

Zinc Gluconate Lozenges for Treating the Common Cold

A Randomized, Double-Blind, Placebo-Controlled Study

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Background: The common cold is one of the most frequent human illnesses and is responsible for substantial morbidity and economic loss. No consistently effective therapy for the common cold has been well documented, but evidence suggests that several possible mechanisms may make zinc an effective treatment.

Objective: To test the efficacy of zinc gluconate lozenges in reducing the duration of symptoms caused by the common cold.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Outpatient department of a large tertiary care center.

Patients: 100 employees of the Cleveland Clinic who developed symptoms of the common cold within 24 hours before enrollment.

Intervention: Patients in the zinc group (n = 50) received lozenges (one lozenge every 2 hours while awake) containing 13.3 mg of zinc from zinc gluconate as long as they had cold symptoms. Patients in the placebo group (n = 50) received similarly administered lozenges that contained 5% calcium lactate pentahydrate instead of zinc gluconate.
Main Outcome Measures: Subjective daily symptom scores for cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever (assessed by oral temperature).

Results: The time to complete resolution of symptoms was significantly shorter in the zinc group than in the placebo group (median, 4.4 days compared with 7.6 days; $P < 0.001$). The zinc group had significantly fewer days with coughing (median, 2.0 days compared with 4.5 days; $P = 0.04$), headache (2.0 days and 3.0 days; $P = 0.02$), hoarseness (2.0 days and 3.0 days; $P = 0.02$), nasal congestion (4.0 days and 6.0 days; $P = 0.002$), nasal drainage (4.0 days and 7.0 days; $P < 0.001$), and sore throat (1.0 day and 3.0 days; $P < 0.001$). The groups did not differ significantly in the resolution of fever, muscle ache, scratchy throat, or sneezing. More patients in the zinc group than in the placebo group had side effects (90% compared with 62%; $P < 0.001$), nausea (20% compared with 4%; $P = 0.02$), and bad-taste reactions (80% compared with 30%; $P < 0.001$).

Conclusion: Zinc gluconate in the form and dosage studied significantly reduced the duration of symptoms of the common cold. The mechanism of action of this substance in treating the common cold remains unknown. Individual patients must decide whether the possible beneficial effects of zinc gluconate on cold symptoms outweigh the possible adverse effects.

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The common cold is one of the most frequently occurring human illnesses in the world. More than 200 viruses can cause common colds in adults, including rhinoviruses (the most frequent cause), coronaviruses, adenoviruses, respiratory syncytial virus, and parainfluenza viruses. In the United States each year, adults develop an average of two to four colds and children develop an average of six to eight colds (1, 2). The morbidity resulting from this disease and the subsequent financial loss in terms of working hours are substantial (3). Many previously described treatments have not provided consistent or well-documented relief of symptoms. Even a treatment that is only partially effective in relieving cold symptoms could markedly reduce physical malaise and economic losses in a large population.

The medical literature describes many possible mechanisms by which zinc may treat the common cold, and seven controlled trials have studied the use of zinc for this purpose. All seven were double-blind, placebo-controlled studies, but each used different formulations and dosages of zinc. Three of these studies showed that zinc had a beneficial effect (4-6) and four did not (7-10). In the studies that examined virus shedding (5, 7), zinc treatment had no effect on this shedding.

We designed a study similar to that of Godfrey and colleagues (6) and used the symptom score developed by these researchers. We emphasized starting treatment within 24 hours after the onset of symptoms, because Godfrey and colleagues found that early treatment was most effective. We used zinc gluconate lozenges, which appeared to be well tolerated and had the best bioavailability profile in previous studies. Other studies (4-7, 9) used lozenges containing 23 mg of zinc. To improve palatability, lozenges in our study contained 13.3 mg of zinc. This provided a local concentration of zinc ions of about 4.4 mmol/L, an amount greater than that necessary to suppress rhinovirus (0.1 mmol/L) (11, 12). The placebo lozenge contained 5% calcium lactate so that it had a medicinal taste similar to that of the zinc gluconate lozenge. Ours was a pragmatic study designed to determine the efficacy of zinc gluconate lozenges in reducing clinical symptom scores under conditions that reflected usual medical care for the common cold (13, 14). We did not seek to define the mechanism of any zinc effect. Although virus cultures or serologic tests might have been desirable, we decided not to do these tests because they are almost never done in the course of standard care.

