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Zinc: Prophylaxis and Treatment for the Common Cold

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Abstract

The common cold is a widespread and frequent illness with limited treatment options, generating costs for individuals and society. A crucial goal is an effective symptomatic treatment and reducing the duration of the illness, which can bring significant global benefits. Several studies suggest that using zinc lozenges within 24h of symptom onset can noticeably shorten the duration of symptoms. Zinc has a complex and not fully understood role in immune regulation. Zinc lozenges are inexpensive, easily accessible, and have few side effects. Based on numerous studies, zinc lozenges seem to be a noteworthy option for symptomatic treatment. The application of therapy in athletes can be of particular importance due to the faster recovery and the avoidance of missing training sessions.

Review methods

A review of the literature from PubMed (1984-2024) was conducted. The articles were selected based on specific keywords and then evaluated for their significance and suitability for inclusion in this review.

Keywords: common cold; zinc lozenges; rhinovirus; immune response

Introduction

The common cold, also known as an upper respiratory tract infection, ranks among the primary reasons people visit physicians. Typically triggered by viruses, it is managed by alleviating symptoms. The prevalence of the common cold leads to considerable economic and social challenges on a global scale. Antibiotics prove ineffective for both children and adults in treating this condition. However, there are studies on use of symptomatic treatment as a prophylactic and treatment option for the common cold. Several studies have investigated the efficacy of zinc in reducing the duration, severity, and incidence of common cold symptoms. Lozenges containing zinc play a significant role due to release of free ions. It turns out that this easily available substance can significantly shorten the duration of illness, reduce the burden on healthcare and decrease general social costs.

The role of Zinc in immunity

Zinc is a vital micronutrient that plays a crucial role in growth, development, and maintenance of immune function. It has an impact on all organs and cell types, forming an essential part of human proteome. This includes numerous important enzymes and transcription factors. Zinc is a key component of around 750 zinc-finger transcription factors that regulate gene expression[1], and it also acts as a catalyst for about 2000 enzymes across six enzyme classes[2]. This highlights the vital role of zinc in various cellular processes such as DNA synthesis, and RNA transcription.[3] Sequestration and toxic accumulation of metals are well-documented antibacterial immune responses. Calprotectin is a prime example, binding and sequestering extracellular calcium and zinc, thus preventing bacterial and fungal overgrowth. Although the impact of antiviral control over zinc balance in humans has not been confirmed, metallothioneins have a wide range of functions, including response to viral infection. The mechanisms are frequently undefined, but metallothionein expression has been linked to either an increase in zinc levels or the redistribution of zinc.[4] Upregulation of metallothionein has been noted in reaction to numerous viruses including HIV[5], HCV[6], coxsackie virus[7]. Numerous studies have assessed the effectiveness of zinc as an antiviral treatment in vitro. Positively charged, ionizable zinc (iZn), rather than bound zinc, exhibits potent antirhinoviral effects by blocking the typical cleavage process of viral polypeptides[8][9][10] Assessing antiviral activity often involves using zinc concentrations

that are significantly higher than physiological levels. Human plasma typically contains zinc in the range of about 10 to 18 μM , while antiviral levels of zinc can be found at concentrations reaching into the mM range. There is no shortage of studies that refer to rhinoviruses, which are considered to be one of the most frequent cause of the common cold[11][9][8]. Moreover ionic zinc blocks intercellular adhesion molecule-1 (ICAM-1), increases interferon-gamma (IFN- γ) 10-fold, inhibits the release of histamine and leukotrienes from basophils and mast cells[10][12]. Considering the aforementioned points, zinc plays a vital role in immune regulation. However, the role of zinc in immune regulation is not yet fully understood, and further research in this area should be conducted.

Zinc deficiency

The worldwide occurrence of zinc deficiency is estimated to vary between 17% to 20%, with the majority observed in developing regions of Africa and Asia.[13] These findings highlight the significance of zinc intake, especially in less developed nations where the likelihood of infection is increased due to inadequate sanitation and public health measures. In high-income countries zinc deficiency is mostly observed among patients in the elderly, with chronic infections such as HPV, HCV, HIV, as well as patients with liver cirrhosis or inflammatory bowel disease[14] [15]. Therefore, some patients are particularly in the risk of deficiency and zinc supplementation can yield above-average benefits.

