Effectiveness of Oral Zinc Supplementation in the Treatment of Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)

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Objective: Investigate the benefit of zinc supplement combined with standard treatment of idiopathic sudden sensorineural hearing loss (ISSNHL) patients.

Material and Method: A prospective, randomized study was designed to evaluate the hearing outcomes in ISSNHL patients treated with zinc supplement. The patients were randomized into two groups, the study and the control group. The study group received oral chelated zinc with standard treatment (oral prednisolone), while the control group received standard treatment alone. Hearing improvement was assessed from pure-tone average (PTA) and speech discrimination scores (SDS). Results: After treatment, significant hearing improvement was noted in both groups regarding PTA value (p = 0.016, 0.025). SDS was also improved in both groups but with no statistical significance (p>0.05). Post-treatment PTA and SDS values between the zinc and control groups were not statistically different (p>0.05). Hearing improvement was documented in eight of 16 patients in the study group and seven of 14 patients in the control group. This was no significant difference (p = 1.000).

Conclusion: Zinc supplementation does not have benefit when combined with standard treatment. Nevertheless, more subjects and well-designed studies are needed to verify the effect of zinc.

Keywords: Zinc, Idiopathic sudden sensorineural hearing loss, Steroids, Prednisolone

J Med Assoc Thai 2015; 98 (4): 400-7
Full text. e-Journal: http://www.jmatonline.com

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as an abrupt onset of sensorineural hearing loss, within three days, and of at least 30 dB at three consecutive frequencies. It is reported to occur in 5 to 20 per 100,000. The etiology of ISSNHL is considered idiopathic, however, many possible causes including viral infection, vascular occlusion, rupture of cochlear membranes, and immunologic diseases are discussed. Several treatments for ISSNHL have been used including steroids, vasodilator, antiviral agents, diuretics, and low-salt diets. However, about 30% to 60% of patients have been reported to have spontaneous recovery, usually within two weeks after onset. High-dose systemic steroids is currently the treatment of choice for the disorder. The exact mechanisms in which steroids may improve hearing are not known. The steroids have strong anti-inflammatory property mediated through glucocorticoid and mineralocorticoid receptors found within the cytoplasm in the inner ear. These effects play an important role in improving function of the cochlea. Many studies have demonstrated the beneficial effects of steroids on cochlear function such as decrease inflammation from labyrinthitis, improve cochlear blood flow from ischemia-induced cochlear injury, improve stria vascularis function and morphology. Since stria vascularis might be a site for potential pathology in ISSNHL, steroids have a chance to recover hearing in ISSNHL therapy. Recently, intratympanic steroid injection has been advocated as an alternative method for treating ISSNHL. This procedure can introduce steroid directly into the middle ear space, resulting in higher perilymph steroid level and reduced systemic steroid toxicity. It has been used as salvage treatment or initial treatment. However, the latest review from the Cochrane database regarding the value of steroids in the treatment of ISSNHL revealed an unclear result because the evidence obtained from randomized controlled trials is contradictory in the outcome. The authors pointed out that this unclear result may occur from the sample size of these studies was too small.
Hyperbaric oxygen therapy (HBOT) is another method for the treatment of ISSNHL. It is believed to improve oxygen supply to the inner ear and result in hearing improvement. From the Cochrane database, the researchers(19) had shown that the application of HBOT significantly improved hearing level. However, the clinical benefit remains unclear due to small number of patients and unappropriated methodology. They found no evidence of a beneficial effect of HBOT on chronic ISSNHL or tinnitus and did not recommend HBOT for the treatment of both conditions.

Two minerals, magnesium and zinc, are used in the treatment of ISSNHL. Magnesium has been investigated for the efficacy in a prospective, randomized, double-blind, placebo-controlled trial(20). Twenty-eight ISSNHL patients were treated with either steroids combined with oral magnesium (study group) or steroids combined with a placebo (control group). They reported a significantly higher proportion of patients with improved hearing (>10 dB hearing level) and significant greater mean improvement in all frequencies in the magnesium-treated group. They concluded that magnesium was a safe and effective combination to steroids for the treatment of ISSNHL.

In another study by Gordin et al(21), 133 ISSNHL patients were enrolled. Seventy-three patients received a combination of carbogen inhalation and intravenous magnesium sulfate while sixty patients received carbogen inhalation alone. They found significant difference in mean improvement rate and total number of patients in the magnesium group compared to the control group.