Methods

Study Design

We determined that a 50% reduction in the duration of symptoms (in days) would represent a significant clinical effect. A previous study of zinc gluconate given during the first day of cold symptoms suggested that the duration of illness was reduced from approximately 8 days to 4 days after treatment began (6). Our previous research on patients with colds who were seen at the Cleveland Clinic suggested that the mean duration (\pm SD) of cold symptoms was approximately 7 ± 6 days (15, 16). We chose a sample size of 100 patients so that we could detect a difference in the mean number of days of symptoms from 8 days in the placebo group to 4 days in the zinc group with a standard deviation of 6 days, a two-sided P value of 0.05, and an approximate power of 90%.

Patients were recruited from among the Cleveland Clinic staff through announcements in internal Clinic publications and by word of mouth. One hundred volunteers were enrolled between 3 October and 4 November 1994. All patients who completed the study as specified by the protocol were enrolled in a raffle for one of two prizes: dinner for two or a trip for two to the Bahamas. The Institutional Review Board at the Cleveland Clinic Foundation approved the study, and participants gave informed consent at the time of enrollment. Participants were informed of the placebo-controlled, double-blind nature of the study.

Patients who volunteered for the study were enrolled only if they had had cold symptoms for 24 hours or less. Patients must have had at least two of the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, or an oral temperature greater than 37.7 °C. Patients were excluded if they were pregnant, had a known immune deficiency, or had had symptoms of the common cold for more than 24 hours.

The zinc gluconate-glycine and placebo lozenges were supplied by the Quigley Corporation of Doylestown, Pennsylvania. The zinc lozenges consisted of a boiled hard-candy base prepared with approximately equal proportions of sucrose and corn syrup, zinc gluconate trihydrate (AKZO Chemie, Amersfoort, the Netherlands), a molar proportion of glycine (aminoacetic acid), and lemon and lime flavoring oils. The mixture was formed into lozenges that weighed 4.4 g and contained 13.3 mg of zinc. Placebo lozenges, also weighing 4.4 g, were prepared from the same flavored hard-candy base and contained 5.0% calcium lactate pentahydrate. Placebo and active lozenges were identical in weight, appearance, flavoring content, and texture. The zinc lozenges, however, were more astringent than the placebo lozenges.

A statistical consultant prepared a computer-generated randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. The study medication was distributed by the study nurse, who was masked to treatment assignments. Patients were given 120 lozenges and were asked to dissolve 1 lozenge in their mouths every 2 hours while awake for as long as they had cold symptoms. The study nurse administered the first lozenge to assess initial tolerability. Participants were asked to take no other cold preparations during the study period. Acetaminophen samples and oral digital thermometers were given to the patients at the time of enrollment. All patients were called on the second day of medication use to make sure that they were not developing a more serious illness and to assess the adequacy of the masking through responses to a questionnaire. By assessing the adequacy of the placebo on the second day of treatment rather than only at the end of treatment, we hoped to decrease the likelihood that a rapid cure would help patients in the zinc group correctly determine that they were receiving the active medication. This questionnaire was also administered at the end of treatment with the addition of questions about the occurrence of specific, previously described side effects of zinc therapy.

Patients returned to the Clinic for the final visit within 1 day of noting that their cold symptoms had resolved. At this visit, they returned unused lozenges so that adherence to the protocol could be checked through lozenge counts, and the study nurse confirmed that cold symptoms had resolved.

Patients were asked to complete a daily log documenting the severity of symptoms and the medications taken throughout the duration of their cold for as long as 18 days. Every day, patients graded each symptom as 0 for none, 1 for mild, 2 for moderate, or 3 for severe. Total symptom scores were calculated by summing the scores of the 10 symptoms for each day. Cold resolution was defined as resolution of all symptoms (a total symptom score of 0) or resolution of all but one mild symptom (a total symptom score of 1).

