Acta Pædiatrica, 2006; 95: 1175–1181

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REGULAR ARTICLES

The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children

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Abstract

Aim: To determine the efficacy of prophylactic administration of zinc sulphate in reducing the occurrence of the common cold in children, and to evaluate the efficacy of zinc sulphate in reducing the duration and severity of cold symptoms. *Methods:* A total of 200 healthy children were randomly assigned to receive oral zinc sulphate (zinc group, $n=100$) or placebo (placebo group, $n=100$). Zinc sulphate (15 mg of zinc) or placebo syrup were administered for prophylaxis once daily during a 7-mo study period. The dose was increased to two times per day (30 mg of zinc) at the onset of cold, until symptoms resolved. *Results:* The mean number of colds in the zinc group was significantly less than in the placebo group (1.2 vs 1.7 colds per child; $p=0.003$). The mean cold-related school absence was 0.9 d per child in the zinc group versus 1.3 d in the placebo group ($p=0.04$). Compared to the placebo group, the zinc group had shorter mean duration of cold symptoms and decreased total severity scores for cold symptoms ($p<0.0001$). Adverse effects were mild and similar in both groups.

Conclusion: Zinc sulphate appears to be an easily administered, safe and well-tolerated alternative for the prevention and treatment of the common cold in children.

Key Words: *Children, prophylaxis, upper respiratory infections, zinc*

Introduction

Common cold is one of the most common illnesses, and is a leading cause of doctor visits and missed days from school and work. Colds are common in children because they are often in close contact with each other at nurseries and schools. In families with children at nursery school, the number of colds per child can be as high as 12 a year [1]. In children, this illness is also more extensive than in adults and usually requires medical attention. Statistics indicate that more than 80% of common colds requiring medical attention affect children and adolescents [1].

There is no proven treatment or prevention method for the common cold. There is no clear evidence whether colds are effectively prevented or treated by antibiotics, antiviral drugs, or other remedies such as vitamin C or Echinacea [2–6]. However, even a medication that is only partially effective in the treatment and prevention of the common cold could markedly reduce morbidity and economic loses due to this illness.

During the past two decades, there has been great interest in zinc. Various preparations of zinc have been evaluated as a cold remedy in several randomized studies [7–21]. Although the studies have shown widely varying results, zinc has been considered as a possible treatment for common cold. A recent meta-analysis and a review concluded that zinc was effective in reducing the duration and severity of symptoms of common cold [22,23].

To our knowledge, almost all zinc studies reported to date have been performed on adults. There is only one randomized, controlled study that has evaluated

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(Received 18 November 2005; revised 16 January 2006; accepted 30 January 2006)

ISSN 0803-5253 print/ISSN 1651-2227 online
DOI: 10.1080/08035250600603024

the efficacy of zinc gluconate lozenges for treating common cold in children and adolescents [15], and one prospective study that determined the therapeutic and prophylactic effectiveness of zinc gluconate glycine lozenges for the common cold in school-aged children [21]. We therefore carried out a follow-up study to determine the efficacy of prophylactic administration of zinc sulphate in reducing the occurrence of the common cold in children. The secondary objective was to evaluate the efficacy of zinc sulphate in reducing the duration and severity of cold symptoms.

Patients and methods

Study design and enrolment criteria

This randomized, double-blind, placebo-controlled, prospective study was conducted at Ege University Nursery and Primary School between October 2004 and May 2005. The study was approved by the local Ethical Committee of the Ege University Medical Faculty. Before enrolment, all parents and guardians of children were informed by the school doctor and the principal investigator about the nature of the study. Parents gave informed consent for their children to participate in the study. Only children with informed consent forms signed by their parents were eligible for enrolment in the study. The children were required to be in overall good health and to be 2 to 10 y of age. Children who had a known chronic disease, immunodeficiency disorder or asthma were excluded. Children were also excluded if they had a history of sensitivity to or an idiosyncratic experience with zinc, or whose parents were unwilling or unable to comply with clinical study procedures.

