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The Effect of Zinc Supplementation on Non-Cholestatoma Chronic Suppurative Otitis Media

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Abstract

Background: Chronic suppurative otitis media (CSOM) is a chronic and persistent inflammation of the middle part of the ear. CSOM is a multifactorial disease that involves interactions between the host, pathogen, genetics, and environment leading to oxidative stress conditions that cause prolonged inflammation. Many studies have been conducted to explain zinc's benefits in fighting oxidative stress. This study aimed to determine the effect of zinc supplementation on non-cholesteatoma CSOM evaluated based on serum zinc and MPO levels and the presence of otorrhea.

Materials and Methods: This study was an experimental research with pre and post-test control group design. This study was conducted in the ENT clinic of Dr. Moewardi Hospital, Indonesia, in July–September 2022. Subjects were divided into two different groups. The first group, or treatment group, was treated with 30 mg tablets/day zinc supplementation for 30 days. The second group, or the control group, was treated with a placebo of 30 mg/day for 30 days.

Results: The result of this study showed that in the treatment group with zinc supplementation, the mean MPO level decreased significantly from 3.50 ng/mL to 0.73 ng/mL (p<0.001), the mean serum zinc level increased significantly from 119.53 µmol/L to 548.28 µmol/L (p<0.000), and 21 subjects recovered from otorrhea symptoms (p<0.000). Meanwhile, the mean MPO, zinc levels, and otorrhea symptoms did not show significant changes in the control group.

Conclusions: Zinc supplementation can reduce serum MPO levels, increase serum zinc levels, and reduce otorrhea symptoms CSOM patients suffer.

Keywords: CSOM, MPO, Otorrhea, Zinc.

INTRODUCTION

Chronic suppurative otitis media (CSOM) is a persistent, chronic, polymicrobial inflammation and infection of the middle part of the ear that can extend to the mastoid cavity.[1,2] The worldwide prevalence of CSOM is estimated at 1-4%, with a higher prevalence in developing countries than in developed countries.[3] CSOM is characterized by discharge from the ear canal (otorrhea) due to perforation of one or both ear tympanic membranes.[4] Infection and inflammation in the middle ear can be caused by various microorganisms, including *Escherichia coli*, *Staphylococcus aureus*, and *Candida spp*.[5] CSOM is one of the most important causes of hearing loss worldwide. Hearing loss due to CSOM is generally preventable.[6]

CSOM is a multifactorial disease that involves interactions between the host, pathogen, genetics, and environment, with the pathophysiology not fully known.[7,8] These factors interact, leading to oxidative stress conditions that cause prolonged inflammation in CSOM. Oxidative stress occurs when there is a significant increase in the production of reactive oxygen species (ROS) beyond the number of antioxidants in the body, disrupting the oxidant-antioxidant equilibrium. ROS are derivatives of oxygen radicals produced by cellular metabolism, including cells such as neutrophils, macrophages, and monocytes.[9] Oxidative stress is characterized by decreased antioxidant levels and increased ROS production that can cause damage to important compounds in the human body, such as DNA, proteins, and lipids.[10]

Myeloperoxidase (MPO) is part of a group of oxidative enzymes that have a primary function as antimicrobials. MPO works by converting H_2O_2 into hypochlorous acid (HOCl). In CSOM, the MPO produced will respond to dead bacteria, thereby inducing lipid peroxidation due to inflammation.[10,11] During inflammation, there is an increase in ROS accompanied by the migration of leukocytes to the site of inflammation. MPO and NADPH oxidase enzymes will be produced due to leukocyte migration. MPO left in the phagosome will produce oxidant HOCI with the help of H_2O_2 and chlorine, which will have a strong bactericidal effect. Increased oxidative stress may result from this series of processes leading to exacerbation of damage to the middle ear and eustachian tubes. Therefore, using antioxidants as maintenance therapy may be an alternative therapy in CSOM patients.[11]

