tests were evaluated. A significant improvement in BC from 23.4 ± 9.7 to 21.2 ± 8.5 dB (P<0.001) and SRT from 44.6 ± 15.8 to 41.2 ± 16.6 dB (P=0.002) was achieved in OFLX treated ears. On the other hand, a considerable deterioration was observed in BC from 22.8 ± 10.4 to 24.8 ± 10.4 dB (P=0.007) in AMOX + CRP treated ears (Table 4).

The percentage of ears in which the elevation of BC or SRT was greater than 5 dB or had a high frequency hearing loss with or without tinnitus (ototoxic rate) was significantly higher in AMOX+CRP treated than in OFLX treated ears (Table 4). Favorably, the tinnitus occurred in only one case from AMOX+CRP group and it disappeared after a discontinuation of the ear drops.

DISCUSSION

In the present study, the pattern of pathogen isolated at entry was slightly different from previous series[3,4,12]. We found that *S. aureus* was the organism most frequently isolated, followed by *P. aeruginosa*, other *Pseudomonas* species and *Klebsiella* species. This study confirmed the consistent *in vitro* activity of ofloxacin against the common pathogens isolated from active CSOM ears. Susceptibility of *S. aureus*, *P. aeruginosa* and *Klebsiella* species to ofloxacin was 100, 90 and 100 per cent respectively. Comparing the susceptibility of *S. aureus* and *P. aeruginosa* to amoxycillin (100 and 0 per cent) and to chloramphenicol (86 and 0

per cent), a marked difference was encountered. Moreover, the MIC of ofloxacin against *S. aureus, P. aeruginosa* and *Klebsiella* species in our series ranged between 0.38 - 0.5, 0.38 - 2 and 0.125-0.38 mg/L, respectively. MIC greater than 4 mg/L was considered a resistant strain, which was found in two samples of *P. aeruginosa* (MICs of 16 and 32 mg/L.). By contrast, MICs of amoxycillin and chloramphenicol to *P. aeruginosa* were above 250 mg/L in all samples. Moreover, the concentration of ofloxacin in the 0.3 per cent ofloxacin otic solution bathing the middle ear is several times higher than the MIC even when mixed with aural discharge. It does not seem necessary to be too cautious about increases in MIC and development of resistance if the use of this otic solution is monitored[13]. Thus ofloxacin, as indicated from bacterial study is a good choice for initial treatment of CSOM with acute exacerbation.

Besides the *in vitro* studies, clinical efficacy of ofloxacin for treatment of active CSOM was also obtained from widely conducted trials in France[14,15], Hong Kong[11,16], Thailand[3,4] and Japan[13]. In our study, after treatment, a significant decrease in otalgia, otorrhea and middle ear inflammation was observed in both treatment groups ($P<0.001$). Response rate was assessed as the percentage of ears improved or cured after treatment. Improvement in otalgia, otorrhea and middle ear inflammation did not differ significantly between treatments. However, a significantly better "cure rate" was encountered in OFLX than in AMOX + CRP treated ears in terms of otalgia ($P= 0.05$) and otorrhea ($P<0.001$). The cure rate of middle ear inflammation was not different between the two treatments; this may perhaps be partly due to an irritative effect from either the antibiotic, preservative or solvent in the ototopical solutions as stated by Barlow et al in his recent work on ototoxicity of topical otomicrobial agents[8]. From these clinical standpoints, OFLX is better than AMOX + CRP in obtaining painless, dry ears.

The dual concerns regarding substances used to treat active CSOM are both effectiveness and safety. Middle ear and cochlear ototoxicity following administration of ototopical agent have been variously demonstrated both in animal models and in humans[8,17-19]. The widely used antibiotics eg: chloramphenicol, gentamycin, neomycin and polymyxin B have been reported to have ototoxic potentials[17,20]. Apart from the ototoxic antibiotics, solvents of otic solutions have also been found to be ototoxic to both the middle ear and cochlea [17,21]. Contrary to those reports of ototoxicity, several reports have suggested that ototopical therapy was safe for patients with CSOM[22,23]. Furthermore, Fairbanks also contended that a few reported cases of ototoxicity resulting from the widespread use of antibiotic ear drops suggested that the risk was not present at all, not very large, or was obscured by the effect of the disease itself[5].

While controversy still exists, a newly developed ofloxacin otic solution has been shown to be non-ototoxic by many investigators[8-10]. In our study, we also compared the cochleotoxic effect of 0.3 per cent ofloxacin otic solution to 1 per cent chloramphenicol ear drop by comparing the audiometric changes from treatment. We used bone-conduction studies speech reception threshold, and a presence of tinnitus as the reliable judgement of ototoxicity. In the OFLX group, a significant improvement of average bone-conduction thresholds (23.4 ± 9.7 to 21.2 ± 8.5 dB; $p < 0.001$) and speech reception thresholds (44.6 ± 15.8 to 41.2 ± 16.6 dB; $P = 0.002$) was revealed. By contrast, a considerable deterioration of average bone-conduction thresholds (22.8 ± 10.4 to 24.8 ± 10.4 dB; $p = 0.007$) was obtained in the AMOX + CRP group. In addition, the "ototoxic rate" was significantly higher in the AMOX + CRP than in the OFLX group. Our findings not only confirmed the non-ototoxic properties of ofloxacin otic solution, but also suggested a somewhat ototoxic potential of the chloramphenicol ear drops. In this study we did not encounter the permanent deterioration of hearing or tinnitus, or any serious complications. Three cases (one in the OFLX and two in the AMOX + CRP group) of fungal superimposition were found at the end of the 2-week treatment, it was eradicated by aural toileting and local application of an antifungal cream. Another unwanted effect was soreness produced by the otic solution. Chloramphenicol ear drops caused a mild to moderate soreness in as much as 37 per cent of treated ears; however, only two cases (5.1%) using the ofloxacin otic solution complained of soreness.