Zinc is another mineral that has a role in hearing function. It is a trace element in the body, but it plays an important role in various kinds of physiologic functions such as body metabolism, memory, growth, and enzymatic activities(22,23). Zinc is found in the synapses of the auditory system(24) and in cochlear tissue in form of the enzyme Cu/Zn superoxide dismutase (SOD)(25). Zinc deficiency has been reported in patients with presbycusis, tinnitus, and imbalance(26,27). Enhanced ototoxicity of gentamicin and salicylate caused by magnesium deficiency and zinc deficiency were also demonstrated in animal study(28). On the contrary, there were few studies reporting on the effect of zinc supplementation in prevention or treatment for cochlear damage. One of these reports revealed the protective function of zinc against pneumolysin toxicity on rat cochlear hair cells(29). Another report demonstrated that zinc had a role in prevention of cochlea from cadmium-induced ototoxicity(30). In human, zinc has been used in the treatment of many diseases including childhood diarrhea, pneumonia, otitis media, and common cold. However, the results of many studies were controversy and meta-analysis of these studies did not reveal enough evidence(31,32) to conclude that zinc supplementation really has benefit as combined therapy for those diseases. There was only one study on the efficacy of zinc in the treatment of ISSNHL (Yang et al)(33). They found a better hearing gain and an increased rate of successful recovery in the zinc group. A significant correlation between serum zinc level changes and post-treatment hearing thresholds was also demonstrated. Moreover, they proposed that zinc might enhance the hearing recovery by its antioxidant and anti-inflammatory effects, which may reduce the oxidative stress of the cochlea in ISSNHL. In the present study, oral chelated zinc as the supplement, in combination with standard regimen, was used for treating ISSNHL patients. Hearing recovery was compared between the patients received and not received zinc supplementation. The purpose of the present study was to evaluate the effectiveness of zinc in the treatment of ISSNHL.

Material and Method

Between July 2012 and January 2014, a randomized, prospective trial was performed in the patients who met the diagnostic criteria for ISSNHL as mentioned and signed the written informed consent. The patients in the study group must accept oral zinc supplementation. The patients with medical conditions that may cause ISSNHL were excluded, such as infections, trauma, diabetes, hyperlipidemia, and patients taking ototoxic drugs. The patients enrolled in the present study must have normal results of auditory brainstem response (ABR). Any patients whose ABR revealed retro-cochlear lesions were excluded and sent for magnetic resonance imaging (MRI) of the temporal bone and brain to further investigate the causes. Nursing and pregnant women were also excluded, as well as those who were contraindicated for oral steroid and zinc supplementation. The present study was approved by the Ethic Review Boards of the Faculty of Medicine, Srinakharinwirot University.

Data collected

Data included age, sex, occupation, site of hearing loss, associated symptoms (tinnitus, vertigo), and duration before treatment. All patients underwent...
complete history, ENT examination, and blood test for complete blood count, blood sugar, lipid profiles, thyroid hormones, and serology for syphilis and HIV. Both pre- and post-treatment serum zinc level were obtained for the study group and only pretreatment zinc level for the control group. ABR was tested in every patients as a screening for retro-cochlear lesions. MRI was done in the patients who showed abnormal ABR to look for abnormal lesions around the area of the internal acoustic canal, temporal bones, cerebropontine angle, brainstem, and brain. Audiologic data consisted of pure-tone average (PTA) and speech discrimination score (SDS) were tested by audiologist. PTA was calculated as an average of the threshold, measured at 0.5, 1.0, and 2.0 KHz. SDS was tested by calculating the percent correct of a phonetically balanced, monosyllabic word list (Ramathibodi Hospital).

Zinc supplementation protocol

All patients were received oral prednisolone, 60 mg/day in adults and 1 mg/kg/day in children, for seven days, combined with betahistine 12 mg and vitamin B1-6-12 three times a day for one month. In the zinc group, oral chelated zinc (75 mg, equivalent to 15 mg elemental zinc; Qualimed, Bangkok, Thailand) one tablet three times after meal was added for one month. Any adverse effects occurred during the therapy were recorded. The patients were followed-up at one week, and one month after the start of treatment. Serum zinc levels were checked at the beginning of both group and at the end of treatment for the zinc group, to detect any change in zinc value. Audiometric values (PTA and SDS) were assessed before treatment and during each visit. The audiometric criterion for successful recovery after the therapy differed in the literature. However, a 10-dB improvement in PTA or a 15% improvement in SDS was considered a successful therapeutic intervention for the present study.