Statistical Analysis

The time to cold resolution was calculated as the number of days from study entry. Resolution rates were estimated using the Kaplan-Meier method, and resolution profiles were compared between groups using the log-rank test (17, 18). We estimated median resolution times using the method suggested by Lee (19). The effect of treatment on individual symptoms was examined by comparing the number of days with each symptom using the Wilcoxon rank-sum test. For analysis of treatment effect, we combined hoarseness, sore throat, and scratchy throat into a category called "throat symptoms" and nasal drainage and congestion into a category called "nasal symptoms." Plots of individual patient symptoms give the percentage of the baseline total

severity score (sum of symptom scores for all patients) by assignment group and study day. When appropriate, we used the Fisher exact test and the chi-square test to analyze associations between the side effects and assigned groups. Patient adherence was examined by comparing the total lozenge counts between the two groups using the Wilcoxon rank-sum test.

These analyses were done using an intention-to-treat framework, regardless of patient adherence (20-22). Before the randomization code was broken, patients who received antibiotic therapy or whose condition was diagnosed by a physician as an illness other than the common cold were considered nonadherent. Patients who wrote their diaries from memory were also considered nonadherent. Patients were considered adherent if they took an average of four or more lozenges per day for the first 4 days of the study (16 lozenges) and if they took no antibiotic agents.

Results

One hundred patients were enrolled in the study; 50 were assigned to the zinc group, and 50 were assigned to the placebo group. All patients were Cleveland Clinic employees older than 18 years of age. One patient in the zinc group withdrew from the study on the first day because she could not tolerate the lozenges; she did not complete the symptom diary. All other patients, as directly observed by the study nurse, indicated that they had good tolerance of the first lozenge. Demographic characteristics of the groups are given in [Table 1](#).

The mean (\pm SD) and median symptom scores at baseline (the first measurement) were 8.6 ± 3.3 and 8 for the entire sample, 9.3 ± 3.6 and 8 for the placebo group, and 7.9 ± 2.8 and 8 for the zinc group. In practice, an increase in score from 8 to 9 entails scoring one symptom one grade higher or developing another mild symptom. Six hours after the study began, the mean symptom scores for the placebo group (9.3 ± 4.2 ; median, 9) and the zinc group (8.7 ± 4.0 ; median, 8) were closer.

The incidence of individual symptoms at baseline was similar in the two groups for all but two symptoms: sneezing (31 of 50 placebo recipients [62%] and 38 of 49 zinc recipients [77.5%]; $P = 0.09$) and sore throat (39 of 50 placebo recipients [78%] and 25 of 49 zinc recipients [51%]; $P = 0.005$). No patients had fever at baseline.

Eight patients (six in the placebo group and two in the zinc group) had colds that did not resolve while they remained in the study. Two of these patients (both were placebo recipients) completed the 18 days of the study, and the remaining six (four were placebo recipients and two were zinc recipients) dropped out after 7 to 16 days. In addition, one patient recorded his symptoms for 18 days but indicated that his cold resolved on day 19.

We used the Kaplan-Meier method to estimate the percentage of patients whose colds completely resolved ([Figure 1](#)) and almost completely resolved on each day of the study. The median time to resolution of all symptoms was 7.6 days in the placebo group and 4.4 days in the zinc group; the median time to resolution of all but one mild symptom (data not shown) was 7.5 days in the placebo group and 3.7 days in the zinc group. The results of the log-rank test and the plot of these distributions indicate that symptoms resolved significantly faster in the zinc group than in the placebo group ($P < 0.001$). This effect was also seen when the end of the cold was defined as almost complete resolution ($P < 0.001$). The study nurse directly observed whether the patients who returned their study forms and unused medication within 1 day of reported resolution of symptoms were free of symptoms.

