Comparative Efficacy and Safety Evaluation of Cefaclor VS Amoxycillin + Clavulanate in Children with Acute Otitis Media (AOM)

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Abstract. Acute Otitis Media (AOM) is the most frequent respiratory tract infection of infancy and childhood that is treated with antimicrobial agents. The most common causative pathogens include Streptococcus pneumoniae, Haemophilus influenzae and Moxarella catarrhalis, and therefore antibacterial management should target against these isolates. Cefaclor, a congener of cephalexin monohydrate, is a semisynthetic cephalosporin antibiotic. It is an orally active cephalosporin which has demonstrated activity against a wide range of organisms in vitro. Present study is designed as a multicentric prospective trial to study and compare the efficacy and safety of cefaclor versus amoxicillin+clav in children with acute otitis media. One hundred and sixty seven patients were evaluated for efficacy endpoints in the cefaclor arm comprised of 104 males and 63 females with a mean age of 5.74±2.80 years and 185 patients in the amoxy-clav group comprised of 118 males and 67 females with a mean age of 4.93±2.92 years. Both cefaclor and amoxy-clav caused a significant improvement in all the signs and symptoms after a 10-day treatment period. However, between-the-group comparisons showed that the reduction in most of the symptoms was significantly more in cefaclor arm as compared to amoxicillin-clav arm. The clinical success (clinical cure + improvement) at the end of therapy was significantly more in cefaclor arm: 98% with cefaclor versus 85% with amoxicillin+clav, p<0.05 (Table 3). Failure cases were prescribed other antibiotics according to the culture sensitivity reports, as rescue medication. Bacterial eradication rates were largely consistent with clinical responses. Bacteriological eradication was seen in 95% of patients in cefaclor group and 78% of patients in amoxicillin+clav group. In conclusion, cefaclor is a well tolerated and effective antibacterial option for acute otitis media in children and it is superior to the combination of amoxicillin+clav in efficacy and tolerability in acute AOM. Moreover, its expanded spectrum of activity, ability to achieve adequate concentrations in tissues, suitability for twice-daily dosing, and proven tolerability suggest that it is a good alternative to agents traditionally used in acute otitis media.

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Acute Otitis media (AOM) is the most frequent respiratory tract infection of infancy and childhood that is treated with antimicrobial agents. Complications of untreated AOM include mastoiditis, meningitis, lateral sinus thrombosis and chronic suppurative otitis media. Earlier, the complications of untreated AOM were infrequent in developed countries because of the efficacy of orally administered antibiotics. However, with the emergence of multidrug resistance among all the major bacterial pathogens, serious complications can occur.

The most common causative pathogens include Streptococcus pneumoniae, Haemophilus influenzae and Moxarella catarrhalis, and therefore antibacterial management should target against these isolates. Increased incidence of beta-lactamase-producing strains of H.influenzae and M.catarrhalis in acute otitis media reinforces the fact that beta-lactamase stable drugs such as second and third generation oral cephalosporins and amoxicillin/clavulanate have become alternative therapies, particularly for patients with recurrent otitis media. Resistance to penicillins is also of increasing concern particularly among strains of S. pneumoniae and AOM patients are more likely to be penicillin-resistant than isolates from any other source. Persistent and recurrent AOM more frequently involves pathogens with increased resistance to antimicrobials.

Cefaclor, a congener of cephalaxin monohydrate, is a semisynthetic cephalosporin antibiotic. It is an orally active cephalosporin which has demonstrated activity against a wide range of organisms in vitro. It is well absorbed when given orally on an empty stomach. Although metabolism may play a role in the disposition of cefaclor, elimination is primarily renal. Cefaclor's spectrum of activity is better than the commonly used first-generation cephalosporins, including a wide range of gram-negative and gram-positive bacteria; in particular, Escherichia coli, Klebsiella spp. Proteus mirabilis,
Salmonella spp. and Haemophilus influenzae are more susceptible to clinically achievable concentrations of cefaclor than cephalixin. Cefaclor has been demonstrated to be effective against beta-lactamase-producing H. influenzae resistant to ampicillin. Efficacy of cefaclor has been demonstrated in urinary tract, upper and lower respiratory tract, and skin and soft tissue infections in adults and children as well as in pediatric otitis media. Adverse reactions, mostly gastrointestinal, are generally mild and occur in few patients. Combination of amoxycillin and clavulanate (a beta-lactamase inhibitor) have been used in various respiratory tract infections including Otitis media.

