Original Research Article

Comparison of the effectiveness and safety of Clarithromycin and Co-Amoxyclav in acute exacerbation of chronic otitis media : a randomized, open-labeled, phase *iv* clinical trial

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Abstract

Objective: To compare the effectiveness and safety of Clarithromycin and co-amoxyclav for the treatment of mild to moderate cases of acute exacerbation of chronic otitis media (AECOM).**Materials and methods:**Adult patients diagnosed with AECOM were screened and patients fulfilling the inclusion criteria were randomized to receive either Clarithromycin (500 mg) twice daily or co-amoxyclav (625 mg) thrice daily orally for 7 days. The primary outcome of this randomized, open-labeled, phase IV clinical trial was clinical success rate at day 14 visit and the secondary outcome was incidence of adverse events (AES). Fifty patients were enrolled : 25 in the Clarithromycin group and 25 in the co-amoxyclav group.**Results :** The clinical success rates were 92.7 % in the Clarithromycin group versus 90.2% in the co-amoxyclav group. These rates are comparable, but no statistically significant difference was observed between the groups.**Conclusion:**The results of this randomized, open-labeled phase IV clinical trial showed that a 7-day course of Clarithromycin is therapeutically comparable to co-amoxyclav in terms of both clinical effectiveness and safety for the treatment of patients with AECOM.

Keywords: Clarithromycin, co-amoxyclav, AECOM, COM (Chronic Otitis Media)

Introduction

Chronic Suppurative Otitis Media (CSOM) is defined as chronic inflammation of the middle ear and mastoid. The disease manifests commonly as hearing loss and intermittent Otorrhoea. Chronic Otitis media can be defined as 'chronic or intermittent Otorrhoea through a persistent non-intact tympanic membrane'. The reference to a non-intact tympanic membrane in most cases denotes a perforation, but can also include discharge through a ventilation tube[1-3]. Perforations in the tympanic membrane are described according to their anatomical location. Central perforations are in the pars tersa and are surrounded by some residual tympanic membrane or at least the annulus. The location of central perforations is denoted by their relationship to the handle of the malleus. These defects can hence be termed as anterior, posterior, inferior or subtotal.Marginal perforations usually occur in the posterior part of the tympanic membrane with pathological loss of the annulus allowing direct exposure of the bony canal wall[4]. Attic perforations occur as defects of the pars flaccida. Central perforations are rarely associated with cholesteatoma. As the presence of cholesteatoma has traditionally been associated with the complications of chronic Otitis media, central perforations are often referred to as 'safe' marginal and attic perforations are commonly associated with cholesteatoma and are often termed unsafe. As central perforations expose the mucosa of the middle ear and Eustachian tube orifice, their presence is often denoted by the term 'tubotympanic disease', marginal and attic defects expose the anatomical structures of the attic, antrum and mastoid cell system and are referred to as 'attico-antral disease'. Pus culture in both types of aerobic and anacrobic com may show multiple organisms. Common aerobic organisms are Pseudomonasacruginosa, Proteus, Escherichia coli, andstaphylococcus aureus, while

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anaerobes include Bacteroides fragilis and an aerobic streptococci[5]. Bacteriological cultures may not be needed to establish the diagnosis of CSOM as exhaustive studies have established that 90-100% of chronic draining ears yield two or more isolates consisting of both aerobic and anaerobic bacteria. The choice of the antibiotic agent depends greatly on the knowledge of the type of bacteria most frequently implicated in CSOM and their sensitivity to antibiotics.Amoxycllin is a semi-synthetic penicillin, an analogue of ampicillin, with a brand spectrum of bactericidal activity against many gram-positive and gram-negative micro-organisms. Amoxycillin is stable in presence of gastric acid and may be given without regard to meals. It acts through inhibition of biosynthesis of cell wall muco peptide. It is indicated in com and other ENT infections due to susceptible strains of Gram negative organisms like H. Influenzae, E. coli, P. mirabilis and N. gonorrhea. Gram positive organisms like streptococci, D. Pneumoniae and non-penicillase producing staphylococci[6]. It is contraindicated in individuals with a history of an allergic reaction to the penicillins & pregnancy. Clarithromycin is a macrolide antibiotic with broad spectrum of activity. The mode of action is by binding to SOS ribosomal unit and suppressing protein synthesis. It is indicated in ENT infections including CSOM, URTI, pharyngitis & sinusitis. It is also indicated in upper and lower respiratory tract infections, skin & soft tissue infections and Otorhinolaryngological infections including com. It is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics. Our present study was planned to compare the effectiveness and safety of Clarithromycin with co-amoxyclav in AECOM. The objective of this study was to demonstrate equivalence between Clarithromycin (test drug) and co-amoxyclav (comparator) with respect to their effectiveness in AECOM. Another objective was to compare their safety and tolerability profile[7-9].

