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Comparison of Efficacy and Safety of Cefpodoxime and Amoxycillin with Clavulanic Acid Combination in Adult Indian Patients with Acute Exacerbation of Chronic Suppurative Otitis Media: A Randomized, Non Interventional, Open-Label, Phase IV Clinical Trial

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Abstract: ***Introduction: Acute exacerbation of chronic suppurative otitis media (AECSOM) has a high risk of complications, if not treated adequately. Amoxycillin with clavulanic acid combination is often used as primary agent in its treatment. Cefpodoxime has good antimicrobial activity and has been studied for use in paediatric AECSOM, but no head-on comparison study is available between these two medications in adult Indian patients for this indication. Aim: To compare the efficacy and safety of Cefpodoxime and Amoxycillin with clavulanic acid combination for the treatment of AECSOM in adults. Materials and Methods: An open-label, phase IV, non-interventional, prospective, randomzed, observational study was conducted on adults diagnosed with AECSOM. One hundred & twenty adults were included in the study: 60 in each group Group A (Cefpodoxime) and Group B (Amoxycillin with clavulanic acid combination). Primary outcome of this study was clinical success rate at day 14 visit and secondary outcome was incidence of Adverse Events (AEs). Results: The clinical success rates were 98.33% in Group A and 96.66 % in Group B. These rates are comparable, but no statistically significant difference was observed between the groups. The incidence of adverse effects like diarrhoea, nausea and vomiting was more in Amoxycillin with Clavulanic acid combination arm than in the Cefpodoxime arm. Conclusion: The results of this prospective study showed that a 7-days course of Cefpodoxime is therapeutically comparable to Amoxycillin with Clavulanic Acid combination in terms of both clinical effectiveness and safety with lesser adverse effects, for the treatment of patients with AECSOM.***

Keywords: Cefpodoxime, Amoxycillin with Clavulanic Acid combination, CSOM, adult patient, India.

1. Introduction

Chronic suppurative otitis media (CSOM) is middle ear inflammation in which there is discharge from the ear for more than three months. It may be a complication of acute otitis media. According to the World Health Organization, CSOM is a primary cause of hearing loss in children [1]. Adults with recurrent episodes of CSOM have a higher risk of developing permanent conductive and sensorineural hearing loss.

CSOM affects 65-330 million people worldwide, mainly in developing countries. It has been estimated that there are 31 million new cases of CSOM per year, with 22.6 % in children less than 5 years old. The populations with the highest reported prevalence of CSOM are the Inuits of Alaska, Canada and Greenland, American Indians and Australian Aborigines (7-46 %). Intermediate prevalence has been reported in the South Pacific Islands, Africa, Korea, India and Saudi Arabia, ranging from 1 to 6 %. In Britain, 0.9% of children and 0.5% of adults have CSOM, with no difference between the sexes. [1]

The incidence of CSOM across the world varies dramatically where high income countries have a relatively low prevalence while in low-income countries the prevalence may be up to three times as great.

Each year 21, 000 people worldwide die due to complications of CSOM. [1]

In the developing world, mastoiditis and other complications are still the most common cause of death from CSOM. Therefore, proper antibiotics with good sensitivity level needs to be started early from the primary care level to ensure early recovery and to prevent future complications.

Due to the rise in antibiotic resistance against Fluoroquinolones due to rampant over-the-counter use in developing countries like India [2], antibiotics like Amoxycillin and clavulanic acid remain the widely used primary antibiotic of choice in AECSOM, due to its high concentration in middle ear fluid [3].

Cephalosporins like Cefpodoxime are a widely used antibiotic, with a good tolerance, side effect profile and good patient compliance. It has good antimicrobial activity and has been studied for use in paediatric AECSOM, but no head-on comparison study is available between these two medications in adult Indian patients for this indication.

Against this background, the present study was done to compare the effectiveness and safety of Cefpodoxime with Amoxycillin with Clavulanic acid combination in AECSOM.

2. Methodology

The study was designed as an Phase IV open-label, prospective, randomized, interventional study.

Total 120 patients were included in the study, 60 in each group.

The study was conducted in the out-patients' Department (OPD) of Department of Ear, Nose and Throat (ENT) KPC Medical College and Hospital, after obtaining ethical clearance from Institutional Ethics Committee (IEC) of KPC Medical College and Hospital, Jadavpur. Patients of either sex, aged between 20 & 60 years, who were diagnosed as tubo-tympanic type CSOM resulting in discharging ear and deafness presenting with clinical symptoms and signs of acute exacerbation of the diseases and base line otological symptoms score (Table: 1) of >4 but </=8, were recruited in the study.