Prophylactic supplementation

Zinc supplementation has been investigated to have prophylactic effects in the common cold. A systematic review of zinc supplementation has been conducted as following. Overall, a total of 1,348 initial occurrences of colds were identified in nine studies. The dosage ranged between 15mg and 200 mg in the form of tablets or lozenges. When vitamin D or zinc was taken as supplements, there was a 4% decrease in the likelihood of catching a cold compared to taking a placebo (RR: 0.96). However, this reduction in risk did not reach statistical significance (95% CI: 0.90, 1.01).[16]. Only a single research study evaluated the partial impact of zinc supplementation on preventing colds, nevertheless it did not reach the significance (RR: 1.06, 95% CI: 0.34, 3.34). The research was conducted with U.S. military

cadets and found that providing a daily supplement of 15 mg zinc gluconate in the form of tablets for 7 months had a significant impact. However, the study revealed that the frequency of reported cold incidents from a weekly survey was approximately 11% lower in the zinc group compared to the placebo group (zinc group: 56.7%, with self-reported cold episodes being at 135 out of 238 survey entries; placebo group: 67.9%, with self-reported cold episodes being at 163 out of 240 survey entries).[\[17\]](#)

Another study involved the prophylactic use of zinc in the pediatric population. During a 7-month research period, 200 healthy children were randomly divided into two groups: the zinc group (n=100) and the placebo group (n=100). The participants in the zinc group received oral zinc sulphate (15 mg of zinc), while those in the placebo group were given a syrup with no active ingredient. 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 ($p=0.04$). This study has showed zinc prophylactic effectiveness. [\[18\]](#)

Another example is a cohort study that tried to define the relationship between zinc intake and the likelihood of contracting the common cold. Daily consumption of vitamin C and zinc was evaluated initially using a dietary survey, the reliability and consistency of which were established in a subset of the community. A total of 1,667 instances of the common cold were identified during 79,240 person-weeks of observation. The consumption of zinc did not appear to be associated with the incidence of the common cold. Compared with the first quartile of intake, women in the fourth quartile of zinc intake showed an adjusted incidence rate ratio 1.1 (95% CI = 0.8-1.5) and the incidence rate ratios for men in the fourth quartile were 1.3 (95% CI = 0.9-1.8).[\[19\]](#)

In summary, prophylactic zinc supplementation may slightly reduce the risk of the common cold; however, studies are inconclusive and, due to mixed results, a strong recommendation for such prophylaxis in the general population cannot be made. More studies should be conducted to properly assess the relationship.

Lozenges Treatment

Numerous studies indicate the effectiveness of using zinc at the onset of cold symptoms. Both the duration and severity of symptoms appear to decrease, however, the studies provide different results. Various studies point to varying effectiveness depending on the type of

preparation and dosage. It turns out that lozenges have the most well-documented effectiveness in treating the common cold. In studies taking tablets or intranasal sprays does not show significant efficacy.

To determine if zinc lozenges could be the cure for the common cold, all double-blind, placebo-controlled data from these 15 double-blind, placebo-controlled clinical trials were used to determine relationships between iZn (or zinc) and reductions in durations of colds and to test for correlations and statistical significance. These tests utilized a Pearson correlation weighted by sample size analysis. All of the zinc lozenges having “cure for common cold” potential can be seen to have had only one ligand (acetate or gluconate) and they had consequent high iZn content, while most failed lozenges had multiple ligands and consequent low or null iZn content. [33]

