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Original Article

Comparing the Synergistic Effects of Zinc, Probiotics, and Amoxicillin in treating Acute Otitis Media in Children

Mohammad Bagher Rahmati[1], Maryam Mojdeh[2*], Elaheh Behboodi[3]

[1]Department of Pediatric Infectious Disease, School of Medicine, Children's Clinical Research Development Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2]Student Research Committee, Department of Pediatrics, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[3]Department of Otorhinolaryngology, Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Abstract

Background: Otitis media is mainly caused by pneumococci and is one of the most common diseases in children. It can lead to hearing problems, thereby resulting in learning and behavioral problems. This study aimed to compare the synergistic effects of zinc, probiotics, and amoxicillin in treating the otitis media.

Materials and Methods: In this double-blinded randomized clinical trial, 94 children aged between 6 months and 6 years with acute otitis media were studied. Children were divided into three groups who were administered with: amoxicillin, amoxicillin plus probiotics, and amoxicillin plus zinc per day. The first group received 80-90 mg/kg amoxicillin; the second group had one sachet of protexin in addition to amoxicillin; while the third group received 10 mg zinc in addition to amoxicillin. The treatment lasted for ten days.

Results: Overall, 72.3% of patients responded to primary therapy and 5.31% had complications among which 5 had perforation. All these 5 cases belonged to the amoxicillin-receiving group. None of the patients showed relapse. In addition, 30 (60%) in the amoxicillin group, 19 (82.6%) in the amoxicillin and zinc group, and 19 (90.47%) in the amoxicillin and protexin group responded to the treatment. There was no statistically significant difference between the three groups in terms of responses to the treatment. Considering the gender of children, 37 girls (82.22%) and 32 boys (65.3%) responded to the treatment.

Conclusion: The results showed that 10-day application of probiotics and zinc along with amoxicillin arose no significantly different response in acute childhood otitis media compared to the treatment with amoxicillin alone; however, it could reduce the complications of the disease. Considering the difference in the results of studies on probiotic effects on the treatment of infections in children, further studies are recommended.

Keywords: Acute otitis media, Children, Amoxicillin

***Correspondence to**
Maryam Mojdeh, Student Research Committee, Department of Pediatrics, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
Mobile: +98 917 474 2530
Email: maryammojdeh413@gmail.com

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Introduction

Otitis media is the inflammatory response of the middle ear due to various factors including infection and dysfunction of the eustachian tube (1, 2). Around 10%-15% of physician referral of children is related to otitis media. Furthermore, 80% of children experience the disease at least once until the age of three (3-5). The disease is usually more common in the cold season, with lower prevalence in the summer. Moreover, children with respiratory problems are more likely to develop acute otitis media (6, 7). If not cured, this disease may lead to otitis media with effusion with probable hearing problems in the child which may cause learning and behavioral problems in the future (3, 8). The aim of the treatment is to eliminate discharge and create normal hearing, as well as preventing future episodes. The most common symptoms of acute otitis media which require proper treatment are earache and fever. Recommended therapies are acetaminophen (rectal or oral, 60 mg/kg/d in 4 to 6 divided doses) or ibuprofen (oral, 20-30

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mg/kg/d in 3 or 4 divided doses); both of these drugs have the same effectiveness in pain and fever control (4). Although many cases recover from the disease within 10 to 14 days, antibiotic therapy is recommended. In this regard, the first choice for antibiotic treatment is amoxicillin (50-60 mg/kg/d in three divided doses for 10 days). The advantages of amoxicillin include good efficacy, high immunity, and low side effects, as well as low cost and acceptable taste (3). In some studies, the effects of auxiliary treatments such as probiotics or zinc have been confirmed which can increase the effectiveness of antibiotics. Probiotics contain sufficient number of living and specific microorganisms which change the microbial flora through placement or colonization in the host body, thereby inducing beneficial effects on the host's health (9). Zinc is an essential mineral for the immune system. It affects both the inherent and acquired immune systems. This mineral is even required in the early stages of defense response. Zinc deficiencies disrupt neutrophil chemotaxis and phagocytosis (10). The results of a study on the effect of probiotics on otitis media showed that in high-risk populations, acquiring high levels of bacteria would increase the incidence of otitis, while reducing the amount of pathogen bacteria and colonization of the nasopharynx by beneficial bacteria instead can reduce the prevalence of otitis media (11). A study on malnourished children indicated the beneficial effect of zinc in reducing the number of otitis media episodes (2). According to the aforementioned and contradictory results in this field, the present study aimed to compare the synergistic effects of zinc, probiotic, and amoxicillin on the treatment of acute otitis media.