Patients unable or not willing to give consent**,** Female patients with pregnancy or willing to go for pregnancy**,** Patients with acute myocardial infarction in recent past**,** severe renal impairment**,** very poor general condition**,** or any other major systemic ailment**,** patients who have participated in any other clinical trial within past 3 months, severe cases of AECSOM for which hospitalization or parenteral antibiotic treatment is required, patients with otological symptom score<=4 and >8, were excluded from the study.

The study was designed as an open label, non-interventional, prospective, observational study. Informed consent was taken. The patients received antibiotic as per the assessment of the treating physician. No changes were made in the treatment decision, schedule or duration during the study period. Two regimens were used-Amoxycillin with Clavulinic acid combination and Cefpodoxime proxetil. Doses used were as per standard regimens [4]. Amoxycillin with Clavulinic acid combination 625mg thrice daily after meal for 7 days.

Cefpodoxime proxetil: 200mg twice daily after meal for 7 days.

Randomization was done by computer programming randomization.

Laboratory parameters for Complete blood count (CBC), Blood biochemistry like urea, creatinine were done. Otological symptom score were recorded on Days 0, 3, 7 & 14.

Patients were questioned regarding adverse drug reactions on Day 3, 7 & 14.

Patients were asked to do CBC report on 12th day & followed up in OPD on Day14 after completion of a 7 days antibiotic course.

Definition of outcome:
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. It was subdivided into two categories: (a) "clinical cure" if the otological symptom score was <3 at day 14 visit or (b) "clinical improvement" if the otological symptom score was between 3 and 5 on day 14. "Treatment failure" was declared if there was no change or increase in the baseline otological symptom score on day 14.

ADRs reported by the patients or elicited by the investigator were recorded and casualty analysis was done as per (Naranjo's) criteria and Otological symptom score was recorded.

Data were collected by using specific proforma, e. g. CRF of clinical, haematological and biochemical observations Otological symptom score (Table1). Monitoring for adverse effects was done based on ADR check list and also collection of laboratory data in CRF and Naranjo's Algorithm.

Adverse Drug Reactions were assessed on parameters like:
i) Blood parameters (Hb%, TLC, DLC & platelet count) &
ii) GI toxicity parameters (Nausea, vomiting, diarrhoea, constipation).

Efficacy was measured by Otological symptom score.

On each visit, parameters like medical history, clinical examination, pulse & blood pressure measurements were assessed & recording of adverse effects was done.

Any medication (other than those permitted by the protocol), that could affect the normal action of the investigating drugs were strictly discouraged and possible effects were described to the family members accompanying the patients. Other medications needed by the patients for co-morbid conditions were allowed to be taken by the patients, provided they did not have any significant interaction with the study drugs.

The collected Data was analysed with the help of SPSS version 25. It was analysed by using different statistical methods. For analysis of demographic profile of the patients mean, standard deviation and percentage were used.

Analysis of ADRs stated by the patients (symptoms) was done by using number of patients complaining a particular ADR and percentage. Statistical analysis of ADRs was done by Chi-squared test. Causality assessment was done by using Naranjo's scale. Unpaired t test was used to compare numerical data between both the groups. Assessment of response was measured by Chi-squared test.

3. Results

Of the 128 subjects screened, 120 fulfilled the selection criteria and were randomized-60 to group A (Cefpodoxime) arm and 60 to group B (Amoxycillin with Clavulanic acid combination).

Table 2 shows the distribution of AECSOM in different age group. Majority of the patients in this trial were young patients (age group 26-35yrs; 70 patients (58%).

The percentage of male patients (total 75; 62%) were more compared to female patients (total 45; 38%), maybe due to the disease being more prevalent in males (Table 3).

In our study, patients residing in urban areas were more, maybe due to the study setting. (95 patients; 79%) (Table 4).

Table 5 showing Intergroup comparison 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 and there was a clinically significant improvement in the signs and symptoms of the AECSOM. Otological symptom score for Cefpodoxime group was 1.42 $\pm$ 0.4 at day 14, whereas for Amoxycillin-Clavulanic acid group it was found to be 1$\pm$ 0.1. Efficacy was calculated from the otological symptom score. Efficacy of Cefpodoxime was found to be 98.33% whereas that of Amoxycillin with clavulanic acid combination was found to be 96.66% ($p>0.05$).

Thus, it can be suggested that both Cefpodoxime and Amoxycillin with clavulanic acid combination are effective in the treatment of AECSOM.