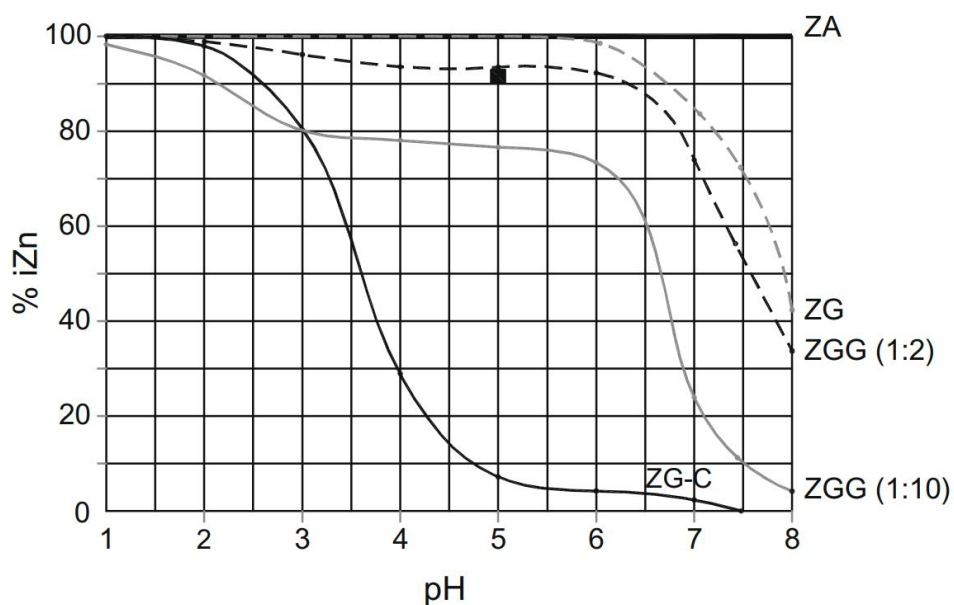


Fig. 1. Percentage of zinc present as iZn by pH. At physiologic pH 7.4, zinc acetate (ZA) yields 100% iZn, zinc gluconate (ZG) yields 72% iZn, zinc gluconate with a 1:2 M ratio of zinc gluconate to glycine [ZGG (1:2)] yields 57% iZn, zinc gluconate with a 1:10 M ratio of zinc gluconate to glycine [ZGG (1:10)] yields 11% iZn, and zinc gluconate with a 1:1.3 M ratio of zinc gluconate to citrate or zinc citrate (ZG-C) yields zero iZn.

[33]

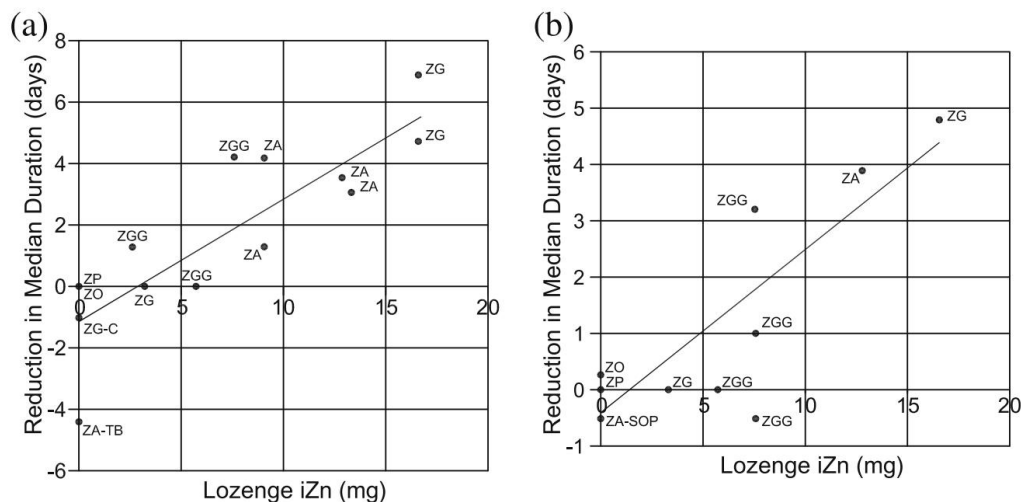


Fig. 2. (a) and (b) Mean and median duration of common colds treated with zinc lozenges.