SUMMARY

The treatment of active CSOM usually requires antibiotic administration orally or locally

or in combination. Based on our bacteriological data, clinical evaluation and ototoxic potential assessment, ofloxacin otic solution is a good choice for the initial treatment of active CSOM. Our comparative study showed that ofloxacin otic solution was significantly more effective and safer than the commonly used regimen of oral amoxycillin plus chloramphenical ear drops.

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การเปรียบเทียบผลระหว่างยาหยอดหูโอฟล็อกซาซิน กับยารับประทานอะม็อกซีย์-ซิลลินร่วมกับยาหยอดหูคลอแรมเฟนิคอล ในการรักษาโรคหูชั้นกลางอักเสบเรื้อรังที่กำลังอักเสบเป็นหนอง

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ผู้วิจัยได้ทำการศึกษาเปรียบเทียบประสิทธิภาพ และความปลอดภัยของยาระหว่างยาหยอดหู 0.3% โอฟล็อกซาซินขนาด 6 หยด วันละ 2 ครั้ง กับยารับประทานอะม็อกซีย์ซิลลิน ขนาด 500 มก. วันละ 3 ครั้ง ร่วมกับยาหยอดหู 1% คลอแรมเฟนิคอล ขนาด 3 หยด วันละ 3 ครั้ง ในการรักษาผู้ป่วยโรคหูชั้นกลางอักเสบเรื้อรังที่กำลังมีการอักเสบเป็นหนอง เป็นระยะเวลา 2 สัปดาห์ ในผู้ป่วยของแผนกผู้ป่วยนอก หู คอ จมูก โรงพยาบาลจุฬาลงกรณ์ จำนวนทั้งสิ้น 80 ราย ที่มีอาการดังกล่าวซึ่งได้รับการคัดเลือกแบบสุ่มเข้าในการศึกษาชนิดไปข้างหน้า โดยผู้วิจัยไม่ทราบข้อมูลของยาที่ผู้ป่วยแต่ละคนได้รับ

ผลการวิจัยพบว่าเชื้อแบคทีเรียก่อโรคที่พบบ่อย ได้แก่ เชื้อ *Staphylococcus aureus* (30.3%) และ *Pseudomonas aeruginosa* (24.7%) โดยที่มีความไวของเชื้อทั้งหมดต่อยาโอฟล็อกซาซิน, อะม็อกซีย์ซิลลิน และคลอแรมเฟนิคอล เท่ากับ 96.4%, 57.1% และ 51.8% ตามลำดับ

การตอบสนองต่อการรักษา บ่งเป็นอัตราการดีขึ้นและอัตราการหายจากอาการต่าง ๆ ได้แก่ ปวดหู มีน้ำหนวกไหล และการอักเสบของเยื่อบุหูชั้นกลาง ซึ่งพบว่า อัตราการดีขึ้นของอาการต่าง ๆ ในกลุ่มที่รักษาด้วยยา OFLX ดีกว่าในกลุ่มที่รักษาด้วยยา AMOX+CRP แต่ไม่มีนัยสำคัญทางสถิติ ส่วนอัตราหาย พบว่าในกลุ่มที่รักษาด้วยยา OFLX ดีกว่ากลุ่ม AMOX+CRP อย่างมีนัยสำคัญทางสถิติ ในส่วนที่ลดอาการปวด ($p=0.05$) และทำให้หูแห้ง ไม่มีน้ำหนวก ($p<0.001$)

พิษของยาต่อหูประเมินจากการที่มีระดับการได้ยินผ่านทางกระดูก (BC) และ/หรือระดับการได้ยินเสียงพูด (SRT) สูงขึ้นมากกว่า 5 dB หรือพบว่ามีการสูญเสียการได้ยินในช่วงความถี่สูง เกิดขึ้นจากการใช้ยา การศึกษานี้พบว่าค่า BC และ SRT ลดลงอย่างมีนัยสำคัญ ในกลุ่มที่รักษาด้วยยา OFLX ($p<0.001$ และ $p=0.007$ ตามลำดับ) แต่ค่า BC ดังกล่าวกลับสูงขึ้นอย่างมีนัยสำคัญในกลุ่ม AMOX+CRP ($p=0.007$) และพบว่าในกลุ่ม AMOX+CRP มีอัตราการเกิดพิษต่อหูมากกว่ากลุ่ม CRP อย่างมีนัยสำคัญ เมื่อประมาณจากค่า BC ($p<0.001$) หรือค่า SRT ($p=0.033$)

โดยสรุป การใช้ยา OFLX ในการรักษาโรคหูชั้นกลางอักเสบเรื้อรังที่กำลังอักเสบเป็นหนองได้ผลดีกว่า และปลอดภัยกว่าการใช้ยา AMOX+CRP ในการรักษาโรคดังกล่าว

คำสำคัญ : โรคหูชั้นกลางอักเสบเรื้อรัง, การรักษาทางยา, ยาหยอดหู, โอฟล็อกซาซิน, อะม็อกซีย์ซิลลิน และคลอแรมเฟนิคอล

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