Materials and Methods

This double-blinded randomized clinical trial (identifier: IRCT20180829040901N1) was conducted in Bandar Abbas pediatric hospital which is the only children's hospital in the city. Children aged 6 months to 6 years living in Bandar-Abbas and diagnosed with acute otitis media were included in the study. Children with no parent consent, receiving zinc or probiotics or having allergy to zinc, phenylketonuria and chronic pulmonary, cardiac disease, and immune deficiency (primary or secondary) were excluded. Therefore, 94 children who suffered from acute otitis media were enrolled. To estimate required sample size, we used sample size formula (type one error (α) = 0.05, type two error (β) = 0.2 (power = 80%)). Based on a previous study, the success proportion in control group was $P1 = 0.102$ and in the zinc group was $P2 = 0.459$. We also took a twice sample size for the control group (only amoxicillin); the sample size with 5% drop out was estimated 46 patients for the control group and 23 patients for each of the treatment groups. To assess randomization code, Random Allocation Software was used. The randomization code was sealed in an opaque envelope which was stored at the hospital. After obtaining informed consent from the parents, the subjects were randomly divided into three groups. The patients enrolled from 2 to 15 may 2018 were assigned to one of the study groups according to a block randomization code. The block randomization method was used at a 2:1:1 ratio to ensure a balanced distribution (Figure 1). The patients and researchers who were performing the treatment even assessing the outcomes, were blinded to the treatment. Three medicines (amoxicillin, zinc, and protexin) had the same appearance, shape, and packaging, so the research physicians and participants were unaware

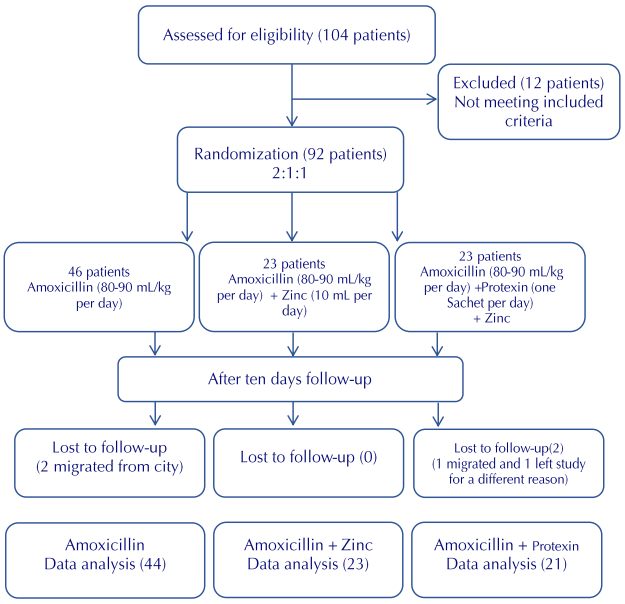

Figure 1. Flowchart of Study Participants.

of the differences. A third person how was not involved in the study assigned amoxicillin with "A", zinc with "B", and protexin with "C" letters. The research physicians and participants were not informed about individual treatment details until the end of the treatment.