Tables source [33]

In 1984 was the first time reported by Eby that zinc gluconate (ZG) lozenges in a 65 patient RCT was an effective treatment for common colds. A single 23-mg zinc (16.56 mg iZn) lozenge or a calcium lactate placebo was dissolved in mouth for 2 hours, 9 times a day. After 7 days of therapy, a significant majority (86%) of the participants treated with zinc showed no symptoms, whereas only 46% of those who received a placebo were asymptomatic ($P = 0.0005$), demonstrating substantial and statistically significant advantages.[\[20\]](#)

Over time, other results began to emerge with mixed conclusions. In 1987 Al-Nakib published another study - zinc gluconate lozenges with 23 mg of zinc (16.56 mg iZn) were administered nine times a day in HRV-2 rhinovirus-induced colds in a randomized controlled trial involving 12 patients. The lozenges dissolved in the mouth within 20 minutes. Zinc was found to lower the average daily clinical score (which represents the severity of several symptoms) from 8.2 in the placebo group to 5.7 in the group receiving zinc treatment, and this reduction showed statistical significance on the second day following virus exposure ($P = 0.05$).[\[21\]](#)

Shortly thereafter, in 1989, a report by Smith emerged regarding the ineffectiveness of zinc lozenges. Lozenges containing either 23 mg of elemental zinc or placebo were taken every 2h and symptoms were rated daily on a scale of 0 (not present) to 3 (severe). Duration of illness, reflected in the proportion of subjects remaining symptomatic on each day, was not significantly reduced (maximum difference of 12.6% on day 7, $P = 0.09$; 95% confidence interval, -6 to 31%) by either treatment. Severity of illness, assessed by using a summed severity score, was reduced incrementally by 7 to 8% on days 5 to 7 ($P = 0.02$) in subjects

taking zinc. Adverse effects, mostly nausea and altered taste, were reported by 50% of subjects taking zinc. The conclusion was that zinc gluconate may produce a small reduction in overall severity of symptoms, but not clinically significant[22].

Other studies appeared to show mixed results but usually confirming the effectiveness of the therapy[23][24][25][26][27]. In study from 2011 including 16 therapeutic trials (1387 participants) and two preventive trials (394 participants) using zinc for at least five consecutive days to treat, or for at least five months to prevent the common cold the findings are as follows. Intake of zinc was associated with a significant reduction in the duration (days) (mean difference (MD) -1.03, 95% confidence interval (CI) -1.72 to -0.34) (P = 0.003), however not the severity of common cold symptoms (MD -1.06, 95% CI -2.36 to 0.23) (P = 0.11). Moreover, the proportion of participants who were symptomatic after seven days of treatment was significantly smaller. Referring to the study there is a significant reduction in the duration of cold at a dose of ≥ 75 mg/day of zinc lozenges and it would be best to use it at this dose throughout the cold.[28]

Intranasal Treatment

There has also been a hypothesis regarding the effectiveness of zinc in nasal spray form - at the most common site of entry for viruses causing common cold into the body. According to a meta-analysis from 2009, the results are as follows.

Five studies were found. Three were relevant to the issue of treatment of common colds with intranasal zinc and the results were combined in meta-analysis. High doses of intranasal zinc preparation (2.1 mg zinc/day) were reported in two studies to shorten the duration and reduce the symptom severity of common cold in healthy adults, when started within 24 to 48 hours of onset of illness. A lower dose study (0.044 mg zinc/day) found no benefit in resolution, but did report a significant improvement in symptoms at day 1 and day 3. Combining the three studies, the relative risk for benefit at day 3 was 0.62 (95% CI 0.18 to 2.19) (random effects). There were no studies with children. There were no significant harms reported. [32]

Another study from 2006 was a double-blind, placebo-controlled clinical trial. The goal was to improve results using a zinc gluconate nasal spray with zinc orotate lozenges. Zinc gluconate nasal spray (10 mmol) or placebo was used every 15 to 30 minutes, and lozenges were used each several hours to reduce duration and severity of common colds. An intention of treatment was to keep the nasal tissues wet with zinc gluconate solution during wakeful hours. After 7 days of treatment, 10 of 16 (63%) zinc-treated patients were asymptomatic

compared to 9 of 17 (53%) placebo-treated patients ($P = .57$). This treatment caused olfactory region pain in some patients and did not reduce the duration or severity of common colds. Treatment did not produce anosmia, which has been reported in other studies following olfactory region administration of ionic zinc in many species and in humans from zinc nasal sprays and gels. [31]

According to research, nasal zinc supplementation not only fails to provide benefits but may also lead to side effects. There is a lack of data on which such action could be considered recommended.