Medication and randomization

Two preparations were used in this study: zinc sulphate syrup and placebo syrup. The licensed zinc syrup consisted of 1.32 g zinc sulphate in 100 cm^3 (15 mg of zinc in a 5-cm^3 spoonful), and glycerin, glucose, sunset yellow, orange essence and nipajin as preservative. Placebo and active syrups were identical in appearance, texture and flavouring content, except that the placebo lacked the zinc component.

A statistical consultant programmed a computer-generated randomization code and prepared the packages of medication. The packages were randomly distributed to the study personnel, all of whom were blind to the group assignments. Children were given two packages of identical medication, one for nursery and one for home. Parents were instructed to give home medication packages to their children at the weekend or on missed school days. All parents were also blind to the group assignments.

Eligible children received zinc sulphate (15 mg of zinc) or placebo syrup once daily during the cold season, from 4 October 2004 through to 3 May 2005. The dose was increased to two times per day (30 mg of zinc or placebo) in children who exhibited at least two of the following 10 symptoms consistent with the common cold: cough, nasal drainage, nasal congestion, headache, hoarseness, muscle ache, itchy throat, sneezing, sore throat and fever (axillar temperature $>37^{\circ}C$). Children received medication two times per day until cold symptoms resolved, up to a maximum of 10 d.

Parents were asked to give no cough and cold preparations, antibiotics, zinc-containing multivitamins or mineral supplements, or other zinc products during the course of the study. However, the children were allowed to use acetaminophen to control fever.

Outcome measures

Throughout the study period, all children were followed up daily by a paediatrician, and the occurrence of common cold and adverse effects from medications were recorded daily on school days. On non-school days and missed school days, parents were asked to complete a daily symptom chart including documentation of symptoms, the usage of cold medications and adverse effects. The paediatrician also called parents to discuss and to review the symptom charts.

The primary outcome measure was the number of colds per study child. Secondary outcome measures were the duration and the severity of cold symptoms. Severity for each symptom was scored as none (0), mild (1), moderate (2) or severe (3). Total symptom severity score was calculated by summing the severity scores of all 10 symptoms. Nasal symptom score was defined as the sum of the scores for nasal symptoms (nasal drainage, nasal congestion and sneezing). The throat symptom score was defined as the sum of the scores for throat symptoms (sore throat, itchy throat and hoarseness). The duration of common cold was calculated as the number of days starting from the onset of symptoms until resolution of cold, as defined by two consecutive symptom scores ≤ 1.

Adverse effects from medications were recorded daily by parents. In addition, we identified adverse effects by each day asking an open-ended question about adverse effects. The duration of all adverse effects was recorded, and events were rated as mild, moderate or severe.

Zinc was assayed using routine methods with atomic absorption spectrophotometry. When a common cold episode developed, a throat swab for testing Group A Streptococcus, and a nasal swab for cell culture to detect influenza A and B viruses were obtained.

Table I. Comparison of characteristics among children in the zinc and placebo groups at enrollment.

Characteristics	Placebo group ($n=100$)	Zinc group ($n=100$)
Age (y), mean ± SD	5.7±2.8	5.5±2.7
Gender, M/F	51/49	48/52
Maternal education level		
Elementary school	3	3
High school	61	58
University	36	39
No. of colds in previous year[a]	3.1±2.2	3.2±2.4
Antibiotic use in previous year[a]	1.3±1.8	1.4±2.1
Smoker in household	41	36
Allergies	13	14
Zinc level (μg/dl), range	81.8 (74–102)	84.2 (72–116)

[a] Values are mean±SD per child.

