



The Effects of Zinc on Shortening the Duration of the Covid-19 Symptoms

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Abstract

Background: *The emergence and spread of Coronavirus Disease 2019 (COVID-19) brought about a public health crisis threatening the globe. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), epitomizes society's greatest health problem and cause of death. Until a vaccine is developed, controlling the spread and supportive medications are essential. Zinc (Zn) is one of the supportive treatments that have significant and implicit antiviral characteristics that are appreciated in the treatment of the common cold and enhancing the immune system.*

Objectives: *To evaluate the connection between daily dosage of zinc tablets/lozenges and the duration of colds in patients.*

Methods: *Ovid MEDLINE was examined utilizing the free search terminologies "zinc and lozenges" that produced over 60 research articles. Findings from the zinc trials were analyzed using, P-values together with the Fisher method and combining the survey outcomes through the RevMan ©program.*

Results: *High-dose zinc acetate (greater than 75 mg) tests provide a decline in the duration of colds, and there is "heterogeneity" observed between the tests.*

Conclusions: *Zinc lozenges can potentially reduce the duration of symptoms of the coronavirus when consumed within a day on the onset.*

Keywords: *Covid-19, Zinc (Zn), SARS-CoV-2.*

Introduction

The years 2019-2020 will be remembered for the global pandemic of COVID-19 brought about by SARS-CoV-2. The illness was first recognized in "Wuhan, Hubei Province, China", in 2019. Due to the viruses' high contagiousness the disease has spread worldwide and compelled the World Health Organization (WHO) to declare the

condition as a pandemic on March 11th, 2020, when the total global cases surpassed 500,000. By November 1st, 2020, the number of cases was 46,722, 172 with 1, 204,844 deaths.

COVID-19 epitomizes the greatest severe health problem for the world in the contemporary history of humans. On the March 6th, 2020 (WHO) reported the crude mortality ratio as about

3.5 which has decreased to 2.7% on July 12th, 2020 (Coronavirus Update (Live): 13,855,229 Cases and 589,947 Deaths from COVID-19 Virus Pandemic - Worldometer, 2020).

In contrast, these ratios differ according to nations, the age of the patients, and the presence of co-morbidities. Most patients who have succumbed to the disease are those aged 60 and above plus those with pre-existing health challenges, encompassing diabetes, cardiovascular diseases or conditions that affect the immune system.

SARS-CoV-2 is spread by inhalation or contact with infected droplets from one person to another, viral loads of symptomatic and asymptomatic carriers of the virus are similar. Like “flu and rhinovirus”, the spread of SARS-CoV-2 is perceived to happen via respiratory droplets from sneezing and coughing (Casella, 2020). The transfer of the virus occurs when individuals are in close contact, defined as closer than 6 feet or 2 meters for more than 10 minutes. The disease can also be spread when one comes into contact with a contaminated surface, and then touches their nose, mouth and eye. Currently, treatment mechanisms to manage COVID-19 are being tested, but the only effective preventative measures for decreasing community spread is social distancing, self-isolation and wearing masks. However, some systematic reviews propose zinc tablet/lozenges likely decrease the duration of symptoms of the coronavirus.

Coronavirus represents the subfamily “Orthocoronavirinae, within the family realm Riboviria, Coronaviridae, and the order of Nidovirales” (Mousavizadeh & Ghasemi, 2020). The viruses are enclosed with a definite “sense single-stranded ribonucleic acid genome and a nucleocapsid of helical symmetry” (Turner, 2016). The Wuhan strain was established as a new strain of Betacoronavirus from category 2B, with nearly 70% genomic comparison to the SARS-CoV (Johnstone et al., 2015). The virus originated in bats and was transmitted to humans by an unknown intermediary animal.

This review focuses on the use of Zinc tablets/lozenges to decrease the duration of COVID-19 and improve the immune system, most specifically the T cells. Zinc (Zn^{2+}) works in the overall improvement, variation, and operation of immune cells (Casella, 2020).