Dosage

There were also emerging considerations regarding the dosage of zinc being administered. In a meta-analysis by Hemilä from 2017, zinc acetate and zinc gluconate were compared, along with the issue of dosage. The mean common cold duration was 33% (95% CI 21% to 45%) shorter for the zinc groups of the seven included trials. Three trials that used lozenges composed of zinc acetate found that colds were shortened by 40% and four trials that used zinc gluconate by 28%. The difference between the two salts was not significant: 12 percentage points (95% CI: -12 to +36). Five trials used zinc doses of 80–92 mg/day, common cold duration was reduced by 33%, and two trials used zinc doses of 192–207 mg/day and found an effect of 35%. The difference between the high-dose and low-dose zinc trials was not significant: 2 percentage points (95% CI: -29 to +32). The conclusions are as following: properly composed zinc gluconate lozenges may be as effective as zinc acetate lozenges. There is no evidence that zinc doses over 100 mg/day might lead to greater efficacy in treatment of the common cold [29]

Zinc lozenges side effect

Taking zinc has relatively few side effects, but for some patients, they may be more burdensome than for others. When using lozenges, a bad taste and nausea are mostly reported. According to review including 14 double-blind placebo controlled trials the results were as follows. Odds ratio (OR) with 95% confidence interval (CI) was calculated. P -value < 0.05 was taken as significant.

Any side-effect was observed [lozenge, 2.15 (1.36–3.38) (P = 0.001) versus syrup, 1.03 (0.64–1.66) (P = 0.9)]; bad taste [lozenge, 3.24 (2.25–4.67) (P < 0.0001) versus syrup, 1.15 (0.55–2.39) (P = 0.71)]; nausea [lozenge, 2.46 (1.56– 4.89) (P = 0.0001) versus syrup, 1.24 (0.50–3.08) (P = 0.64)]; diarrhoea [lozenge, 2.09 (0.92–4.75) (P = 0.08) versus syrup, 1.34 (0.30–6.09) (P = 0.7)]; dry mouth [lozenge, 1.42 (0.95–2.11) (P = 0.09) versus syrup, 1.13 (0.43–3.01) (P = 0.8)][\[30\]](#). Therefore use of zinc lozenges should be adjusted to a risk-benefit assessment.

Discussion

Prophylactic use has demonstrated partial efficacy in individual studies; however, it is challenging to draw recommendations for regular use from them. Nevertheless, zinc lozenges have shown effectiveness in shortening the duration of the cold as well as reducing the severity of symptoms. Therefore, recommendations for their use seem justified. There were no significant differences observed between zinc supplementation in the form of gluconate and acetate. Additionally, no greater efficacy was demonstrated with doses exceeding 100mg per day. Supplementation within the range of 75-92mg, equivalent to approximately 3-4 lozenges releasing around 23mg of elemental zinc, seems considerable in patients with the common cold. This appears to be a cost-effective, easy, and efficient way to reduce the duration of the illness and not only affects increasing comfort of individuals but also carries significant societal implications by decreasing substantial collective costs.

Disclosure

Author's contribution

Conceptualization: Szymon Piaszczyński and Joanna Wojtania ; Methodology: Andrzej Czajka; Software: Michał Łepik ; Check: Kacper Reguła and Zofia Uszok; Formal analysis: Joanna Wojtania and Szymon Piaszczyński; Investigation: Krzysztof Rosiak, and Bartłomiej Szymański; Resources: Zofia Uszok; Data curation: Kacper Reguła Writing - rough preparation: Kacper Pleska and Kacper Reguła; Writing - review and editing: Michał Łepik and Kamil Waloch; Supervision: Joanna Wojtania; Project administration: Szymon Piaszczyński and Kacper Pleska; Receiving funding - no specific funding.

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The authors deny any conflict of interest

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