Statistical analyses

All data were statistically analysed using SPSS version 13.0 on an IBM computer (SPSS PN 30963001, serial no. 9579410). Test of differences in the resolution time of cold symptoms among the zinc and placebo groups was based on the Wilcoxon rank-sum test. The mean total symptom severity scores and the mean individual symptom scores during the first 5 d of cold episodes were also compared using the Wilcoxon test.

Relative risk was used to determine whether prophylactic use of zinc sulphate is associated with a decrease in the risk of common cold. Adverse effects were compared between groups using the χ^2 test and Fisher exact test. A p value of <0.05 was considered statistically significant.

Results

A total of 200 healthy children were enrolled in the study. The children received either oral zinc sulphate (zinc group, $n=100$) or an identically packaged placebo (placebo group, $n=100$). Overall, 97% ($n=194$) of the children (97 in the zinc group and 97 in the placebo group) completed the 7-mo study period; six (3%) discontinued, four for non-compliance and two for adverse effects due to medication.

Enrolment characteristics of the children in the zinc and placebo groups are compared in Table I. As can be seen, baseline characteristics of the children, including age, distribution of sex, proportion whose parents smoked, prevalence of allergies, number of colds and the number of prescriptions for antibiotics in the previous year were similar between the two groups. Serum zinc levels were also similar in the two groups; all children had normal serum zinc levels.

Effect of zinc sulphate on the occurrence of common cold

The mean number of colds was 1.2±1.4 colds per child in the zinc group; significantly less than the 1.7±1.2 colds found in the placebo group (Table II). Prophylactic administration of zinc sulphate significantly reduced the median number of colds from 2 to 1 per year ($p<0.001$).

The prophylactic use of zinc sulphate was associated with a decrease in the risk of common cold (relative risk 0.4, 95% CI 0.2–0.6, $p<0.05$). With zinc sulphate prophylaxis, 33% of the children did not experience any cold during the cold season, compared to 14% of the children taking placebo.

Effect of zinc sulphate on school absences and antibiotic use

There were a total of 175 d of cold-related school absence in the study children, including 104 d of absence (among 39 children) in the placebo group and 71 d of absence (among 28 children) in the zinc group. The mean cold-related school absence was 0.9±2.1 d per child in the zinc group, which is significantly less compared to the 1.3±1.9 d in the placebo group ($p=0.04$).

During the 7-mo study period, a total 179 antibiotic prescriptions were written for enrolled children; 87.2% of these were for diagnosis of otitis media, sinusitis, streptococcal pharyngitis, pneumonia or urinary tract infections. Only five colds required concomitant antibiotic therapy in the zinc group, compared to 18 colds in the placebo group.

Effect of zinc sulphate treatment on cold duration

Overall, 313 cold episodes were detected during the 7-mo follow-up period: 184 colds in the placebo group and 129 colds in the zinc group. Fifty-two colds were excluded from the cold analyses, because patients

Table II. Comparison of primary study outcomes in children in the zinc and placebo groups.

Outcome	Placebo group ($n=97$)	Zinc group ($n=97$)	p
No. of colds	1.7±1.2[a]	1.2±1.4	0.003[b]
Cold-related school absence (d)	1.3±1.9	0.9±2.1	0.04
No. of colds requiring concomitant antibiotic therapy	0.13±0.5	0.05±0.3	0.009

[a] Values are mean ± SD per child.
[b] Wilcoxon rank-sum test.

Table III. Duration of common cold symptoms (days).