Seventeen of the 100 patients (10 in the zinc group and 7 in the placebo group) were considered nonadherent. Of these 17, 6 (2 zinc recipients, 1 of whom also took antibiotic agents, and 4 placebo recipients) did not take enough medication for reasons that were not stated; 5 (all zinc recipients) stopped taking the lozenges because of adverse effects (bad taste in 3 patients, sore mouth in 1 patient, and a "lump in back of throat" in 1 patient); 4 (2 zinc recipients, 1 of whom

also could not tolerate the taste of the medicine, and 2 placebo recipients) took antibiotic agents; 2 (both zinc recipients) reconstructed their diaries from memory; and 2 (1 zinc recipient and 1 placebo recipient) stopped keeping a record for reasons that were not stated. When data were analyzed after these 17 nonadherent patients were excluded, the study conclusions remained the same. No significant relation was seen between adherence status and group assignment ($P > 0.2$). Even when the 17 nonadherent patients were excluded, symptoms in the zinc group still resolved significantly faster according to both definitions of symptom resolution ($P < 0.001$). The median duration of symptoms for the adherent patients in the placebo and zinc groups was 7.2 and 3.9 days, respectively, for complete resolution and 5.7 and 3.4 days, respectively, for near-complete resolution.

[Figure 2](#) and [Figure 3](#) show the percentage of the original symptom score (each day by group assignment) for nasal symptoms and throat symptoms. The zinc group had significantly fewer days with any symptom, nasal symptoms, throat symptoms, coughing, headache, hoarseness, nasal congestion, nasal drainage, and sore throat. The groups did not differ significantly in the resolution of muscle ache, scratchy throat, sneezing, or fever ([Table 2](#)).

We calculated the total number of lozenges from counts of returned lozenges and from patient diaries. When we found discrepancies, we used actual lozenge counts. During the entire study, the placebo group took a mean of 49 ± 30 lozenges (median, 42 lozenges) and the zinc group took a mean of 36 ± 22 lozenges (median, 28 lozenges) ($P = 0.03$). The placebo group took an average of 5 ± 2 lozenges per day (median, 5 lozenges per day), whereas the zinc group took an average of 6 ± 2 lozenges per day (median, 5 lozenges per day) ($P = 0.20$). Because their colds lasted longer, the placebo group used significantly more lozenges than the zinc group, but the number of lozenges per day of symptoms did not differ between the two groups.

Use of acetaminophen did not differ significantly between the two groups ($P = 0.10$); the placebo group took a median of 6 acetaminophen tablets, and the zinc group took a median of 4 tablets. Despite instructions to the contrary, 15 patients (10 placebo recipients and 5 zinc recipients) took other cold medications during the study ($P = 0.17$).

Questions to evaluate the efficacy of masking to group assignment were asked after the first day of treatment and at the end of the study. Patients were asked to guess their assignment from among seven choices: certainly placebo, probably placebo, possibly placebo, do not know, certainly active, probably active, or possibly active. By assigning all guesses that mentioned "placebo" as placebo and all guesses that mentioned "active" as zinc, the following results were obtained. On the initial questionnaire, 50% of the placebo recipients (25 of 50) and 55.2% of the zinc recipients (27 of 49) correctly guessed their study assignment. At the end of the study, 54% of the placebo recipients (27 of 50) and 53.1% of the zinc recipients (20 of 49) correctly guessed their treatment assignment. Sixty-five of the 99 patients (65.7%) maintained their original guess at the end of the study. Because no clear pattern of movement of guesses was seen between the groups, masking appears to have been maintained during the study.

After the first day of treatment, 46% of the placebo recipients and 59% of the zinc recipients said that the study medication had helped alleviate their symptoms ($P = 0.19$). At the end of the study, 44% of the placebo recipients and 59% of the zinc recipients said that the study medication had helped improve the cold symptoms ($P = 0.13$). When the zinc and placebo groups were subdivided into the seven subgroups on the basis of how certain the patients were about their group assignment on the first day of treatment, the mean and median durations of symptoms in the zinc group were always shorter than those in the placebo group.

Thirty-eight of 50 placebo recipients (76%) and 28 of 49 zinc recipients (57%) described the taste of the lozenges as sweet. Patients were also asked to choose other tastes that applied to their medication, including sour, bitter, and salty. Eight placebo recipients (16%) and 12 zinc recipients (25%) reported that the lozenges tasted sour; 6 placebo (12%) and 20 zinc (41%) recipients reported a bitter taste; and 4 placebo (8%) and 4 zinc (8%) recipients reported a salty taste. Many

patients reported that the lozenges had an aftertaste. Thirty-four of 50 placebo recipients (68%) and 6 of 49 zinc recipients (12%) reported no aftertaste ($P < 0.001$). Twelve placebo recipients (24%) and 22 zinc recipients (45%) reported a mild aftertaste; 2 placebo (4%) and 17 zinc (35%) recipients reported a moderate aftertaste; and 1 placebo recipient (2%) and 3 zinc (6%) recipients reported a severe aftertaste. Two patients (1 in the placebo group and 1 in the zinc group) did not answer the question.