Materials & methods

This was a prospective, randomized, open-labeled study. The study was approved by the Institutional Ethics committee (permission No: → RKC/Ethics/343, Dated 26.04.2019) and conducted according to the ICMR guidelines for Biomedical Research on Human subjects, 2006 and the Declaration of Helsinki. Subjects were recruited in the ENT out patient Department of a tertiary care teaching hospital and the study was conducted between May 2019 to September 2019.The objective of the study was to demonstrate equivalence in the effectiveness between the two treatment groups.[10-12].A difference of 10% in clinical cure rates was assumed to be the largest clinically acceptable effect for which equivalence could be accepted (equivalence limit). Considering the true mean difference between the two treatment groups as zero and the expected standard deviation of 10% in the study population, 90% power and $\infty = 0.05$, the number of subjects required in each treatment group was 21. The sample size was calculated subsequently [using primer of biostatistics software (version 5.0)]

Inclusion criteria: Adults of either sex, between age group 16 to 65, were considered. Clinically documented cases of tubo-tympanic variety of com with clinical signs & symptoms of acute exacerbation of the disease and baseline otological symptom score of >4 but ≤ 8 were included in the study[13].

Exclusion criteria: Pregnant and Lactating females were excluded from this study. Severe cases of AECOM for which, hospitalization on parenteral antibiotic treatment is required and patients with otological symptom score of ≤ 4 and > 8 were also excluded from the study.Patients with foul-smelling Ear discharge and those who, received antibiotics in the preceding 4 weeks of screening were excluded from the study[14].

Effectiveness parameters: Number of subjects achieving 'treatment success' in each treatment group was considered to be the effectiveness parameter. Treatment success was based on changes in the otological symptoms scores at day 14 visit. 'Treatment failure' was declared if there was no change or increase in the baseline otological symptom score on day 14.

Study visits_: Each patient was evaluated for 2 weeks. The first week was the active treatment period. The following week was treatment – free follow-up. Patients were evaluated clinically at baseline (day 0) and at subsequent follow-up visits on Days 3,7 and 14. At each visit, otological symptom score was recorded.

Grouping: Patients who fulfilled the selection criteria were randomly allocated in both treatment groups. Patients in group A received Clarithromycin (500 mg) and group B received co-amoxyclav tablet (625 mg). Study medication were dispensed twice (for Clarithromycin) and thrice (for co-amoxyclav) during the study period; first during baseline visit for 3 days and next during day 3 visit for the next 4 days.

Table 1 : Otological symptom score

SIGNS / SYMPTOMS	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Tinnitus	Absent	Mild	Moderate	Severe
Amount of discharge	Absent	Mild	Moderate	Severe
Type of discharge	Absent	Mucoid	Muco-purulent	Purulent
Mucosal edema	Absent	Mild	Moderate	Severe

Patients were advised to take Clarithromycin (500 mg) orally twice daily and co-amoxyclav (625 mg) orally thrice daily for the first 7 days.Compliance was assessed by the traditional pill count method at each follow-up visit at the end of the study.Patients with worsening clinical conditions or treatment failure were withdrawn prematurely from the study. No concomitant medication was advised to the patients apart from the study drugs. All patients were advised to quit smoking & alcohol consumption during the study period. Patients were monitored continuously throughout the study for any adverse event (AE). Safety monitoring was meticulously performed throughout the study. All AES spontaneously reported by the subjects or elicited by the investigators were recorded and causality analysis was done as per the WHO-UMC criteria.

