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Effect of oral supplementation of zinc on treatment of otitis media with effusion

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Abstract

Objective: To determine the effect of oral zinc sulfate supplementation given with coamoxiclav when compared with coamoxiclav alone for treatment of otitis media with effusion (OME). The efficacy of the drug was assessed 3 and 6 weeks after administration.

Methods: In a double-blind, randomized trial 4 to 14 years old children with OME who referred to ear, nose and throat clinic, were randomly assigned into two groups:

1) Zinc group: Zinc sulfate + Coamoxiclav + Pseudoephedrine + Nacl nasal drop

2) Placebo group: Placebo + Coamoxiclav + Pseudoephedrine + Nacl nasal drop.

A total of 52 children were studied consisting zinc group 29 and placebo group 23 children. Children were examined by otoscopy and tympanometry at entry and after 3 weeks of treatment. For children who had not been cured completely after 3 weeks, treatment continued for more 3 weeks (total of 6 weeks).

Results: At the end of the first course of treatment (3 weeks) 62.1% of children in the zinc group had clinical improvement compared with 43.5% of children in placebo group. Tympanometrically, 70.9% of children in zinc group had improvement compared with 65.5% for placebo group with no statistically significant difference. There was no significant difference between the two groups at the end of second course of treatment (6 weeks). But the response rate of zinc group was better than the placebo group (43.8% versus 12.5% clinically and 56.3% versus 40% tympanometrically). Zinc administration and cycles of treatment had no significant relationship.

Conclusion: Although in this study oral zinc sulfate supplementation had not significant effect on treatment of OME, the response rate was better in zinc group compared to placebo group specially in longer administration.

According to the findings, it seems more studies about oral zinc supplementation in the treatment of OME is needed.

Keywords: supplementation of zinc, otitis media with effusion, tympanometry.

Introduction

Otitis media with effusion (OME) is characterized by the accumulation of fluid in the middle ear space behind an intact tympanic membrane without symptoms of acute inflammation.

It may lead to complications such as hearing loss, speech and language delay or poor balance.

OME is highly prevalent among young chil-

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dren and it is the most common cause of acquired hearing loss in childhood [1].

Approximately 90% of children experience OME at some time before school age, with peak incidence in 6 months to 4 years [2,3].

Pathogenesis of OME is not well understood, but a low-grade infection, specially with species similar to acute otitis media [4,5], Eustachian tube drysfunction, inflammatory response following acute otitis media and complex interactions of biochemical, immunologic and inflammatory mediators in middle ear and adenoid hypertrophy have all been implicated [1,4-6].

The optimal treatment strategy for OME remains contraversial. Decongestant with or without antihistamin was a popular treatment for OME, but clinical trials found no efficacy of these medications [11-13].

The limited efficacy of antimicrobial agents for OME has also been reported in several meta - analysis studies[14,15].

Corticosteroids in different forms (intranasal or systemic) have been investigated in treatment of OME, but their effect were not significant [16-17].

Zinc is a trace element which plays an important role in body metabolism and an essential nutrient for proper functioning of the immune system.

Zinc deficiency results in susceptibility to bacterial,viral and fungal infections. children with Vitamin A, zinc and iron deficiency are more susceptible to upper respiratory and ear infections [7-10,24].

in a community - based, randomized controlled trial on 249 students, zinc gluconate glycine lozenges (10mg, orally dissolved 5 or 6 times a day) were not effective in treating cold symptoms in children and adolescents[26].

On the other hand, in a randomized double blind, placebo controlled study on 100 employees of Cleveland clinic, zinc gluconate lozenges (containing 13.3 mg of zinc), significantly reduced the duration of symptoms of common cold [18]. the efficacy of zinc on prevention and treatment of upper respiratory tract infection was not clear. As a result some physisions recommend zinc supplements for people with recurrent ear infections, suggesting 25 mg per day for adults and lower amounts for children [19,28-29]. In a study serum zinc level was meassured in 25 children with OME and it was significantly lower than control group. These findings were also related to degree of retraction of tympanic membrance [6].

Frequent middle ear infections seemed to account for most of the differences in the serum levels of iron and zinc in children [9]. In another study the investigators reported that superoxide dismutase enzyme containing zinc, may play a role in protecting eustachian tube mucosa from free radical injury during acute otitis media in an animal model [25]. In a retrospective basic and clinical study it has been suggested that copper and zinc-containing superoxide dismutase in cholesteatoma epithelium prevents complications by supporting cathepsin L activity [27].