We ascertained side effects in two ways. During the study, we asked patients to list all of the side effects of their medication. This open-ended question was the only one asked during the study period. Seventeen of 49 zinc recipients reported that no side effects developed with their medication before the conclusion of the study. In these patients, the mean (4.7) and median (4.0) numbers of days until only one mild symptom remained was the same as the number in the 32 patients with identified side effects. The zinc recipients with and without identified side effects also had a similar mean (5.1 days and 5.5 days, respectively) and median (4.5 days and 6.0 days, respectively) time until symptoms completely resolved ($P > 0.2$).

The second method used to determine side effects entailed listing all of the common side effects of zinc and asking patients at the end of the study whether these or other side effects developed while they were taking the study medication (Table 3). As expected, patients described more side effects in response to this question than in response to the open-ended question alone. Patients in the zinc group reported more side effects per person (25 zinc recipients and 5 placebo recipients had two or more side effects; $P < 0.001$), significantly more nausea (10 patients compared with 2 patients; $P = 0.02$), and more bad-taste reactions (39 patients compared with 15 patients; $P < 0.001$). The other symptoms described (vomiting, abdominal pain, diarrhea, constipation, mouth irritation, and dry mouth) did not differ significantly between the two groups.

Discussion

The common cold still has no definitive cure. At best, available over-the-counter medications minimally alleviate cold symptoms (23). Our study showed that the time to resolution of all symptoms was significantly shorter in the zinc group. The zinc group had significantly fewer days with coughing, headache, hoarseness, nasal congestion, nasal drainage, and sore throat but had more patients with side effects. The fact that zinc recipients and placebo recipients did not differ significantly in their subjective overall impression of whether the study medication had helped alleviate their cold symptoms is somewhat surprising. However, global assessment by patients may be based largely on subjective estimates of how long a cold "should" last rather than on objective knowledge of the duration; this created much variation in subjective estimates of whether the actual duration of the patients' cold symptoms were or were not "improved" with either treatment.

The results of our study are similar to those of previous studies that showed a beneficial effect of using zinc for treating the common cold, particularly when zinc is started within the first 24 hours of onset of symptoms. Of the four studies that did not show a beneficial effect, three (7-9) were criticized for using a lozenge formulation that inactivated the zinc (24-26) and one (10) used a possibly ineffective dose of 4.5 mg of zinc per lozenge. Of the three studies that did show a beneficial effect, one (4) reported a strong treatment effect ($P < 0.001$) at 7 days (14% of zinc recipients compared with 54% of placebo recipients had symptoms at 7 days) but also noted a high rate of side effects in the zinc group. This finding caused some investigators to question the validity of the masking and therefore the validity of the study results (27). Al-Nakib and colleagues (5) used zinc gluconate lozenges in persons with experimentally induced colds and found no benefit in giving zinc prophylactically, but they did note a reduction in mean daily clinical scores compared with scores in placebo recipients on days 4 ($P < 0.01$) and 5 ($P < 0.05$) of treatment. The treatment was well tolerated, and the placebo lozenge was not distinguished from the zinc lozenge by taste or appearance.

Godfrey and colleagues (6) compared a nonchelating formulation, zinc gluconate-glycine, which releases 93% of contained zinc in saliva, with a placebo containing highly astringent tannic acid and saccharin. They reported a 26% reduction in the duration of colds when treatment was begun during the second day of symptoms and a 42% reduction (from 9.1 days to 5.3 days) when treatment was begun on the first day of symptoms. Our study was similar to that of Godfrey and colleagues; we used the same symptom score, emphasized starting treatment within 24 hours after onset of symptoms, and used a reduced dose of zinc to improve the palatability of the lozenge.