Statistical analysis : Data were analysed as per modified intention to treat basis subjects reporting for at least one postbaseline follow-up visit were analysed. All patients who were randomized were considered for safety analysis. Data in ordinal scale were analysed by Firedman's test for intragroup comparison and by Mann-Whitney U test for inter-group comparison. Categorical data were analysed by Chi-square test P-value <0.05 was considered to be statistically significant.

Results

Of the 64 subjects screened, 50 fulfilled the selection criteria and were randomized – 25 to group A (Clarithromycin) arm and 25 to group B (co-amoxyclav). The mean age of patients was 37.2 and 26.3 years in the Clarithromycinand co-amoxyclav groups, respectively 70% were male in the Clarithromycin group and 78% were male in the co-amoxyclav group. There was no statistically significant difference in the baseline demographic profile and baseline otological symptom score changes in otological symptom score from baseline have been shown in figures 2 and 3.

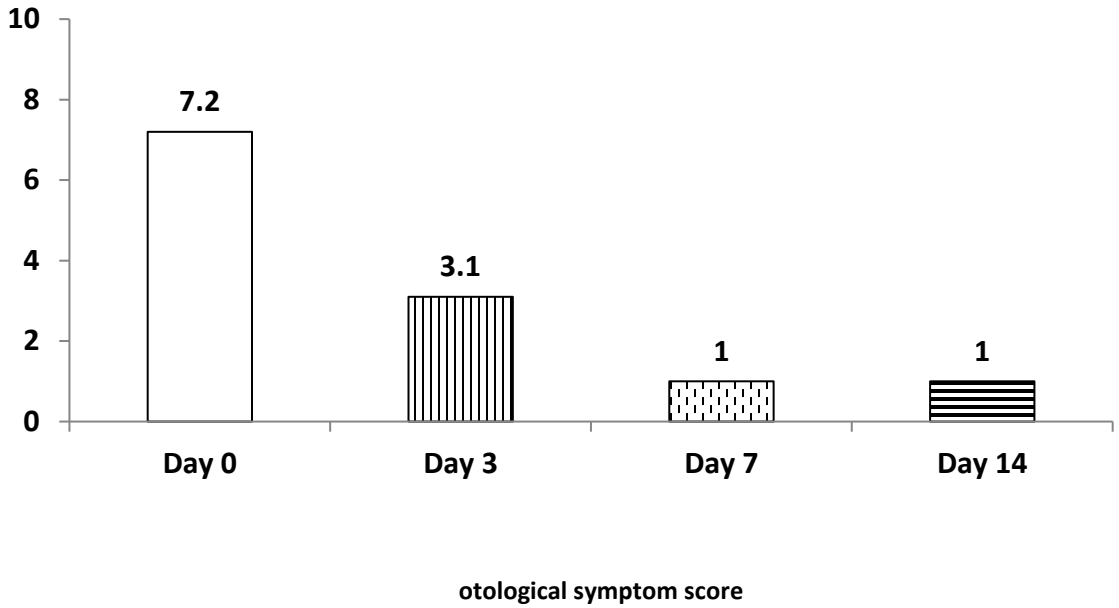

Fig 2: Changes in otological symptom score in the Clarithromycin group (Group A) p < 0.05 – Day 3,7,14 vs Day 0.

