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ROLE OF ANTIMICROBIAL IN TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

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ABSTRACT

Antimicrobial treatment decreases the signs and symptoms of acute otitis media (AOM). The effect of antimicrobial treatment on the duration of middle ear effusion (MEE) and concomitant hearing impairment is still not known. The study was conducted to determine whether the antimicrobial treatment of AOM reduces the duration of MEE. This randomized controlled trial included a total number of 84 children with AOM with age between 6 months and 15 years. Participants were recruited from the start of September , 2021 to January 2022 from among children attending an AOM prevention trial and children visiting ENT outpatient department at Santosh university. The Middle ear effusion disappeared 2 weeks (13.7 days) earlier (P = .02) in antimicrobial group than in placebo group . Normal otoscopy findings were observed 1.4 weeks earlier in the antimicrobial group than in placebo group (P = .02). On day 14, 69% of the children in antimicrobial group and 38% in placebo group had normal tympanometry findings . On day 60, 2 children (5%) in antimicrobial group and 10 children (24%) in placebo group had persistent MEE (P = .01). Antimicrobial treatment has effectively reduced the duration of MEE and possible concomitant hearing impairment in children with AOM. Antimicrobial treatment also reduced the risk for persistent MEE.

Keywords: acute otitis media, middle ear effusion , antimicrobial therapy

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INTRODUCTION

The antimicrobial treatment of acute otitis media (AOM) has proved to be effective in the randomized clinical trials (RCTs); however, its effect on the relieving symptoms has been modest.[1-4] It has been suggested that antimicrobial treatment of AOM should be limited to the children with significant symptoms.[1] In addition to relieving symptoms, the antimicrobial treatment of AOM could be important in alleviating impaired hearing. Conductive hearing loss due to middle ear effusion (MEE) in early childhood could result in poorer speech development and cognitive skills later at school age, although in RCTs, prompt tympanostomy tube placement did not improve the later cognitive outcome of children with chronic MEE.[5-9] The effect of the antimicrobial treatment of AOM on the duration of MEE and concomitant hearing impairment is not known.[2] In most RCTs, the follow-up using tympanometry or otoscopy has been performed at weekly or monthly intervals after the initial episode.[3,10-15] Thus, the lack of evidence show- ing that the MEE disappears faster after antimicrobial treatment can result from the inaccurate measure of MEE or it can be due to new respiratory tract infections and the new development of effusion in the middle ear after the initial episode. To improve the measurement accuracy, ideally the middle ear status of children attending a trial should be examined daily. Because tympanometry is reliable tool for determining the amount of MEE[16,17] and hearing impairment,[18] we designed a placebo-controlled RCT of anti-microbial treatment of AOM and trained the parents to perform tympanometry daily with a handheld device at their home. With this approach, we aimed to clarify that whether the antimicrobial treatment of AOM reduces duration of the MEE and concomitant hearing impairment.

MATERIAL AND METHODS:

This was a randomized controlled trial in the children between age of 6 months and 15 years, conducted in Santosh university. Only those children whose parents provided written informed consent were taken in the trial. Patients were recruited from September 2021, to January, 2022 from among children in day care centers attending an AOM

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prevention trial at the Department of ENT, Santosh University Hospital.

Eligible participants were between age of 6-months to 15-years children with an AOM episode. Only children with acute symptoms of respiratory infection and/or ear-related symptoms and signs of tympanic membrane inflammation together with MEE detected in pneumatic otoscopy performed by a study physician were eligible for trial.[20] The otoscopists were validated against the tympanometry and tympanocentesis. Exclusion criteria were AOM complication, ventilator tubes,Down syndrome, amoxicillin allergy, congenital craniofacial abnormality, and immunodeficiency. The families of total 120 children with AOM were invited to participate when a portable tympanometer was available . First, 31 children underwent tympanometry screening prior to study; children who had normal tympanometry findings on screening and later developed symptomatic AOM during a respiratory tract infection were eligible for the trial.[19] In addition to this, 53 children were included from the outpatient clin ics and accepted into the study provided they had no history of AOM diagnosis within previous month and had developed symptomatic AOM during a respiratory tract infection .

The children were randomly assigned to receive either an oral mixture of amoxicillin-clavulanate for 7 days (40 mg/kg of amoxicillin/day divided into 2 daily doses) or a placebo mixture. A randomization list was created by computer in blocks of 4 and was kept in the pharmacy , which delivered the study drugs to the families according to the consecutive study number. Both product bottles were in distin guishable and the dosing was similar in both groups. The placebo mixture was artificially flavored to resemble the taste of the amoxicillin-clavulanate mixture. The children, their families, and all participants of the study group were blinded to the treatment group until the data entry and checking were completed for all of the children.