Outcomes	Placebo group ($n=97$)	Zinc group ($n=97$)	p
Duration of cold symptoms	5.3±0.7 (5.1–5.4) [a]	4.7±0.8 (4.6–4.9)	<0.0001 [b]
Duration of nasal symptoms	3.8±1.5 (3.6–4.1)	3.2±1.4 (3.0–3.5)	<0.0001
Individual symptoms			
Duration of cough	3.2±2.0 (2.9–3.5)	2.9±1.6 (2.7–3.2)	0.008
Duration of nasal drainage	3.2±1.8 (2.9–3.5)	3.0±1.5 (2.7–3.3)	0.001
Duration of nasal congestion	1.4±1.0 (1.3–1.6)	1.2±0.8 (1.1–1.4)	0.004
Duration of headache	0.1±0.4 (0.04–0.2)	0.1±0.7 (0.06–0.3)	0.682
Duration of hoarseness	0.1±0.7 (0.02–0.3)	0.08±0.4 (0.01–0.2)	0.555
Duration of muscle ache	0.2±0.7 (0.07–0.3)	0.1±0.3 (0–0.1)	0.076
Duration of itchy throat	0.3±0.8 (0.2–0.4)	0.1±0.6 (0.03–0.3)	0.041
Duration of sore throat	2.4±1.8 (2.1–2.7)	1.8±1.4 (1.6–2.0)	0.01
Duration of sneezing	0.3±0.6 (0.2–0.4)	0.1±0.5 (0.06–0.2)	0.035
Duration of fever	1.1±1.3 (0.9–1.3)	1.0±1.2 (0.8–1.2)	0.56

[a] Values expressed as mean±SD (95% CI).
[b] Wilcoxon rank-sum test.

received cold palliatives and/or antibiotics, or had a positive culture for group A Streptococcus or a positive cell culture for influenza A and B viruses. Eventually, 281 colds (160 in the placebo group and 121 in the zinc group) were analysed to assess whether zinc sulphate would reduce the time to resolution of cold symptoms.

The mean duration of cold symptoms was significantly shorter in the zinc group (4.7±0.8 d, 95% CI 4.6–4.9 d) compared to the placebo group (5.3±0.7 d, 95% CI 5.1–5.4 d) ($p<0.0001$) (Table III). Similarly, the duration of nasal symptoms was significantly shorter in the zinc group than in the placebo group (3.2 and 3.8 d, $p<0.0001$). Duration of cough (2.9 and 3.2 d, $p=0.008$), sore throat (1.8 and 2.4 d, $p=0.01$) and itchy throat (0.1 and 0.3 d, $p=0.041$) was also shorter in the zinc group than in the placebo group. Duration of headache, hoarseness, muscle ache and fever was similar in the two groups (Table IV).

Table IV. Frequency of adverse effects in the zinc and placebo groups.

Adverse effect	Placebo group ($n=100$)	Zinc group ($n=100$)	Total ($n=200$)
Bad taste	9	8	17
Nausea	5	6	11
Vomiting	3	4	7
Diarrhoea	2	2	4
Constipation	2	1	1
Mouth irritation	7	8	15
Headache	7	5	12
Sleepiness	1	0	1
Itching	2	1	3
Abdominal pain	0	2	2
Dry mouth	5	4	9
Dizziness	1	2	3
Any adverse effect	33	35	68

Effect of zinc sulphate on symptom severity

The overall severity scores for cold symptoms are shown in Figure 1. At baseline, the total symptom severity score was similar in the zinc and placebo group (6.8 vs 6.7, respectively). However, the total symptom score was significantly lower in the zinc group, compared to the placebo group, starting from the first day of cold episode through to day 7 (Figure 1).

Nasal symptom score was also significantly lower in the zinc group starting from the first day of cold episode (Figure 2). In the analysis of individual symptoms, the mean score was lower in the zinc group compared to the placebo group for cough ($p=0.008$), sore throat ($p=0.01$) and itchy throat ($p=0.041$), but not for headache, hoarseness and muscle ache. Fever $\geq 38.5^{\circ}$C was present in five children in the zinc group and six children in the placebo group.