Each of the patients were followed up for 10 days (from 10 to 24 May 2018). During follow-up, no analysis was done. The first group received elemental zinc (Farabi Co.) for 10 days (zinc syrup containing 10 mg/10 mL elemental zinc) and amoxicillin (Farabi Co.) at the dosage of 80-90 mg/kg daily for 10 days. The second group was prescribed with probiotics (protexin; one sachet per day from Nikotech Co.) and amoxicillin at the dosage of 80-90 mg/kg/d for 10 days. The third group received amoxicillin (80-90 mg/kg/d) for 10 days.

At the end of the 10-day period, the patients were evaluated by a specialist using otoscope. Children were assessed for liquid accumulation in the middle ear, and redness and swelling of tympanic membrane. The patients were also examined by an audiologist using tympanometry. Abnormal and normal tympanometry were considered as Types B and A, respectively. In case of no recovery after 48 hours, incidence of any complications including tympanic membrane rupture, acute mastoiditis, meningitis, and serous otitis media were evaluated.

Data analysis was done using IBM SPSS statistics (version 22.0). The chi-square test was used to compare the proportions of sex in three groups. The one way analysis of variance (ANOVA) was used to compare the mean age of patients in three groups. Moreover, to compare the success of treatment in three therapeutic methods, unadjusted (crude) and adjusted odds ratios (OR) were estimated by bivariate and multivariate logistic regression analyses with 95% CIs, respectively. For all statistical tests, $P<0.05$ was considered as significance level.

Power analysis was based on a comparison between "amoxicillin" and "amoxicillin + zinc" and obtained as 88.9%, and based on a comparison between "amoxicillin" and "amoxicillin + protexin" and obtained as 74.3%.

Results

Table 1 shows the baseline characteristics of the study subjects in the three groups. Overall, the mean age of patients in three groups was not significantly different ($P=0.083$). Likewise, the results of chi-square test showed that the distribution of male and female subjects in three groups was not statistically different ($P=0.521$).

The results of adjusted logistic regression showed that there was not any relationship between ages ($P=0.09$). The results also showed that risk of type A tympanometry in both male and female subjects was not statistically different (OR = 1.08; (95% CI: 0.35-3.29); $P=0.90$) (Table 2).

Furthermore, the results of adjusted logistic regression displayed that patients who received amoxicillin with zinc were at risk of type A tympanometry 2.44 times less than the patients who received only amoxicillin though this was not statistically significant (OR = 0.41, 95% CI: 0.11-1.51; $P=0.181$). Moreover, according to the results, patients who were treated with amoxicillin and protexin were at risk of type A tympanometry 6.67 times less than the patients who received only amoxicillin (OR = 0.15, 95% CI: 0.03 - 0.83; $P=0.030$) (Table 2).

Discussion

Regarding high prevalence of acute otitis media and its complications, several studies have been conducted on the treatment of the disease (1). Some studies have

Table 1. Baseline Characteristics (Age and Sex) of Patients in Three Groups

Characteristics		Amoxicillin (44)	Amoxicillin+ Zinc (23)	Amoxicillin+ Protexin (21)	Statistics	*P* Value
Age(year), mean ±SD	-	3.55±1.78	3.64±1.57	2.64±1.63	2.56	0.083*
Sex, n (%)	Male	32(65.3)	9(18.4)	8(16.3)	6.38	0.521**
	Female	18(40.0)	14(31.1)	21(28.9)		

SD, standard deviation.
*One way analysis of variance, **Chi-square test

Table 2. Results of Crude and Adjusted Logistic Regression Models for Factors Affecting Tympanometry in Children

Characteristics	Subgroups	Unadjusted Logistic Regression		Adjusted Logistic Regression	
		OR (95% CI)	*P*-value	OR (95% CI)	*P* Value
Age	-	0.82 (0.61-1.10)	0.180	0.75 (0.54-1.04)	0.09
Sex	Female	-	-	-	-
	Male	1.78 (0.65-4.85)	0.261	1.08 (0.35-3.29)	0.90
Treatment	Amoxicillin	-	-	-	-
	Amoxicillin + zinc	0.41 (0.12-1.41)	0.167	0.41 (0.11-1.51)	0.181
	Amoxicillin + protexin	0.20 (0.04-0.99)	.049*	0.15 (0.03-0.83)	0.030*

*$P<0.05$

addressed the efficacy of probiotics and zinc alone or in combination with antibiotics such as amoxicillin.