Many studies have been conducted to explain the benefits of antioxidants in fighting oxidative stress, including using zinc. Zinc has benefits up to cellular and vascular levels and is an important mediator of cellular signaling. Zinc can maintain the stability of cell membranes, regulates genes expressing antioxidant enzymes, and has anti-inflammatory capabilities.[11] Study conducted by Izadi *et al*. on providing oral zinc supplements to manage otitis media effusion showed that oral zinc sulfate supplementation was statistically insignificant in providing therapeutic effects. However, long-term use showed a positive response.[12] Another study conducted by Abba *et al*. on zinc supplementation for the prevention of otitis media showed significant differences regarding the low incidence of otitis media and the low episodes of otitis media in children. In addition, zinc supplementation also shows therapeutic benefits in treating marasmus.[13] Based on the above background, we designed this study to determine the effect of zinc supplementation on non-cholesteatoma CSOM evaluated based on serum zinc and MPO levels and otorrhea symptoms.

MATERIAL AND METHODS

This study was an experimental research with pre and post-test control group design. This study was conducted in the ear, nose, and throat (ENT) clinic of Dr. Moewardi Hospital, Surakarta City, Indonesia, in July – September 2022. For this purpose, all subjects diagnosed with CSOM were invited to join the study. Subjects who were willing were then asked to sign informed consent. The next step was the selection of subjects that met the predetermined inclusion and exclusion criteria. Subjects were then divided into two different groups. The first group, or treatment group, was treated with 30 mg tablets/day zinc supplementation for 30 days. Meanwhile, the second group, or the control group, was treated with a 30 mg/day placebo for 30 days.

Inclusion criteria

The inclusion criteria in this study were:

1. Active phase CSOM.
2. Non-cholesteatoma CSOM
3. Aged over 18 years old.

Exclusion criteria

The exclusion criteria in this study were:

1. Subjects with systemic infection.
2. Subjects with immunocompromised or currently using immunosuppressant drugs.

Measurement of serum zinc and MPO levels

A venous blood sample was taken from each subject and ELISA test was performed to determine the levels of zinc and MPO. Serum zinc and MPO levels were assessed 30 days after zinc supplementation and placebo treatment.

Assessment of otorrhea symptoms

The subject's otorrhea symptoms were assessed by checking whether or not there was still discharge (otorrhea) coming out of the subject's ear on day 30 post-treatment.

Data analysis

The effect of zinc supplementation on serum zinc and MPO levels and otorrhea symptoms was assessed using the IBM SPSS statistics version 25 (Chicago, USA). We evaluated whether there were significant differences in the three assessment parameters (zinc, MPO, and otorrhea symptoms) between the treatment and control groups after zinc supplementation and placebo using statistical tests (paired T-test and Wilcoxon test).

Research ethics

Before carrying out the study, a research approval letter was prepared from the Head of the ENT Department of Dr. Moewardi Hospital Surakarta and forwarded to the Standing Committee for Medical Research Ethics of Dr. Moewardi Hospital, Surakarta, Indonesia. This study has been approved by the ethics commission of Dr. Moewardi Hospital with Ethical Feasibility Number 1.101/VIII/HREC/2022.

RESULT

A total of 25 subjects in the treatment group and 27 subjects in the control group were included in this study. The highest number in the treatment and control groups was in the 20-25-year age group. Gender distribution was almost balanced between males and females in the treatment group. Meanwhile, in the control group, it was more dominated by males. The number of subjects suffering from hearing loss in the treatment group was found to be quite high, where 15 subjects (64.3%) suffered from mild hearing loss and 6 subjects (24%) had a moderate hearing loss. Meanwhile, in the control group, 20 subjects (74.1%) suffered from mild hearing loss and 3 subjects (11.1%) had moderate hearing loss (Table 1).