Primary outcome measure was the time to the disappear ance of MEE as defined by a normal tympanogram finding (A curve) from both ears on 2 consecutive measurement days either at home or at the study clinic. Analysis was performed per child. If tympanometry was not successful, the next available tympanogram was used in the analysis.

The Secondary outcome measures were the time to improved tympanogram findings (ie, A or C curve) from both the ears and time to normal pneumatic otoscopy or

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Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

otomicroscopy findings from both the ears. The proportions of children with persistent MEE on days 7, 14, and 60 were compared between both the groups. The disappearance of pain and fever, the use of pain medication, and data on possible adverse effects of antimicrobial treatment were recorded and compared between both the groups.

The study physician examinedall the children with pneumatic otoscopy or otomicroscopy and tympanometry at study en try, after 3 and 7 days, and then weekly until both the ears were healthy according to the pneumatic otoscopy or otomicroscopy. In addition to the scheduled visits, families were also encouraged to contact the study physician during the office hours or any emergency, at any time if the study participant experienced severe symptoms. In this case, either the study physician or an emergency department physician stopped administering the study drug and began the rescue treatment with amoxicillin-clavulanate in a nonblinded manner . Parents were advised to use a symptom sheet diary throughout the follow-up to collect daily data on other symptoms (fever, cough, ear ache, throat ache, rhinitis, vomiting, diarrhea, conjunctivitis, sleeping difficulties, and eating diffi culties), as well as the number of study drug doses and other medications administered.

Sample size was calculated by sample-size calculation for survival analysis. The calculations were based on median duration of the MEE (I.e 7.5 days) evaluated with daily tympanometry in our previous study.[21] We regarded longer median duration of MEE in the placebo group as clinically significant if the difference in median survival times was 7 days (7 days in the amoxicillin-clavulanate group and 14 days in the placebo group). Each group required 38 children for a type I error of 0.05 and a type II error of 0.20 (power, 80%). To achieve this in the final comparison, we decided to recruit 84 participants.

Statistical Analyses

We used the Kaplan-Meier survival analysis to analyze durations of MEE and ear pain and the log-rank test to test the differences between the groups. We used a standardized normal deviate test to compare the proportions of the children with resolved MEE between the amoxicillin-clavulanate group and the placebo group, and we calculated the number needed to treat based on the absolute differences of the proportions between the study groups as well as 95% CIs for the differences. All analyses were

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performed in the intention-to-treat population . All children provided follow-up time until their ears were healthy or their parents terminated the study vis- its. Analyses were carried out with IBM SPSS Statistics version 20 and Stats Direct software 2.7.8.

RESULTS

A total of 84 children underwent randomization . The clinical characteristics of the participants at study entry were similar across the study groups . One child in the amoxicillin-clavulanate group and 3 children in the placebo group prematurely discontinued the follow-up . In total, 15 children in the amoxicillin-clavulanate group and 11 children in the placebo group developed new symptoms of viral respiratory tract infection (after being asymptomatic at least for 2 days) before the MEE was resolved. The proportions of the study drug doses administered as planned were 96% in the amoxicillin clavulanate group and 95% in the placebo group. The mean (SD) numbers of tympanograms were 18.3 (6.4) per child for each ear in the amoxicillin-clavulanate group and 20.7 (7.3) in the placebo group. Tympanometry proved successful in 95.8% of all examinations at the study clinic and in 86.5% of examinations at home. The child's anxiety or crying was the main cause of failure of the examination at the study clinic.

The duration of MEE was shorter in the amoxicillin- clavulanate group than in the placebo group. Middle ear effusion disappeared 2.0 weeks earlier (P = .02) in the anti- microbial group than in the placebo group. The mean duration of MEE per AOM episode decreased by 8 days among children younger than 2 years of age, by 20 days among children 2 to 6 years of age, and by 1 day among older children. The median time to MEE disappearance was 8.0 days in the amoxicillin-clavulanate group and 29.0 days in the placebo group.

Normal otoscopy findings appeared 9.7 days sooner (P = .02) in children treated with amoxicillin-clavulanate than in those in the placebo group . When combined tympanometry and otoscopy findings were used in the analysis, MEE resolved 11.5 days (P = .002) sooner in the antimicrobial group than in the placebo group On days 7 and 14 after administration of the study drug, the proportion of children with resolved MEE was greater among children who received amoxicillin-clavulanate than among those who received placebo . The absolute difference in the percentage

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Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

of children with resolved MEE between the study groups was 31% on day 14; 3.2 children required treatment with amoxicillin- clavulanate to prevent 1 child from exhibiting abnormal tympanometry findings. Two children (5%) treated with amoxicillin-clavulanate had persistent MEE (≥60 days), and 10 children (23%) in the placebo group had persistent MEE at the end of the trial (P = .01). To prevent persistent MEE at 2 months in 1 child, 5.3 children required treatment with amoxicillin-clavulanate .