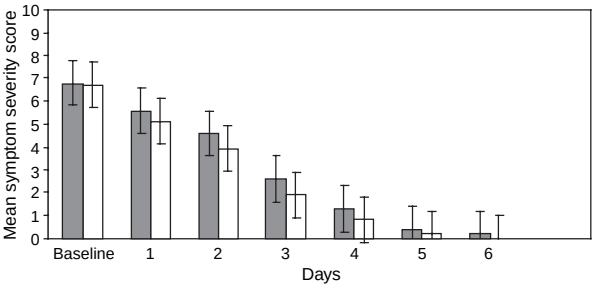

Figure 1. Comparison of total symptom severity scores by day. Shaded bars indicate placebo group, and open bars indicate zinc group. Error bars extend ±1 SE from the mean. At baseline, the mean symptom severity score was similar in the zinc and placebo groups (6.8±1.8 vs 6.7±1.9, $p=0.114$). However, the symptom severity score was significantly lower in the zinc group, compared to the placebo group, for days 1 (5.1±2.1 vs 5.6±1.6, $p=0.04$), 2 (3.9±1.8 vs 4.6±1.3, $p=0.000$), 3 (1.9±1.0 vs 2.6±1.0, $p=0.000$), 4 (0.8±0.8 vs 1.3±0.9, $p=0.000$) and 5 (0.2±0.5 vs 0.4±0.6, $p=0.013$).

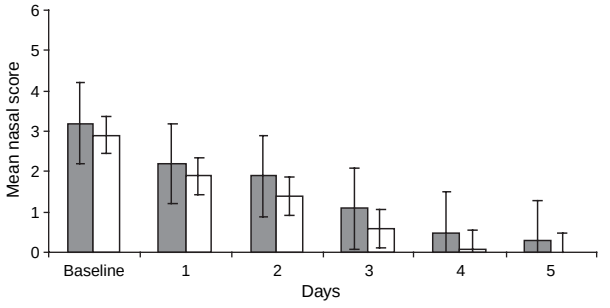

Figure 2. Comparison of mean nasal symptom scores by day. Shaded bars indicate placebo group, and open bars indicate zinc group. Error bars extend ± 1 SE from the mean. Nasal symptom score was significantly lower in the zinc group compared to the placebo group, starting from the first day of cold episode, on days 1 (2.9 ± 1.5 vs 3.2 ± 1.5, $p = 0.023$), 2 (1.9 ± 1.2 vs 2.2 ± 1.2, $p = 0.000$), 3 (0.6 ± 0.7 vs 1.1 ± 0.8, $p = 0.000$), 4 (0.1 ± 0.4 vs 0.5 ± 1.3, $p = 0.000$) and 5 (0 vs 0.3 ± 0.5, $p = 0.017$).

Adverse effects

Adverse effects were rare and mild in both the zinc and placebo groups. The frequency of adverse effects was similar in the two groups (Table IV). Bad taste was the most common adverse effect reported in both groups.

No serious adverse effect related to the use of zinc sulphate was reported. Only one child discontinued the prophylactic administration of zinc sulphate, because of suffering from bad taste. Similarly, one child in the placebo group withdrew from the study because of suffering from mouth irritation.

Discussion

The results of this prospective study indicate that prophylactic administration of zinc sulphate significantly decreases the occurrence of common cold in children. Furthermore, zinc sulphate substantially reduces cold-related school absences and inappropriate use of antibiotics. Study results also suggest that zinc sulphate shortens the mean duration of colds and reduces the severity of cold symptoms.

Previous studies have provided mixed results regarding the prophylactic efficacy of zinc. Takkouche et al. [4] reported that a high intake of vitamin C and zinc in the regular diet had no protective effect on the risk of developing a common cold episode in a cohort study in adults. In contrast, Al-Nakib et al. [12] reported that administration of zinc gluconate lozenges beginning 1 d before virus inoculation was associated with reduced duration and severity of cold symptoms in a placebo-controlled, double-blind study, which was carried out to determine the prophylactic effect of zinc gluconate lozenges on rhinovirus challenge. Recently, McElroy and Miller [21] carried out a prospective study to determine the therapeutic and prophylactic effectiveness of zinc gluconate glycine lozenges for the common cold in school-aged children. The results of the study showed that the use of zinc gluconate lozenges significantly reduced the risk of colds, cold-related school absences, and antibiotic use and misuse. The significant results in our study are consistent with those of McElroy, showing that prophylactic administration of zinc sulphate significantly lessens the occurrence of the common cold in children. The current study also suggests that zinc sulphate provides a dramatic reduction in antibiotic use. Only five colds required concomitant antibiotic therapy among children using zinc sulphate, which is dramatically less compared to the 18 colds in the placebo group. These results represent a significant financial saving as well as preventing the overuse of antibiotics.