The mechanisms through which zinc affects the common cold remain to be determined, but several possibilities have been described. Zinc prevents the formation of viral capsid proteins, thereby inhibiting in vitro replication of several viruses, including rhinovirus (11, 12, 28-30). Zinc combines with the carboxyl termini (negatively charged canyons) of rhinovirus coat proteins, which may prevent the virus from combining with the tissue-surface protein (intracellular adhesion molecule type 1) and entering the cell. This process stops further reproduction (31, 32). Extracellular zinc may exert antiviral effects by stabilizing and protecting cell membranes by uncertain means (30, 33-36). In vitro studies have suggested that zinc may induce production of interferon (37). Zinc ions also have human prostaglandin metabolite-inhibiting properties at 0.01 to 0.1 mmol (38), which may also account for the ability of zinc to help relieve symptoms of the common cold.

Our study has some limitations. First, we did not establish a microbiological diagnosis of the common cold. We relied solely on patients' subjective information and clinical evaluation by the study nurse. We elected not to do microbiological studies of rhinovirus because the expense of such studies is prohibitive, and our goal was only to determine whether zinc helped to relieve cold symptoms. The fact that the study was done early in the influenza season, when no cases of influenza had been reported at the Cleveland Clinic, supports the assumption that most of our patients did have a common cold. Doing the study at a different time of year could have involved different types of viruses, which might have altered the results. The absence of fever at baseline in all patients suggests that certain viruses, such as influenza, parainfluenza, and adenovirus, were unlikely causes of common cold in our patients. Second, the fact that more patients in the zinc group than in the placebo group had sore throats at baseline could suggest that different viruses were responsible for common cold in the two groups. This difference, however, diminished within the first 12 hours of the study. Third, we assessed compliance with the assigned treatment by reviewing patients' diaries and lozenge count. We did not check zinc or calcium blood levels, but it is difficult to predict whether these levels would have been meaningful, given that these elements have several other dietary sources.

The fourth limitation of our study is that our results cannot be applied to immunocompromised or pregnant patients, because neither group was included in our study. Fifth, we did not provide information on the cumulative effect of the repeated use of zinc or explore the possibility of development of resistance. We emphasize that we used only short-term zinc therapy for common colds. Habitual or long-term ingestion of large doses of zinc may be hazardous by causing imbalances in levels of copper (39) and possibly other nutrients. We also avoided zinc dosages greater than 150 mg/d, which have been associated with adverse effects (40). Sixth, although our results indicated clinical improvement when zinc was used to treat the common cold, we do not know the actual mechanism by which this occurred. Finally, if patients had complied with the protocol (one lozenge every 2 hours while awake), they would have taken seven or eight lozenges each day. Zinc lozenges were actually taken about four to eight times daily (median, five lozenges). This may raise concerns about compliance, but the number of lozenges taken appears to have been effective. A recent review (41) and a MEDLINE search showed no evidence that calcium lactate causes adverse effects in the doses used in our study. Thus, we do not believe that our results reflect an adverse effect of the placebo administration.

In our study, the only statistically significant adverse effects of zinc therapy were bad taste and nausea. Although the incidence of mouth irritation did not differ significantly between the two groups, mouth irritation may still be a clinically significant adverse effect because the placebo may also have been irritating. We assessed the possibility that patients withdrew from the study because of side effects before their colds had completely resolved. We hypothesized that patients who recognized side effects of medication before the end of the study may have decided to violate the protocol and discontinue their medications before they were completely well, either intentionally (because of the perceived unpleasantness of the side effects) or unintentionally (because the side effects masked their cold symptoms). No statistically significant association was seen between the presence or absence of medication side effects recognized before the conclusion of the study and the duration of the patients' illnesses. This is further evidence that patients adhered to the protocol and did not prematurely stop taking their assigned medication because of side effects. Individual patients must decide whether the possible beneficial effects of zinc on their cold symptoms outweigh the possible adverse effects.

Our data suggest that zinc gluconate in the form and dosage tested was helpful in reducing the duration of common cold symptoms. Although we used a lower dose of zinc, our results were nearly identical to those reported by Godfrey and colleagues in their subset of 44 patients who were randomly assigned to a treatment similar to ours after fewer than 24 hours of symptoms. In addition, multi-institution studies that obtain virologic data on the infecting organisms are needed to confirm our findings.

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