Qualitative variables were compared with Chi-square or Fisher’s exact test, whereas quantitative variables were done with Student’s t or Wilcoxon nonparametric test. The criterion for statistical significance was \( p < 0.05 \).

Results

At the end of the study, 40 patients were collected. Ten patients were excluded, and 30 patients remained in the study. Of ten patients excluded, one had acoustic neuroma, one had diabetes, three had hyperlipidemia, three had drug adverse effect (nausea, vomiting, and vertigo), and two were lost to follow-up. There were sixteen patients in zinc group and fourteen patients in control group. The basic characteristics of the patients in both groups were no statistically difference (Table 1). The average age of the patients was 57.5±10.2 years in the zinc group and 64.6±11.3 years in the control group, which was no statistically significant \( (p = 0.080) \) (Table 1). The male-to-female ratio was 9:7 in the zinc group and 4:10 in the control group. The mean duration from onset to start of the therapy was 26.6±37.8 days in the zinc group and 29.8±40.9 days in the control group. Both sex ratio and duration of the initial treatment were no significant difference \( (p = 0.127, 0.692) \) (Table 1). There was also no significant difference related to the affected sites in the zinc and the control group \( (p = 0.732) \) (Table 1). The initial PTA was 68.1±25 dB and SDS was 56.5±38.3% in the zinc group when compare to initial PTA at 56.1±19.7 dB and SDS at 63.4±35.7% in the control group, there were no statistical difference \( (p = 0.160, 0.614) \) (Table 2). After finishing the treatment, significant hearing improvement was noted in both groups regarding PTA value \( (p = 0.016, 0.025) \) (Table 2). SDS was also improved in both groups but no statistical significance \( (p = 0.223, 0.144) \) (Table 2).

Table 1. Comparison of the basic characteristics between the zinc supplementation group and the standard treatment group

<table>
<thead>
<tr>
<th></th>
<th>Zinc supplementation</th>
<th>Standard treatment</th>
<th>p-value*</th>
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<tbody>
<tr>
<td>Number</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>57.5±10.2</td>
<td>64.6±11.3</td>
<td>0.080</td>
</tr>
<tr>
<td>Site (right:left)</td>
<td>9:7</td>
<td>7:7</td>
<td>0.732</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>9:7</td>
<td>4:10</td>
<td>0.127</td>
</tr>
<tr>
<td>Duration from onset to treatment in days (mean ± SD)</td>
<td>26.6±37.8</td>
<td>29.8±40.9</td>
<td>0.692</td>
</tr>
</tbody>
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* p-value tested by independent t-test or Chi-square test or Wilcoxon rank sum test
Summary

Clinical improvement was found in eight of 16 patients in the zinc group, and seven of 14 patients in the control group, which was not statistically different ($p = 1$) (Table 3). The pretreatment serum zinc level was 63.5±12.9 ug/dL in the zinc group, and 63.0±15.3 ug/dL in the control group, which was not significantly different ($p = 0.934$) (Table 4). After treatment, the serum zinc level in the study group was 74.1±12.1 ug/dL, significantly higher than pretreatment value ($p = 0.021$) (Table 4). There were intolerable adverse effects including nausea, vomiting, and vertigo in three patients whom were excluded from the study.

Discussion

There were no statistical differences in age, sex, site of ISSNHL, and duration between the zinc and control group. The initial PTA and SDS values were also shown no significant difference between both groups. After therapy, there was significant improvement of PTA values in both groups. SDS values were also shown improvement but no statistical significance. When comparing the results of the therapy in both groups, the zinc group did not show better improvement in number of patients, PTA value, and SDS value than the control group. The results of the present study were differed from the study of Yang et al[33]. They reported significant better hearing recovery in the zinc group than the control group, regarding hearing gain (25 dB vs. 14 dB) and percentage of hearing recovery (50% vs. 32%). Furthermore, they found the greater elevation in zinc level the higher percentage of recovery. They postulated that zinc might play a role by various mechanisms. First, elevation of zinc may enhance the normal function of the stria vascularis as it is a component of enzyme Cu/Zn superoxide dismutase (SOD)(25) and the auditory nerve pathway by improving of synaptic activity(24). Rarey et al(25) had studied in rat cochlea and found the activity of this enzyme. The presence of Cu/Zn SOD may also indicate the existence of a defense system against free oxygen radical injury in cochlear tissues. Zirpel et al[26] demonstrated that zinc is localized in the eight nerve presynaptic calyces and is released by nerve stimulation or potassium chloride depolarization. The presence of zinc is necessary for homeostasis of chick cochlear nucleus neurons. Second, the antioxidant effects of zinc may also have a role in better hearing outcome in the zinc group. Although the relationship between oxidative stress and ISSNHL was not known, there were some researches revealed a better recovery in the patients receiving antioxidants as an additional