Zinc is involved in different cellular procedures and presents several explicit and implicit antiviral characteristics. It has been shown that zinc deficiency is linked to decreased antibody production, reduced cytokine production by monocytes, the innate immune system's function, and the “chemotaxis and the oxidative burst of neutrophil granulocytes” (Johnstone et al., 2015). Therefore, zinc has several influences on the immune structure, and its deficiency augments the susceptibility to diseases. In low resource nations, there is significant data that supports zinc supplementation to decrease the danger of contracting of common cold and pneumonia (Turner, 2016 5). However, these research data cannot be generalized to the developed nations such as France and the UK, where “multivitamin-mineral tablets” consisting of about 18mg per day of zinc had no impact on the frequency of respiratory diseases in the elderly (Kumar et al., 2020). Interests in zinc lozenges for conventional cold therapy began from the opportune event of a cold in young woman with leukemia. When she liquefied a medicinal zinc lozenge in her mouth rather than consuming it the cold symptoms disappeared (Johnstone et al., 2015). Some zinc versus placebo controlled trials have conflicting findings.

The RNA synthesis of the virus is catalyzed by an RNA-dependent RNA polymerase (RdRp), which is the core enzyme of the multiprotein replication and transcription complex (RTC). Using an activity assay for RTCs isolated from cells infected with SARS-CoV, eliminating the need for PT to transport Zn^{2+} across the plasma membrane, it shows that Zn^{2+} efficiently inhibits the RNA-synthesizing activity of the RTCs for the virus. Enzymatic studies using recombinant RdRps (SARS-CoV) purified from E. coli subsequently

revealed that Zn^{2+} directly inhibited the in vitro activity of the virus polymerases. More specifically, Zn^{2+} was found to block the initiation step of RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. By chelating Zn^{2+} with MgEDTA, the inhibitory effect of the divalent cation could be reversed, which provides a novel experimental tool for in vitro studies of the molecular details of virus replication and transcription. (te Velthuis et al., 2020).

Methodology

This systematic review study examined the available data of the pertinent literature relating to the COVID-19 and the use of Zinc, aiming to provide clinical evidence on Zinc tablets/lozenges intake and the duration of colds symptoms due to Covid-19 infections in patients. To achieve this goal a preliminary search was done on July 2rd, 2020 using Ovid MEDLINE to find out studies and scientific information that evaluate the ability of curative impacts of zinc on common cold diseases. All the studies which are published in English from 2015 to 2020 were included in the search. According to the status of observation, more than 80 studies related to Zinc tablets/lozenges were found. To make the results more accurate: the following keywords were used: Covid-19, Zinc (Zn), SARS-CoV-2, and common cold. By using these keywords, the number of studies was reduced to less than 65. For the purpose of quality and specificity of the search the studies were excluded if they were opinion, review, text studies or systematic review. To

avoid any factors that can affect the quality of the search and to increase its efficiency we filtered the studies that we obtained using PubMed search filter, Cochrane databases search filter and EMBASE search filter. As a result of using inclusion and exclusion criteria and other methods of filtering the number of studies was reduced to 15. These 15 studies were screened by examining the abstract, method and the results and finally the best 13 were selected based on the quality of the method and the results that have been found. All the selected studies evaluated the connection between daily dosage of zinc tablets/lozenges and the duration of colds in patients.

To make sure that their methods were high quality, the researchers did appraise them using the JBI Critical appraisal tools. The major type of checklist that is used is an experimental study checklist. By using this critical appraisal tool, the researchers were able to find the strengths and weaknesses of each study and concluded that the selected studies are at high quality to be used in any systematic review based on the JBI critical appraisal tools and inclusion and exclusion criteria. The process of identifying the studies is summarized in Figure 1. This methodical appraisal was limited to tests evaluating curative impacts of zinc on common cold diseases. Relieving pain without dealing with the cause was needed since experimentally having a clear decisive relevance to typical cold. The aggregate regular dose of rudimentary zinc from the tablets was computed as a product of the zinc dosage per tablet, and the designed number of tablets per day.