Table 1. Demographic characteristics of the subjects

Parameter	T (n = 25)	C (n = 27)
Age (years)		
20 – 25	17 (68%)	19 (70.4%)
26 – 30	6 (24%)	4 (14.8%)
31 – 40	2 (8%)	1 (3.7%)
41 – 50	0 (0%)	2 (7.4%)
> 50	0 (0%)	1 (3.7%)
Gender		
Male	13 (52%)	18 (66.7%)
Female	12 (48%)	9 (33.3%)
Hearing Loss		
Mild	15 (64.3%)	20 (74.1%)
Moderate	6 (24%)	3 (11.1%)
Severe	0 (0%)	0 (0%)

Data are presented as n (%); T = treatment group; C = control group

Mean MPO levels decreased significantly from 3.50 ng/mL to 0.73 ng/mL (p<0.001) after intervention with zinc supplementation in the treatment group compared to the control group from 3.40 ng/mL to 3.14 ng/mL (p = 0.217). The mean serum zinc level significantly increased from 119.53 µmol/L to 548.28 µmol/L (p<0.001) after intervention with zinc supplementation in the treatment group compared to the placebo group from 116.16 µmol/L to 123.31 µmol/L (p = 0.258) (Table 2 & 3).

Table 2. MPO levels before and after treatment

Group	Pre	Post	p
C	3.40 ± 1.50 ng/mL	3.14 ± 1.48 ng/mL	0.217
T	3.50 ± 1.85 ng/mL	0.73 ± 0.50 ng/mL	<0.001*

Data are presented as means±SD; C=control group; T=treatment group; *=statistically significant

Table 3. Zinc levels before and after treatment

Group	Pre	Post	p
C	116.16 ± 84.56 µmol/L	123.31 ± 87.25 µmol/L	0.258
T	119.53 ± 84.56 µmol/L	548.28 ± 128.64 µmol/L	<0.001*

Data are presented as means±SD; C=control group; T=treatment group; *=statistically significant

In the control group, 27 subjects experienced otorrhea symptoms. After being treated with a 30 mg placebo for 30 days, 1 subject stopped suffering from otorrhea symptoms, so the number of subjects who experienced otorrhea was reduced to 26 subjects (p = 0.317). Meanwhile, in the treatment group, 25 subjects experienced otorrhea symptoms. After being treated with 30 mg zinc supplementation for 30 days, 21 subject stopped suffering from otorrhea symptoms, so the number of subjects who

experienced otorrhea was reduced to 4 subjects (p<0.001) (Table 4). In general, based on the findings of this study, there was a significant effect of zinc supplementation on serum zinc and MPO levels and reduction of otorrhea symptoms compared to the control group.

Table 4. Otorrhea symptoms before and after treatment

Group	Pre	Post	p
C	27 (100%)	26 (96.2%)	0.317
T	25 (100%)	4 (16%)	<0.001*

Data are presented as means±SD; C=control group; T=treatment group; *=statistically significant

DISCUSSION

The first finding in this study is zinc supplementation can significantly reduce serum MPO levels. This is in accordance with the study of Ganatra et al.[14] Zinc is one of the enzyme cofactors that play an essential role in the body's antioxidant defense mechanism. In addition, zinc acts as a pro-oxidant enzyme that protects cells against oxidative damage because it can stabilize the cell membrane, induce metallothionein synthesis, and inhibit NADPH-Oxidase. In patients with CSOM, MPO will be produced in large quantities due to chronic inflammatory processes that occur in the body. Zinc, which functions as part of the antioxidant defense mechanism, will reduce the body's MPO levels by converting it into non-destructive molecules, namely hydrogen peroxide and molecular oxygen.[15] This is the reason why MPO levels decrease after zinc supplementation.