<table>
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<th>Table 2. Comparison of average PTA and SDS improvement in the zinc supplementation and standard treatment group</th>
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<tr>
<td><strong>PTA before (dB)</strong></td>
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<tr>
<td>Zinc supplementation</td>
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<tr>
<td>Standard treatment</td>
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<td>*p-value tested by paired t-test or independent t-test</td>
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<th>Table 3. Clinical outcome in summary</th>
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<td><strong>Zinc supplementation</strong></td>
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<tr>
<td>Improvement (cases)</td>
</tr>
<tr>
<td>Failure (cases)</td>
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<tr>
<td>Total</td>
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*p-value tested by Chi-square test

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<th>Table 4. Comparison of average serum zinc levels in the zinc supplementation and standard treatment group</th>
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<tr>
<td><strong>Pretreatment (ug/dL)</strong></td>
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<tr>
<td>Zinc supplementation (mean ± SD)</td>
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<tr>
<td>Standard treatment (mean ± SD)</td>
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<td>*p-value tested by independent t-test or paired t-test</td>
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treatment\textsuperscript{14,35}. Joachims et al\textsuperscript{34} reported that patients treated with the addition of vitamin E achieved better recovery than did the control patients. Hatano et al\textsuperscript{35} also demonstrated that patients additionally received vitamin E (tocopherol nicotinate, 600 mg/day) and vitamin C (1,200 mg/day) orally had significant improvement in the hearing gain and recovery rate when compared to the control group. Finally, zinc may improve hearing in ISSNHL by its anti-inflammatory and immune modulator effects. These functions account for the viral etiology, which is one of the possible mechanisms of ISSNHL. The study in temporal bone of ISSNHL patients by Merchant et al\textsuperscript{36} did not demonstrate any findings suggested viral cochleitis, vascular insults, or inner membrane ruptures. They proposed a hypothesis that ISSNHL may result from a stress response. This response may be triggered by virus or other events, which activate the cochlea nuclear factor-kappa B (NF-kB) that finally resulting in the production of two inflammatory cytokines, interleukin-1 (IL-1), and tumor necrosis factor alpha (TNFa). Inhibitory effect on NF-kB of cytokines, interleukin-1 (IL-1), and tumor necrosis factor alpha (TNFa). Inhibitory effect on NF-kB of steroids is an important mechanism in the treatment of ISSNHL. Zinc has also been found to inhibit the activation of NF-kB by up-regulating the zinc-induced A20 zinc finger protein\textsuperscript{37}. Therefore, zinc supplementation may have a synergistic action with steroids in ISSNHL treatment.

Nevertheless, the results of the present study contrast with the study by Yang et al\textsuperscript{33}. This may occur from some factors such as age, number of the patients, and duration before start treatment. Age is considered by some authors as a prognostic factor for ISSNHL treatment. The older patients have a worse outcome than the younger ones\textsuperscript{17,38}. Besides, Aamodt et al\textsuperscript{39} reported that human zinc absorption decreased with age. The mean age of 57.5±10.2 years in the present study was older than in Yang et al (48.8±15.5 years). The initial serum zinc level of the zinc group was 63.5±12.9 ug/dL in the present study, which was lower than normal level (70-170 ug/dl) and much lower than the level in Yang et al study (78.7±13.17). Furthermore, zinc value after treatment was 74.1±12.1 ug/dL which was still lower than 93.9±20.53 ug/dL in Yang et al study. Even though the post-treatment zinc level in the present study showed significant higher than the pretreatment level, the results of treatment were no statistical difference between both groups. The age factor may reflect poorer zinc distribution into the inner ear, which causes outcome failure of the study. Other factor may be the number of the patients in the present study was too small, 30 cases, compare to 66 cases in Yang et al study, which may cause different results. The duration from ISSNHL onset to starting the therapy was another prognostic factor that had been discussed. The sooner treatment is initiated, the better is the outcome\textsuperscript{13,14,40}. Ho et al\textsuperscript{13}, and Plaza and Herrera\textsuperscript{14} had reported that from onset to therapy within seven days was related to more hearing improvement. Hanes et al\textsuperscript{40} found a better result when the treatment was started within fourteen days. In the present study, the average starting time of treatment was 26.6 days in the zinc group and 29.8 days in the control group. The duration was much longer than the previous reports for good recovery, and longer than in Yang et al study (average 4.8 days in the zinc group and 5.2 days in the control group). The difference in duration may cause different results of both studies.