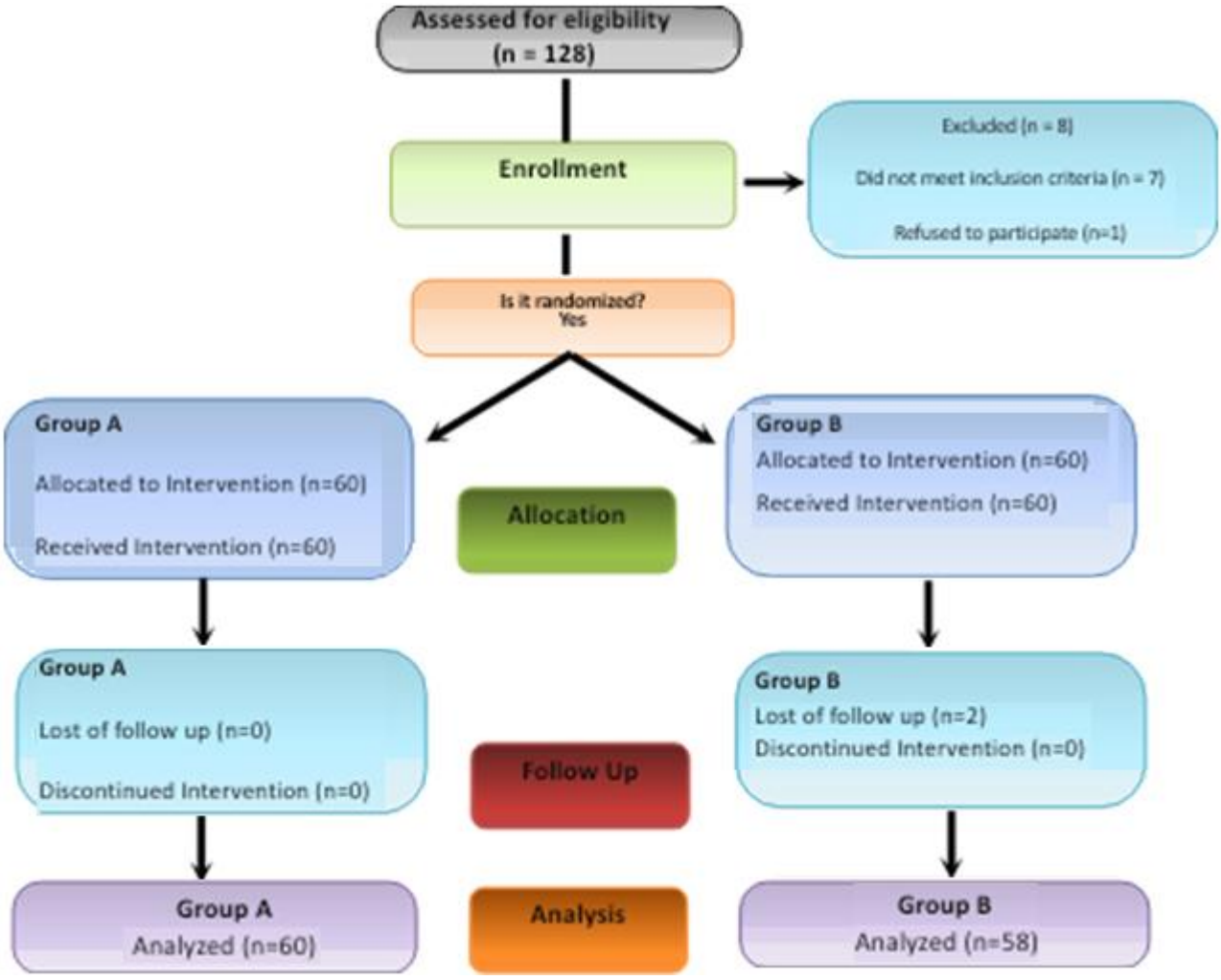
Table 6 denotes the association of diarrhoea between two groups of drug.

Diarrhoea was more common in the Amoxycillin group (26%; 16 patients) compared to 3% (2 patients) in Cefpodoxime group.

The incidence of nausea and vomiting was more in Amoxycillin with Clavulanic acid arm (109 patients; 92%), than in the Cefpodoxime arm. (8%; 9 patients) (Table 7).

Two subjects were lost during follow-up in group B and did not attend the hospital after the first visit.

The CONSORT flow chart:



4. Discussion

AECSOM has a high prevalence in developing countries like India, and can lead to many complications if not adequately treated with proper antibiotics. Different antibiotics have been used for this indication.