We attemped to determine the efficacy of oral zinc supplementation with a course of an antimicrobial agent, according to Rosenfield and Williamson, on treatment of OME[14,15]. We examined children clinically and tympanometrically 3 and 6 weeks after treatment. At the end we determined the relationship between zinc supplementation and cycles of treatment was determined.

Methods

We conducted a randomized double - blind, clinical trial,which was registered by RCT code number:138809292893N1, on 52 patients with OME referred to our ear, nose and throat tertiary clinic in shahid Mostafa Khomeini hospital in Tehran from a specific area with similar socioeconomic status between November 2006 and October 2007.

Patients were excluded if they had any of the followings: ruptured tympanic membrane and otorrhea, a history of hypersensitivity to peni-

cillin or zinc derivatives, antimicrobial treatment in the preceding 30 days, diseases such as sinusitis or pneumonia or anemia, recent episode of acute otitis media,previous adenoidectomy or ventilation tube insertion, compromised immunity or any pathology of the ear, nose and throat or factors that could preclude completion of treatment or follow - up. Children were randomly assigned into two groups (zinc group and placebo group).

The research ethic committee of the university approved the study protocol. A written informed consent was obtained from each patients' parents before enrollment.

The zinc sulfate syrup and a placebo with similar appearance, taste, consistency, smell and package were dispensed in identical opaque bottles, which were numbered sequentially. Each zinc bottle contained 10mg elemental zinc in 10ml. Total volume of each bottle was 100ml.The research group and parents were blinded to medication throughout the study and randomization information was accessible only to the trial pharmacist.

Each child received either zinc sulfate syrup (10mg/daily) or placebo for 3 weeks. Dosage of zinc supplement was selected at RDA level [21-23].

We also prescribed Coamoxiclav suspension (40mg/kg/in 3 divided doses daily, Nacl 0.9% nasal drop (3 times daily) and pseudoephedrine tab or syrup (15mg / 3 times daily) for 3 weeks as the selected treatment for all children.

After 3 weeks children reassessed clinically and tympanometrically.

If clinical and tympanometric findings didnot show improvement or showed worsening, then the course of 3 weeks treatment was repeated and children reassessed at the end of second 3 weeks.

If there was not any improvement, children were admitted for further investigation and possible surgery.

Clinical assessment with otoscopy performed by an otolaryngologist and evidence of middle ear effusion defined as following signs: opacity, redness, bulging or retraction of tympanic membrane.We trusted parents for administration of drugs to children .

Tympanemetry was performed by a trained audiologist and tympanometer instrument (Model AZ26 intracoustic, 227 Hz).

A handheld tympanometer was applied to make a seal at the external auditory canal.

A graph and pressure measurement were then printed out and placed in a sealed envelope.

Clinical examination and tympanometry were performed at enrollment and at 3 weeks and 6 weeks after diagnosis.

Tympanogram was classified as abnormal if the tympanic peak pressure was less than - 300 mm H_2O (type B) or between - 300 to - 150 mm H_2O (type C) [20].

A type A curve was interpreted as normal when the tympanic peak pressure was greater than - 150 mm H_2O [20].

All statistical comparisons used two sided significance tests and analysis were conducted by using Mann-whitney u and Wilcoxon W tests, Fischer's exact test and χ^2 test. Differences were considered statistically significant at $p < 0.05$.

Results

A total of 52 children were enrolled in the study from November 2006 to October 2007 who referred to ear, nose and throat clinic due to otitis media with effusion. The patients, ages ranged from 4 to 14 years (mean 8.48 ± 2.02 in the placebo group and 8.21 ± 2.27 in the zinc group). There were 29 patients in zinc group of whom 14 were female and 15 were male and 23 patients in placebo group of whom 9 were female and 14 were male.

Twenty nine children received zinc sulfate syrup and 23 received placebo added to treatment with coamoxiclav, pseudoephedrine and Nacl nasal drop.

There were no statistically significant differences between two groups due to demographic

Table 1. Demographic characteristics of patients.

Characteristic	Zinc	Placebo	P value
Number of patients	29	23	
Sex			
Female	14	9	0.353
male	15	14	
age (Mean±SD)	8.21 ±2.27	8.48±2.02	0.413
number of siblings (Mean±SD)	2.34±1.45	2.13±1.06	0.137
Parents' smoking			
Smoker	7	6	0.52
Non smoker	22	16	

characteristics (Table 1).