The limitations of the present study were the clinical experience from a single institution and small number of subjects. Other limitations might be lack of comparing between zinc level in the ISSNHL patients and normal subjects. This would show whether the zinc level in ISSNHL patients was lower than normal value. If the zinc level was low, then the zinc supplement is reasonable in those cases.

**Conclusion**

The present study demonstrated that zinc supplementation in treating ISSNHL did not have further benefit when combined with standard treatment of steroid. The results were contrast with the previous studies, which may occur from the age, number of the subjects, and the starting time of the treatment. Nevertheless, larger sample sizes and well-designed studies are needed to verify the effect of zinc.

**What is already known on this topic?**

Despite the etiology of ISSNHL was considered idiopathic, many kind of treatments had been tried. Steroids are currently the treatment of choice. Zinc is a trace element that essential for the functions of various organs including the cochlea. There was only one study conducted and showed the efficacy of zinc in the treatment of ISSNHL.

**What this study adds?**

The present study revealed that zinc supplementation combined with standard treatment did not get better results in treating ISSNHL than standard treatment alone. The contrast outcomes compared to the previous study may need more
sample sizes, earlier treatment, and well-designed studies to verify these effects of zinc.

Acknowledgement
The authors thank Asst. Prof. Kittipong Kongsomboon MD, for assistance in statistical analysis.

Potential conflicts of interest
None.

References


ผลการใช้ยาสังกะสีนิดกินร่วมกับการรักษาตามมาตรฐานในโรคหูดับเฉียบพลันโดยไม่รู้สาเหตุ

นิรันดร หุ่นฉายศรี, สุประพล จันทพันธ์, อรินทร์ ศิริรัตนพันธ์

วัตถุประสงค์: เพื่อให้ทราบประสิทธิภาพของการรักษาโรคหูดับเฉียบพลัน (idiopathic sudden sensorineural hearing loss, ISSNHL) โดยการให้ยาสังกะสีนิดกินร่วมกับการรักษาตามมาตรฐาน

วัสดุและวิธีการ: เป็นการศึกษาแบบ prospective, randomized เพื่อประเมินผลของการให้ยาในผู้ป่วยโรคหูดับเฉียบพลันโดยไม่รู้สาเหตุ (ISSNHL) ที่ได้รับการรักษาด้วยการให้ยาสังกะสีนิดกิน โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มนี้จะได้รับการรักษาด้วยการให้ยาสังกะสีนิดกินร่วมกับการรักษาตามมาตรฐานหรือเพียงการรักษาตามมาตรฐานเท่านั้น การสังเกตการณ์อาการรุนแรงมีการประเมินจากค่า pure tone average (PTA) และค่า speech discrimination scores (SDS) ผลการศึกษา: พบการได้ยินดีขึ้นอย่างมีนัยสำคัญทางสถิติของผู้ป่วยทั้งสองกลุ่มในค่า PTA (p = 0.016, 0.025) ส่วนค่า SDS นั้น ดีขึ้นแต่ไม่มีนัยสำคัญทางสถิติ ส่งเสริมการให้ยา PTA และ SDS หลังการรักษาไม่พบว่ามีความแตกต่างกันทางสถิติระหว่างกลุ่ม (p>0.05) ในกลุ่มทดลองพบการได้ยินดีขึ้น 8 ใน 16 ราย ส่วนในกลุ่มควบคุมพบการได้ยินดีขึ้น 7 ใน 14 ราย ซึ่งในมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 1.000)

สรุป: การให้ยาสังกะสีนิดกินร่วมกับการรักษาตามมาตรฐานสำหรับการรักษาผู้ป่วยโรคหูดับเฉียบพลันไม่ได้ผลสืบกับการรักษาตามมาตรฐานเพียงอย่างเดียว อย่างไรก็ตามควรจะมีการศึกษาเพิ่มเติมในกลุ่มประชากรจำนวนมากเพื่อที่จะให้ได้ข้อสรุปที่แน่นอนต่อไป