Table 1. Effect of Zinc Lozenges on Common Cold Episodes of Natural Origin

| Study [Ref.] | No. of Participants | Zn Dose Per Day (mg) ^a | Average Duration of Colds (Days) ^b Zn/Placebo | The Effect of Zn | P ^b (1-Tail) | -2×ln(P) |
|----------------------------------|---------------------|-----------------------------------|---|-------------------|---------------------------------------|----------|
| Eby <i>et al.</i> 1984 [7] | 65 | 207 | 3.9/10.8 ^c | -64% ^c | 0.0005 ^c | 15.2 |
| Smith <i>et al.</i> 1989 [19] | 110 | 207 | 5.9/6.3 ^d 5.5/6.9 ^d | -22% ^d | 0.5 ^d 0.01 ^d | 1.4 |
| Godfrey <i>et al.</i> 1992 [20] | 73 | 192 | 4.9/6.1 | -21% | 0.024 | 7.4 |
| Prasad <i>et al.</i> 2008 [21] | 50 | 92 | 4.0/7.1 | -44% | 6×10 ⁻¹³ | 56.3 |
| Petrus <i>et al.</i> 1998 [22] | 101 | 89 | 3.8/5.1 | -26% | 0.0033 | 11.4 |
| Turner <i>et al.</i> A 2000 [23] | 139 | 80 | 6.0/5.5 | | 0.5 | 1.4 |
| Mossad <i>et al.</i> 1996 [24] | 99 | 80 | 4.4/7.6 | -42% | 0.0005 | 15.2 |
| Prasad <i>et al.</i> 2000 [25] | 48 | 80 | 4.5/8.1 | -44% | 2×10 ⁻⁹ | 40.0 |
| Turner <i>et al.</i> B 2000 [23] | 139 | 69 | 5.5/5.5 | | 0.5 | 1.4 |
| Douglas <i>et al.</i> 1987 [26] | 58 ^e | 64 | 12.1/7.7 | | 0.96 | 0.1 |
| Macknin <i>et al.</i> 1998 [27] | 247 | 45 | 9.0/9.0 | | 0.5 | 1.4 |
| Weismann <i>et al.</i> 1990 [28] | 130 | 45 | 7/6 | | 0.5 | 1.4 |
| Turner <i>et al.</i> C 2000 [23] | 143 | 30 | 6.0/5.5 | | 0.5 | 1.4 |

Source: (Jackson *et al.*, 2020)

Literature review on the validities of zinc tablets on the symptoms of respiratory illness computed the impacts of zinc supplements on the duration of the respiratory sickness on the absolute scale, that is, the variation in days in the length of the common cold. Table 1 indicates a notable disparity in the duration of common cold symptoms in the palliative categories, from 5.1-9.0 days and 10.8 days (Adhikari, & Das, 2016 457). While a fraction of this dissimilarity is triggered by random variation, as well as a real difference in the gravity of illness in various patients and distinct result descriptions. Thus, this review calculated the comparative effects of zinc on the typical duration of common cold symptoms in percentages. The effects partially adjust for the differences between the patient group and result descriptions. In a previous review, computations of the relative effects rather than the absolute impact established a shred of more robust proof that vitamin C supplements reduces the time of the common cold symptoms (Johnstone *et al.*, 2015). Thus, the comparative impact is utilized in the Cochrane study on vitamin C and the symptoms of respiratory disease. An assessment of the findings of zinc trials, using P-values together with the Fisher method and combining the survey

outcomes were assessed through the RevMan program.