On this background present study is designed as a multicentric prospective trial to study and compare the efficacy and safety of cefaclor versus amoxicillin+clav in children with acute otitis media.

**MATERIALS AND METHODS**

**Study Design**

Under a prospective, open, comparative and multicentric study patients were treated as out-door patients or hospitalized during the treatment period and this was at the discretion of the investigator. All participating patients or their legal guardians provided consent prior to enrollment. And the Institutional Review Board or Independent Ethics Committee of each site approved the study protocol.

**Patients**

In the study only the patients aged 6 months to 12 years with clinical symptoms and tympanic membrane signs of AOM, otoscopic evidence of acute inflammation (dullness, cloudiness, erythema or bulging, perforation) plus tympanometric-confirmed middle ear effusion in at least 1 ear were enrolled. Both fresh and recurrent cases (without complications like mastoiditis) were included. Eligible patients were not on any other antibiotic therapy when enrolled in the study.

The study excluded the patients with appearance and history more suggestive of chronic otitis media with effusion, ventilation tube, perforated tympanic membrane, and chronic suppurative otitis media; serious chronic disease (for example, cystic fibrosis, valvular heart disease); previous complications (septic complications, hearing impairment); children with complicated AOM (eg. mastoiditis), facial abnormalities, that would confound evaluation of the therapeutic response; known severe renal disease; patients hypersensitive/contraindicated to study drug.

**Study procedure**

Either cefaclor 20 mg/kg – 40 mg/kg per day in 3 divided doses for 10 days (cefaclor arm) or Amoxyclillin + clavulanate = 45mg/kg every 12hrlly or 40mg/kg every 8hrlly for 10 days (amoxycillin arm) was administered to those patients fulfilling the inclusion criteria of the study. No topical aural antibacterial within 2 days before the study or any systemic antibacterial within 2 days before the study or during the study were allowed. Before initiating the antibiotic therapy, the ear canal was cleansed with an antibiotic and tympanocentesis was performed in order to obtain middle ear fluid for isolation of bacterial pathogens as well as determination of antibiotic susceptibilities.

From the first day up to the end of therapy (on 10th day) the patients were evaluated. Wherever possible, tympanocentesis was repeated if there was no clinical improvement after 72 hour of treatment or as clinically indicated. Patients requiring antacids containing aluminium and magnesium salts were administered 8 hours before or after cefaclor/amoxyl-clav administration. If the symptoms were not controlled or worsened, additional medications could be given depending at the attention of the investigator and this rescue medication was recorded in the CRF.

Patients were considered to be compliant with the study medication if at least 80% of study medications were taken according to the prescribed regimen (as judged by the investigator by asking questions to the patient and/or their parents/guardian. Otherwise patient was considered to be normal.

**Evaluation Visits**

After keen observation of the patient the physician recorded for adherence to therapy, any adverse drug reactions and the clinical response on the following days:

- Visit 0: Day 0 (inclusion w.r.t, eligibility criteria)
- Visit 1: Day 1, start of study medications
- Visit 2: Day 10, end of therapy.

In order to assess the tympanic membrane for severity of erythema, opacification, loss of light reflex, fullness or bulging, drainage, perforation, mobility and middle ear effusion autopsy was performed at each visit. Tympanometry was interpreted to confirm the presence (abnormal) or absence (normal) of middle ear effusion.

At each visit symptoms of otalgia, irritability, anorexia, lethargy, decreased hearing, vertigo and fever were assessed. For any complications patients were also monitored.

**Efficacy Assessment**

Primary outcome measures were listed as follows

1. At the end of the therapy clinical resolution of tympanic membrane (otoscopic) signs and symptoms of AOM determined.
2. No. of cases in which change of antibiotics was needed
3. Physician Global Evaluation of patient condition (using a 5-point scale)
   - 1=Excellent, 2=Very Good, 3 = Good, 4= Fair, 5 =Poor
4. Clinical Outcome was defined as follows:
   - *Clinical Cure*: Defined as absence of fever, otalgia,