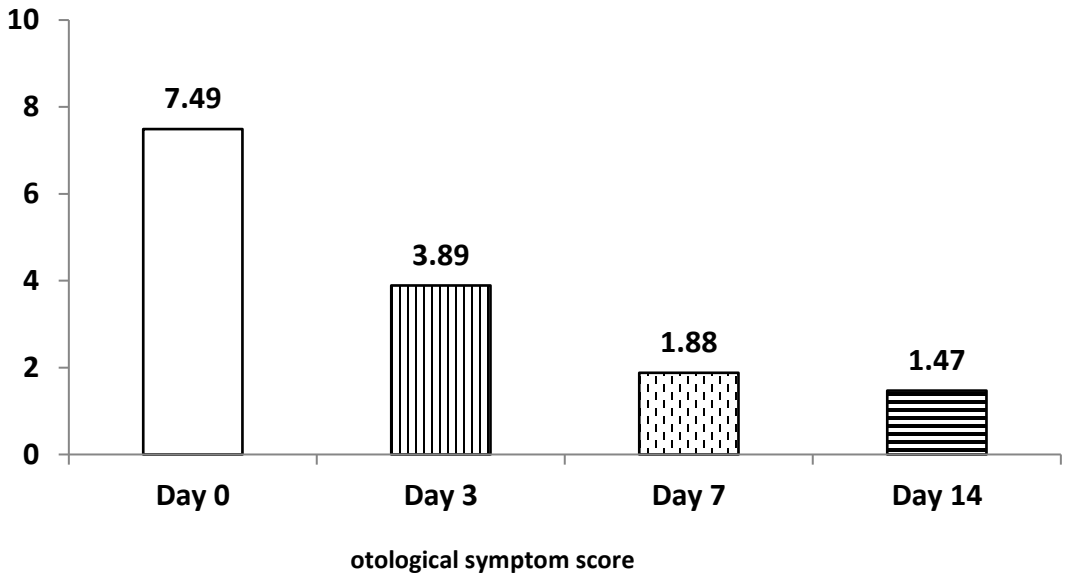

Fig 3: **Changes in otological symptom score in the co-amoxyclav group (Group B) p < 0.05 – Day 3,7 and 14 vs Day 0.**

Table 2: Comparison of treatment success rate

Scores	Clarithromycin Group (n=25)	co-amoxyclav group (n=25)	P-value
Treatment success	23 (92%)	21 (84%)	
Clinical cure	20	17	
Clinical improvement	3	4	0.25
Treatment failure	2 (8%)	4 (16%)	

Intragroup analysis of otological symptom score at baseline (day 0) against day 3, day 7 and day 14 scores showed a highly significant decrease in both groups. [Figures 2 and 3] and there was a clinically significant improvement in the signs and symptoms of the AECOM. Therefore, it can be suggested that both Clarithromycin and co-amoxyclav are equally effective in the treatment of AECOM.

Table 2 shows the number and the percentage of patients categorized as "treatment success" and "treatment failure" at the day 14 visit. Twenty-three subjects of the 25 enrolled in the Clarithromycin group achieved "treatment success", i.e. either clinical improvement or clinical cure, and the remaining 2 subjects were categorized as treatment failure. Similarly in the co-amoxyclav group, 21 subjects of the 25 evaluated showed "treatment success" either clinical improvement or clinical cure and the remaining four (4) were categorized as treatment failure.There were two patients in the Clarithromycin group and four patients in the co-amoxyclav group who were categorized as treatment failure and had to be put on other antibiotics after the day 7 evaluation safety analysis was carried out as per the Intention to Treat (ITT) analysis. All patients who wererandomized were considered for safety analysis. Only three AES were noted during the entire study period. Two(2) patients in the co-amoxyclav group reported to have moderate diarrhea. One (1) patient in the Clarithromycin group reported to have mild diarrhea. These AES were mild in nature and did not require any dose reduction or withdrawal of the study medications. Therefore the safety and tolerability profile of both the study drugs were good without any reported cases of serious AE.