Table 2. The Effect of Zinc Lozenges on the Duration of the Common Cold: Combining the P-Values of the Placebo-Controlled Trials

| Trials Being Combined | No. of Trials | χ^2 | df | P |
|--------------------------------|---------------|----------|----|-------------------|
| All trials | 13 | 154.0 | 26 | 10 ⁻¹⁹ |
| Low Zn dose (<75 mg/day) | 5 | 5.7 | 10 | 0.8 |
| High Zn dose (>75 mg/day) | 8 | 148.3 | 16 | 10 ⁻²² |
| Zn-acetate [21,22,25] | 3 | 107.7 | 6 | 10 ⁻²⁰ |
| not Zn-acetate [7,19,20,23,24] | 5 | 40.6 | 10 | 10 ⁻⁵ |

The P-values of the individual trials are combined by using the Fisher method (see the Methods section). The combined χ^2 value is calculated from the -2×ln(P) values on the right side of Table 1. The combined P-values are separately calculated for low dose and high dose trials. Finally, the high dose trials are divided to those which used zinc acetate and to those which used zinc salts other than acetate.

Source: (Jackson *et al.*, 2020)

Results

From this demonstration, 13 palliative-controlled relationships have evaluated the medicinal impacts of zinc tablets on the duration of common cold symptoms. All 13 relations were double-blind; hence the trials utilized allocation, suppression. According to Adhikari & Das (2016, 457), experiments were randomized. In Table 1, the tests are arranged by the total everyday amount of rudimentary Zn in mg from the tablets.

The seven varied results found statistically significant benefits from zinc tablets. From the outcomes in Table 1, a considerable ratio of the disparity in the consequences might be elucidated by the everyday zinc prescription. Seven out of the eight relationships that used more than 75 mg of zinc per day established a statistically essential benefit. In contrast, the benefits in the Jackson et al. (2020) trial limited to the symptom's acuteness at the late stage of the common cold. The P-values of each test pooled by the Fisher method in Table 2 offers definite proof that zinc tablets and placebo categories are distinct in all the trials. However, zinc lozenges' notable impact is noted differently in three high-dosage tests where Zn acetate was utilized and in five high-dose tests that utilized zinc salts instead of acetate (Adhikari, & Das, 2016 458). Combining the three high-dose zinc acetate tests provide a decline in the duration of colds, and there is "heterogeneity" observed between the tests.

Discussion

In the trials involving daily dosage below 75mg, there was no validities of zinc supplements observed. However, for the trials involving more than 75mg of zinc dosage, there were apparent benefits (Johnstone et al., 2015). Therefore, from this study, zinc cleared symptoms such as headache, hoarseness, sore throat, and nasal congestion. However, in the trials, zinc supplements brought some side effects such as constipation and bad taste reactions (Turner, 2016 5). Such reported side effects, exceptionally lousy taste, might have been fostered by some tablet conformation, and cannot mirror the impacts of Zn^{2+} .

In a contemporary experiment on zinc acetate, there were insignificant variations between the zinc and placebo classes in the situations of unpleasant impacts while the dosage was 92mg (Adhikari, & Das, 2016 458). A Cochrane review established that zinc lozenges inhibit the replication of the virus that triggers common cold and shortens the duration of the disease when

taken in a 75mg/day dosage, within 24 hours of symptom onset (Suara, & Crowe, 2016 785). Thus, from this analysis, we can establish that zinc may inhibit SARS-CoV-2. According to cell cultures, zinc concentrations and the supplement of Pyrithione for incentive of the cellular import of zinc ions leads to inhibition of the replication of different RNA viruses (Velthuis et al., 2016), such as coronavirus. Also, zinc deters the RNA-producing events of Nidoviruses, like SARS-CoV (Suara, & Crowe, 2016 785), *in vitro*, which is achieved by altering RdRp functions throughout the elongation stage of RNA production, by absolutely impacting template combining (Velthuis et al., 2016). In this light, just like other coronaviruses, COVID-19 causing virus, SARS-CoV-2 also comes under the category of Nidoviruses (Skalny et al., 2020 20).