Clinical improvement defined as a change in opacity, redness and bulging or retraction of tympanic membrane to brightness, grayish or silver color without decreasing in bulging or retraction.The clinical improvement for all children at 3 weeks were 62.1% for zinc group and 43.5% for placebo group.

The trympanometric improvement defined as an alteration in maximum tympanic membrane movement from negative pressures to less negative or zero.Tympanogram was classified as abnormal if the tympanic peak pressure was less than - 300 mm H_2O (type B) or between - 300 to - 150 mmH_2O (type C).The tympanometric improvement (from B or C type to A type and from B to C type) at 3 weeks were 70.9% for zinc group and 65.5% for placebo group with no statistically significant differences.

Treatment continued for children who had not completed clinical and tympanometric improvement for more 3 weeks. All the children received drugs completely had perfect fellow ups.

At the end of second course of treatment, the clinical improvement were 43.8% for zinc group and 12.5% for placebo group.

The tympanometric changes after this time were 56.3% for zinc group and 40% for placebo group (Table 2).

Although there were no significant differences in the rates of clinical resolution and tympanometric changed after 3 and 6 weeks of treatment, but differences between two groups were noticeable.

Mann-Whitney u test did not show any significant difference between cycles of treatment (3 weeks or 6 weeks) in zinc and placebo group, but improvement was better for children who received zinc for longer time.

Discussion

We report the results of administration of zinc sulfate syrup in comparison to placebo in the treatment of otitis media with effusion. We found a difference in the proportions of children who had OME after 3 weeks and 6 weeks of treatment with zinc sulfate and coamoxiclav compared to those who received only coamoxiclav, but the differences were not statistically significant.There are few studies about association between zinc and pathophysiology and treatment of OME, but in 25 children with OME, serum zinc level was meassured and it was significantly lower than control group. These findings were also related to degree of retraction of tympanic membrance [6]. Several studies on the relationship between zinc level and rate of upper respiratory and ear infection

Table 2. clinical and tympanometric improvement according to treatment cycles.

treatment Cycles		Treatment groups		P value
		Zinc group	Placebo group	
First cycle (3 weeks)	Clinically	62.1%	43.5%	0/26
	tympanometrically	70.9%	65.5%	0/56
Second cycle (6 weeks)	Clinically	43.8%	12.5%	0/18
	tympanometrically	56.3%	40%	0/68

have been conducted and results are in controversy. Studies differed in zinc formulation, dose and duration of treatment. In a community - based, randomized controlled trial, zinc glucanate glycine lozenges containing 10mg zinc were not effective in treating cold symptoms in children and adolescents as in our study[26]. But in another randomized, double-blinded, placebo-controlled study, zinc gluconate lozenges containing 13.3 mg of zinc within the first 24 hours from the beginning of symptorns were significantly reduced the duration of symptoms of common cold [18].

In other studies beneficial effects of zinc has been reported [18-19,28-29].Therefore the efficacy of oral zinc for upper respiratory infections remains in controversy. The mechanisms by which zinc may affect the OME is not clear, but several possibilities have been suggested. Zinc is a trace element which enhances host resistance to infection and plays a critical role in hemostasis of immune system and researchers have found that children with vitamin A, zinc and iron deficiency were more susceptible to upper respiratory and ear infections [7,8,24]. Superoxide dismutase enzyme containing zinc, may play a role in protecting eustachian tube mucosa from free radical injury during acute otitis media in an animal model [25]. A retrospective basic and clinical study suggested that copper and zinc-containing superoxide dismutase in cholesteatoma epithelium prevents complications by supporting cathepsin L activity [27].

Because the mechanism of action of zinc in treating OME was unknown, the optimal dose of medication was also unknown. But its therapeutic dose was 10-40 mg elemental zinc according to references [21-23].

In our study children who received zinc for longer time (6 weeks) had better results than shorter time (3 weeks). Therefore duration of zinc administration may be an important factor for better results. Zinc deficiency is a health problem in Iranian children and administered dose of zinc in this study may be enough only for meeting daily requirements and additional has no effect on treatment of disease [30,31].

Although we coul not find any significant difference between the two groups, but clinical and tympanometric improvement were seen in zinc group and longer administration of zinc gave better results. But further studies on larger sample size and different type and dose and duration of administration of zinc in OME is recommended.

Conclusion

Although in this study oral zinc sulfate supplementation had no significant effect on treatment of OME, the response rate was better in zinc group compared to placebo group specially in longer administration.

According to the findings, it seemed that

more studies about oral zinc supplementation in the treatment of OME is needed.

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