The effect of zinc treatment on the duration or severity of common cold symptoms has been examined in numerous randomized trials. Some studies showed that zinc had a beneficial effect on cold symptoms [8–14], but others found no effect [15–20]. The variety of methodologies, using different doses or formulations of zinc, having small sample sizes, subjective outcome measures, or inadequate blinding may cause these conflicting results [24]. In fact, in three trials with similar study designs, methodologies and efficacy assessments, zinc lozenges were found to be effective in reducing the duration and severity of common cold symptoms in healthy adults [8,10,25]. Reports of trials with zinc nasal gel support the results of the three zinc lozenge studies [9,13]. A meta-analysis published in 2004, the re-analysis of all published reports of double-blind, placebo-controlled clinical trials of zinc lozenges against the duration of colds, showed a statistically significant correlation between total daily dosages of positively charged zinc species and reductions in median and mean duration of common colds in these trials [22]. Similarly, a review published in 2004 concluded that zinc was effective in reducing the duration and severity of symptoms of common cold [23]. The current study also demonstrated that treatment with zinc sulphate was effective in reducing cold duration and symptom severity. In addition to its effect on symptom duration, zinc sulphate also significantly reduced the time to resolution of nasal drainage and congestion, cough, and sore throat.

None of our patients' baseline plasma zinc levels were below reference values [26]. All patients enrolled in the current study were previously healthy, and none of the children were determined to have zinc deficiency. We therefore believed that the effect of zinc was prophylactic, and was not related to correction of zinc deficiency.

In previous studies of zinc lozenges, the most commonly reported side effects were taste alteration,

mouth irritation and/or mouth dryness, gastrointestinal disturbances (primarily nausea and constipation), and headache [23]. In some studies, the incidence rates for some adverse effects were higher among patients receiving zinc formulations than among those given a placebo [8,10,11,15]. In a review by Marshall [27], it was concluded that zinc gluconate lozenges were effective in reducing the symptoms and duration of the common cold, but the side effects and particularly bad taste might limit patient compliance. However, the current study suggests that zinc sulphate is well tolerated and is an easy-to-administer therapy. Adverse effects are mild and have no significant association with the use of zinc. The increased incidence of bad taste and nausea found by Mossad et al. [8], bad taste, nausea, mouth irritation and diarrhoea found by Macknin et al. [15], bad taste and mouth irritation found by Eby et al. [11], and constipation and mouth dryness found by Prasad et al. [10] may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself.

In summary, the results of this prospective study indicate that prophylactic administration of zinc sulphate significantly reduced the risk of colds in children. Zinc sulphate also reduces cold-related school absences and the overuse of antibiotics, and provides a cost saving. Additionally, zinc sulphate therapy significantly reduces the duration and severity of cold symptoms. Thus, zinc sulphate appears to be an easily administered, safe and well-tolerated alternative for the prevention and treatment of the common cold in children.

Acknowledgements

We thank all of the children and families who participated in this study. We also thank Berko Ilaç Company, Turkey, for supplying the active and placebo medications, and for supplying the digital thermometers. The company did not participate in designing the study, collecting and analysing the data, or in writing the report. Additionally, we would like to thank Timur Köse, PhD, for statistical analyses; and Tahir Atik, MD, and Birsen Askale for their contributions to this study.

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