Discussion

The results of our study showed that Clarithromycin and co-amoxyclav are equally effective in clinically diagnosed cases of AECOM both in terms of effectiveness and in terms of safety. After treatment

with a 7-day course, the clinical success rates were comparable, i.e. 92% in the Clarithromycin group and 84% in the co-amoxyclav group. The incidence of AES was also minimal, only two in the co-amoxyclav group and one in the Clarithromycin group. These AES were non serious in nature and did not require dose modification or withdrawal of drug therapy. Patient compliance was also good in both the groups.We did not perform bacteriological culture of the cases as exhaustive studies have established that 90-100% of chronic draining ears yield two or more isolates consisting of both aerobic and anaerobic bacteria. Another reason is that, very often, clinicians start antimicrobial therapy at outpatient setting before the bacteriological culture report arrives, which takes about 72 hours. Therefore, we conducted this study mainly to provide information to clinicians on the comparative effectiveness of these two antibiotics as initial antibiotics for AECOM patients based on clinical assessment scores.

Conclusion

The results of this study demonstrated that a 7-day course of Clarithromycin is comparable to co-amoxyclav interms of both clinical effectiveness and safety for the treatment of AECOM in an outpatient setting. Although cost of drug therapy was higher with Clarithromycin as compared with co-amoxyclav, it should not be considered as a drawback. Future trials are warranted to evaluate the bacteriological cure and relapse rates of these two drugs to provide additional supportive scientific evidence.

References

1. Verhoeff M, van der Veen EL, Rovers MM, Sanders EAM, Anne GM,Schilder AGM. Chronic suppurative otitis media: A review. Int J PediatrOtorhinolaryngol 2006;70:1-12.
2. Brobby GW, Zadik P. Bacteriology of otitis media in Ghana. Trop Doct1987;17:91-2.
3. Fairbanks DN. Antimicrobial therapy for chronic suppurative otitis media.Ann Otol Rhinol Laryngol Suppl 1981;90:S58-62.
4. Chronic suppurative otitis media-Burden of Illness and Management Options. [monograph on the internet]. World health organization; 2004. Available from: http://www.who.int/entity/pbd/deafness/activities/hearing.../otitis_media.pdf
5. Bluestone CD, Kenna MA. Chronic suppurative otitits media: Antimicrobialtherapy or surgery? Pediatr Ann 1984;13:417-21.
6. Gehanno P. Multicenter study of the effectiveness and safety of oral ciprofloxacin in the treatment of chronic suppurative otitis media in adults.The French Study Group. Otolaryngol Head Neck Surg 1997;117:83-90.
7. Baba S, Murai K, Kinoshita H, Kawai T, Koyama K, Tsukiyama M. Doubleblindcomparative trial of cefroxadine and cephalexin in the treatment ofacute suppurative otitis media and acute exacerbation of chronic suppurativeotitis media. Jpn J Antibiot 1989;42:212-47.
8. Baba S, Mori Y, Suzuki K, Unno T, Kawabori S, Yanai T. Evaluation of the effectiveness of ceftriaxone in acute suppurative otitis media and acuteexacerbation of chronic suppurative otitis media. A comparative study withcefotiam as the control. J Med Assoc Thai 2000;83:61-8.
9. Al-Abbasi AM. Effectiveness of Povidone Iodine in Treatment of ActiveChronic Suppurative Otitis Media. J Indian Med Assoc 2006;38:118-22.
10. Edwards R, Aronson JK. Adverse Drug Reactions: Definitions, diagnosisand management. Lancet 2000;356:1255-9.
11. Esposito S, D'Errico G, Montanaro C. Topical and oral treatment of chronicotitis media with ciprofloxacin. A preliminary study. Arch Otolaryngol Head Neck Surg 1990;116:557-9.
12. Dohar JE, Alper CM, Rose EA. Treatment of chronic suppurative otitis media with topical ciprofloxacin. Ann Otol Rhinol Laryngol 1998;107:865-71.
13. Block SL, Kratzer J, Nemeth MA, Tack KJ. Five-day cefdinir course vs. tendaycefprozil course for treatment of acute otitis media. Pediatr Infect Dis J 2000;19:S147-52.
14. Kafetzis DA. Review Multi-investigator evaluation of the efficacy and safetyof cefprozil, amoxicillin-clavulanate, cefixime and cefaclor in the treatment ofacute otitis media. Eur J Clin Microbiol Infect Dis 1994;13:857-65.

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