In the present study, the effect of monotherapy with amoxicillin and its effect in combination with zinc or protexin on acute otitis media was studied in a population of 94 patients. Although the groups were not significantly different in their responses to the treatment, the response to treatment in the amoxicillin plus zinc group and in the amoxicillin plus protexin group was 1.22 and 3.43 times higher than that in the amoxicillin group, respectively. This difference reflects the positive effect of probiotics and zinc on otitis media. The insignificance of difference can be attributed to the small number of subjects in each group.

Protexin was effective in treating the otitis media due to its impact in suppressing the growth or the mucosal attachment of pathogenic bacteria, improvement of the protective barrier against infection, as well as modulating the immune system, which induces the production of protective cytokines and inflammatory suppressive cytokines such as TNF in mucus.

Marchisio et al found that application of propolis and zinc suspensions could reduce the risk of otitis media in children (12). John et al also observed that probiotics can decrease the outbreak of otitis media. The results of these two studies are not in line with the present study possibly due to the difference in probiotics used (11).

Furthermore, in the study of Hatakka et al, probiotics were not effective in decreasing the incidence of otitis media; this result corroborated the results of the present study (13). Based on the studies, there is no agreement between different results, and the present study also failed to demonstrate whether probiotics and zinc are useful in acute otitis media. Hence further studies are required.

Another notable point is the absence of complications in the two groups of probiotic and zinc compared to the amoxicillin group in such a manner that all cases of tympanic perforation were in the amoxicillin group. Similar studies have also confirmed this result, demonstrating the safe use of probiotics and zinc, which can be used in subsequent studies without concerning about the probable increase of the risk of complications due to the side effects of probiotics and zinc.

The relapse of the disease after treatment is also a significant issue. No recurrence was recorded for the patients of this study and there was no difference between the three groups. Rautava et al similarly found that probiotics can reduce the risk of otitis media and its relapse; this is consistent with the results of the current study in terms of relapse rates. Patients should be followed up for a longer period to check the relapse rate (14).

The results of a double-blind, placebo-controlled trial done by Cohen et al showed that the treatment and control groups did not differ in the incidence of acute otitis media, lower respiratory tract infections, or number of antibiotic treatment courses. Moreover, treatment was not associated with recurrent acute otitis media and did not reduce its risk, recurrence, antibiotic use or lower respiratory tract infections in a one-year period (15).

It is possible that some limitations have influenced the results obtained. One of the limitations of this study is the small sample size due to the low prevalence of otitis media during conducting the study. Inadequate cooperation of the patients' families in correct administration of the medicine can be mentioned as the other limitation of the current study.

Conclusion

The results of this study indicated a several-fold higher response rate to the treatment in the probiotic group and the zinc group compared to the amoxicillin group, although this difference was not statistically significant. According to the results of this study and similar studies on the effect of zinc and probiotics on the recovery of children suffering from acute otitis media and their positive effects in preventing the complications and recurrence of disease, it seems that probiotics and zinc can be used in the treatment of otitis media in children and reducing its complications.

Conflict of Interest Disclosures

The authors declare that there is no potential conflict of interests.

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Ethical Statement

The current study was approved by the Ethics Committee of Hormozgan University of Medical Sciences (Ethics code: IR.HUMS.REC.1397.020). The study was also registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT20180829040901N1).

Authors' Contributions

MBR: wrote the proposal, designed and performed the experiments.
MM: analyzed data, wrote and submitted the paper.
EB: wrote the proposal and designed the experiments.

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Informed Consent

The volunteers signed informed consent forms after the study objectives were explained to them.

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