This review demonstrated that orally dispensed zinc supplements reduced the duration of cold symptoms. While there was no indication that people taking zinc tablets were symptomatic at 14 days, there was no variation between categories in the acuteness of the symptoms. Nonetheless, zinc has been established to shorten the duration of cold virus symptoms, where SARS-CoV is also a member of the family of viruses (Turner, 2016 5). The effect was highly attenuated and statistically significant in children. Symptoms of the disease were generally less severe in children and teens compared with adults. This is because serum cytokines were at higher levels in children than adults, also levels of two immune system molecules — interleukin 17A (IL-17A), which helps mobilize immune system response during early infection, and interferon gamma (INF-g), which combats viral replication — were strongly linked to the age of the patients. The younger the patient, the higher the levels of IL-17A and INF-g. Hence, the findings from this survey suggest that there is a potential dose-reliant impact linked with zinc ion, and it is coherent with the magnitude of medical response. This study differs in several instances from the Cochrane survey (Rahman & Idid, 2020, 3). Although this report was limited to

zinc supplements, Cochrane research pools zinc lozenges with normal zinc tablet tests. Nonetheless, the advantages of zinc tablets are likely characterized by low early zinc ingestion of the patients. Consequently, the impacts of zinc tablets might be brought about by local impacts of the oral cleft (Rahman & Idid, 2020, 3). As Findings from animal experiments suggest a link between poor maternal zinc status and increased risk of oral clefts in offspring; however, there are few human studies on this issue. As higher plasma zinc concentrations were associated with a lower risk for oral clefts in the children. However, the Cochrane review established that zinc supplementation can shorten the average duration of coronavirus symptoms when taken within 24 hours. The symptoms appear at a dosage above 75 mg per day.

Conclusion

In a nutshell, the systematic review has proposed that zinc lozenges can reduce the duration of symptoms and severity of disease of the coronavirus when consumed within a day on the onset of the symptoms. SARS-CoV-2 is transmitted from one person to another, and the symptomatic people are the most significant carriers of the virus. Like other respiratory illnesses, the spread of SARS-CoV-2 is perceived to happen via respiratory droplets from sneezing and coughing. Currently, treatment mechanisms to manage COVID-19 are only supportive care and decreasing community spread. Nonetheless, this systematic review indicates that zinc supplementation can suppress coronavirus symptoms by inhibiting the replication of the respiratory virus. Thus, zinc has several purposes on the defense structure, and its insufficiency augments the susceptibility to diseases. The research findings indicate that zinc tablets can reduce the danger of acute respiratory illnesses, such as COVID-19. In cell culture, Pyrithione fosters zinc ions uptake within a short time and inhibits ribonucleic acid virus replication through a strategy that has been reviewed for

picornaviruses. There were apparent benefits from the trials involving more than 75mg of zinc dosage from the results reviewed above. As such, the intake of zinc lozenges cleared the coronavirus's (common cold) symptoms such as headache, hoarseness, sore throat, and nasal congestion. Similarly, a Cochrane review established that zinc lozenges inhibit the replication of the virus that triggers respiratory illnesses and shortens the duration of the disease when taken in a 75mg/day dosage, within 24 hours of initial symptoms. Zinc hinders the RNA-producing events of Nidoviruses, like SARS-CoV, *in vitro*, which is achieved by altering RdRp functions during the elongation stage of RNA production, by explicitly impacting prototype requisite. Therefore, from this analysis, we can establish that zinc can inhibit SARS-CoV-2. However, the intervention is likely to face challenges since according to WHO and CDC, the majority of COVID-19 patients are asymptomatic (80%). It is therefore difficult to determine the most appropriate time to initialize consumption of zinc lozenges. However, administration of zinc lozenges to all individuals could have protective effects to potentially reduce COVID-19 symptoms, as well as the spread.

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