The mean (SD) times to disappearance of the ear ache were 2.2 (2.2) days in the amoxicillin-clavulanate group and 3.2 (2.3) days in the placebo group (; P = .08). The proportion of the children with ear ache differed statistically 5 days after administration of the study drug; at that time, none of the children in the amoxicillin- clavulanate group experienced ear pain, whereas 17% in the placebo group did (P = .004). The number of children requiring antimicrobial treatment to prevent 1 child from experiencing ear pain on day 5 was 5.8. Differences in the dosage or duration of the pain medication between the groups were not statistically significant nor were differences in the disappearance of fever statistically significant.

DISCUSSION

Middle ear effusion disappeared significantly earlier than in children who received amoxicillin-clavulanate than in those children who received placebo in our study. In children receiving antimicrobial treatment, the mean duration of MEE was reduced by 2 weeks and the median duration of MEE was reduced by 3 weeks per AOM episode. To prevent 1 child from exhibiting abnormal tympanometry findings at 2 weeks, 3 children required antimicrobial treatment. Thus, antimicrobial treatment effectively reduced the duration of the MEE and possible concomitant hearing impairment in children with AOM.

Our findings contradict those of the several RCTs and those of 2 meta-analyses, which concluded that the antimicrobial treat ment has no impact or affect on the duration of MEE evaluated by tympanometry or otoscopy.[1,2,10-14] The most likely expla nation for this discrepancy is that we obtained daily informa tion on middle ear status. In this way, we had an accurate measurement of the duration of MEE and avoided including new respiratory tract infections and the subsequent development of new MEE in the

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, Oct 2022

study population. In addition, the propor tion of children with chronic MEE at study entry was low in our study. Thus, we were able to determine the benefit of antimicrobial treatment in the disappearance of MEE during 1 AOM episode.

Our results are important because MEE impairs hearing, which may cause long-term harm to later linguistic or other cognitive skills. Among children with MEE, flat tympanograms reportedly correspond to hearing levels ranging from 20 to 50 dB,[22] whereas a peaked tympanogram eliminates the risk for hearing impairment.[23] In a meta-analysis of prospective studies, both receptive and expressive language were more impaired in children who had previously had otitis media with effusion than in control participants.[24] However, in randomized trials, prompt tympanostomy tube placement did not markedly improve the later cognitive outcome of children with chronic MEE over that of children who underwent the procedure later.[7-9]

The recommended treatment of otitis media with effusion after an acute infection episode is a watchful waiting period of 3 months, with interval visits to a physician to document persistent effusion.[25] In unresolved cases, hearing should then be examined and surgery should be considered.[25] Approximately 700 000 myringotomies with the insertion of a tube and more than 100 000 adenoidectomies are performed annually in the India in children younger than 15 years of age.[26] Our study was not designed to estimate the differ ence of follow-up visits and subsequent surgery owing to chronic otitis media with effusion between the study groups. However, we are concerned that limiting the antimicrobial treatment of AOM may increase the need for subsequent follow-up visits and possible surgery because this study showed that the risk for persistent MEE at 2 months among children in the placebo group was 5-fold higher than in the antimicrobial group.

In young children and infants with AOM, antimicrobial treatment appears to have a modest effect on the proportion of ab- normal otoscopy findings at 1 week[4] and on the rate of remaining MEE at 3 weeks.[3] However, in our study, the magnitude of the effect was greater, which may be owing to the older age of our study population. Pneumococcal resistance to penicillin is low in India.[27] Consequently, the antimicrobial dosing ap propriate for our setting may be insufficient for settings in other countries. Most of the study

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participants had not received pneu mococcal conjugate vaccine, which can influence the spectrum of otopathogens.[28] The optimal duration of antimicro bial treatment was not studied in this trial. We evaluated the efficacy of 1 week of antimicrobial treatment. Although the accuracy of tympanometry in detecting middle ear fluid is good,[16,29] few studies have used handheld tympanometry for daily surveillance at home.[21] Our approach was feasible as most of the home measurements were successful.

CONCLUSIONS

We conclude that the antimicrobial treatment of AOM in children is beneficial because it significantly reduces the duration of MEE. Thus, hearing impairment due to AOM can likely be resolved faster in children treated with antimicrobials.

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