The second finding of this study is zinc supplementation can increase serum zinc levels. The CSOM patients in the study were mostly zinc deficient, with an average serum zinc level below 457.8 µmol/L. Serum zinc levels in a healthy adult population are 70-120 µg/dL, or if converted into µmol/L units, the lower limit of normal serum zinc levels is 457.8 µmol/L.[16] This is in line with the study of Barnett et al., who found that serum zinc levels can increase significantly after zinc supplementation. Giving zinc supplementation at a dose of 30 mg for 30 days will increase serum zinc levels in the blood because zinc supplementation is absorbed in the digestive tract and carried into the bloodstream. Increased serum zinc levels will increase the proliferation and number of T cells. This increase in proliferation and number of T cells occurs through suppressing the apoptosis process of T cell precursors and inducing T cell production in the body. Increased levels of T cells can improve the immunity of patients with CSOM.[17] Therefore, it is for this reason that otorrhea symptoms in the zinc group can experience a significant decrease after zinc supplementation, which is the third finding of this study.

CONCLUSION

The results of this study indicate that zinc supplementation can reduce serum MPO levels, increase serum zinc levels, and reduce otorrhea CSOM patients. Zinc has an effect as an antioxidant defense mechanism and as an immunomodulator. This will improve the condition of patients with CSOM, which can be assessed by decreased serum MPO levels as inflammatory markers, increased serum zinc levels as a marker of immunity, and reduced otorrhea symptoms, as evidenced by an improvement in the patient's clinical condition. The findings in this study open up the possibility of routine use of zinc supplementation as adjuvant therapy for CSOM to obtain optimal results in treating patients suffering from CSOM.

Conflict of Interest

The authors affirm no conflict of interest in this study

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تأثير مكملات الزنك على التهاب الأذن الوسطى القيحي المزمن غير الكوليسترولي

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الملخص

الخلفية والأهداف: التهاب الأذن الوسطى القيحي المزمن (CSOM) هو التهاب مزمن ومستمر في الجزء الأوسط من الأذن. CSOM هو مرض متعدد العوامل يتضمن تفاعلات بين المضيف ومسببات الأمراض وعلم الوراثة والبيئة مما يؤدي إلى حالات الإجهاد التأكسدي التي تسبب التهابًا طويل الأمد. تم إجراء العديد من الدراسات لشرح فوائد الزنك في مكافحة الإجهاد التأكسدي. تهدف هذه الدراسة إلى تحديد تأثير مكملات الزنك على CSOM غير الكولسترولية التي تم تقييمها على أساس مستويات الزنك في الدم وMPO ووجود سيلان الأذن.

منهجية الدراسة: كانت هذه الدراسة عبارة عن بحث تجريبي بتصميم المجموعة الضابطة قبل وبعد الاختبار. أجريت هذه الدراسة في عيادة الأنف والأذن والحنجرة بمستشفى الدكتور موواردي بإندونيسيا في الفترة من يوليو إلى سبتمبر 2022. وتم تقسيم الأشخاص إلى مجموعتين مختلفتين. عولجت المجموعة الأولى، أو مجموعة العلاج، بمكملات الزنك بجرعة 30 ملغ/يوم لمدة 30 يومًا. تم علاج المجموعة الثانية، أو المجموعة الضابطة، بدواء وهمي قدره 30 ملغ / يوم لمدة 30 يومًا.

النتائج: أظهرت نتيجة هذه الدراسة أنه في مجموعة العلاج بمكملات الزنك، انخفض متوسط مستوى MPO بشكل ملحوظ من 3.50 نانوجرام/مل إلى 0.73 نانوجرام/مل ($p<0.001$)، وزاد متوسط مستوى الزنك في المصل بشكل ملحوظ من 119.53 ميكرومول/لتر إلى 119.53 ميكرومول/لتر. 548.28 ميكرومول/لتر ($p <0.000$)، وتم شفاء 21 شخصًا من أعراض الإسهال ($p <0.000$). وفي الوقت نفسه، لم يظهر متوسط MPO ومستويات الزنك وأعراض الإسهال تغيرات كبيرة في المجموعة الضابطة.

الاستنتاجات: مكملات الزنك يمكن أن تقلل من مستويات MPO في الدم، وتزيد من مستويات الزنك في الدم، وتقلل من أعراض سيلان الأذن التي يعاني منها مرضى CSOM.

الكلمات الدالة: CSOM، MPO، ثر الأذن، الزنك.