Several published studies have shown the effectiveness of ciprofloxacin for the treatment of AECSOM in adult patients. Few studies have also proved the effectiveness of Cephalexin and Ceftriaxone in adult patients with AECSOM. From the literature, it has been found that Baba et al. conducted a clinical trial that showed that ceftriaxone was effective in 65% patients with acute otitis media and 72% patients with AECSOM. [5] Another trial by Baba et al. reported that Cephalexin has a 35.5% failure rate in patients with AECSOM [6]. A study reported by Block et al. [7] compared the effectiveness of Cefdinir with Cefprozil, and

the results showed that the overall clinical cure rate with Cefdinir was 80% versus 82.5% with Cefprozil in the treatment of paediatric acute otitis media. Another study by Kafetzis showed that the overall clinical cure rate with cefixime was 85% in patients with acute otitis media [8]. A clinical trial done in 2012 by Arijit Ghosh et al, showed that a 7-day course of Cefpodoxime is therapeutically comparable to Ciprofloxacin in terms of both clinical effectiveness and safety for the treatment of patients with AECSOM. (95.6% in the Cefpodoxime group versus 90.9% in the Ciprofloxacin group) [9]. Some studies have evaluated the effectiveness of oral third-generation Cephalosporins in pediatric patients with otitis media. A prospective multicenter study involving 1380 children in Egypt, used Cefpodoxime and found the overall combined cure and improvement rate of all related signs and symptoms to be 98.9% [10]. A prospective longitudinal study was conducted on children diagnosed with acute otitis media, which found that a 10-day course of Cefpodoxime is therapeutically comparable to Amoxycillin with clavulanic acid combination in terms of both efficacy and safety (88% in Cefpodoxime group vs 93% in Amoxycillin with clavulanic acid group) [11]. A similar study involving 229 paediatric patients found cure rate of 68% for Cefpodoxime vs 65% for Amoxycillin with clavulaninic acid group, with lesser side effects in the Cefpodoxime group (20.9%) vs Amoxycillin with clavulanic acid group (30.6%) [12]. Gehanno P et al did a similar study and came to the conclusion that the higher clinical cure rate and equivalent safety profile of Cefpodoxime indicates that it is an acceptable alternative to Amoxicillin with clavulanic acid for the treatment of acute otitis media in children. [13]

Efficacy & clinical experience of Cefpodoxime in treatment of acute otitis media in children was reviewed by Cohen. R. and was found to be effective. [14] No head-on comparison study is available between Cefpodoxime and Amoxycillin with clavulanic acid in adult Indian patients for the treatment of AECSOM.

Due to high prevalent resistance patterns against Fluoroquinolones, we need to look at other antibiotics which can be efficacious in treating AECSOM.

In our study, efficacy of Cefpodoxime was found to be 98.33% whereas that of Amoxycillin with clavulanic acid combination was found to be 96.66%. ($p>0.05$). Thus Cefpodoxime has a good efficacy in treatment of adult Indian patients with AECSOM.

Adverse drug reactions (ADR) like gastrointestinal complaints were the most frequently reported drug-related side effect in both drugs: 11.8% of Cefpodoxime-treated patients and 21.1% of those given Amoxycillin with clavulanic acid combnation [12].

Incidence of diarrhoea, as well as nausea-vomiting in our study was found to be more in Amoxycillin-clavulanate group than in the Cefpodoxime group.

Primary care physicians should be aware of local resistance patterns of common antibiotics used for AECSOM. This will help them to prescribe antibiotics from the primary care level, with good tolerance as well as low resistance patterns, leading to overall reduced disease burden & lesser complications. This study will help them in deciding on the primary choice of antibiotic in adult Indian patients with AECSOM.

Some limitations of this study were as follows. A double-blind study could not be conducted due to financial constraints and logistic problems. Secondly, 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 h. Therefore, we conducted this study mainly to provide information to clinicians on the comparative effectiveness of these two antibiotics as initial antibiotics for AECSOM patients based on clinical assessment scores.

5. Conclusion

Our study result depicts Cefpodoxime proxetil to be equally efficacious in managing AECSOM and equivalent in efficacy to Amoxycillin with clavulanic acid combination against the most common bacteria that cause otitis media. Clinical and microbiologic cure rates were similar for both drugs, and drug - related side-effects were not statistically different.

The cost of Amoxycillin with clavulanic acid combination (we used brand AUGMENTIN, costs170INR/10 tabs.) is higher than that of Cefpodoxime (we used brand CEPODEM that costs 167INR/10 tabs). The pharmacoeconomic advantage of the latter drug can be considered as an important criteria for prescribing the drug in low socioeconomic group of patients.

The results of this study demonstrated that a 7-day course of Amoxycilllin with Clauvulanic acid combination is comparable to Cefpodoxime in terms of both clinical effectiveness and safety for the treatment of AECSOM in an outpatient setting. Although cost of drug therapy was higher with Amoxycilllin with Clauvulanic acid combination compared with Cefpodoxime, 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.

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