A clinical trial of Nicergoline to prevent temporary threshold shift

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Abstract

Background: In Thailand, military personnel attending the annual firing practice are at risk for noise-induced hearing loss (NIHL). Nowadays, hearing protection devices have been approved to prevent NIHL. Furthermore, N-acetyl-cysteine, Vitamin B12 or Magnesium were proved to be effective against temporary threshold shift (TTS). However, limited research regarding the effectiveness of nicergoline on preventing TTS has been reported.

Methods: A randomized controlled trial was conducted. Two hundred twenty-four participants were evaluated for general physical status, hearing threshold levels and blood chemistry. After the informed consent form was explained and signed, the participants were divided into 2 groups. Nicergoline 30 mg twice daily intake was prescribed to the study group (n=119) for 3 weeks. The placebo was prescribed to the control group (n=105) for 3 weeks, as well. At the end of the second week, they had to attend the firing practice. All participants had to wear the silicone ear plugs. In addition, the audiometry was measured within 48 hours after the end of the firing practice. Moreover, aural symptoms (tinnitus and aural fullness) and the side effects of the medication were recorded.

Results: TTS was detected in both groups 14 ears – 10 ears from the control group and 4 ears from the study group ($p=0.075$). The post-firing practice audiometry showed that the average hearing threshold levels of the study group significantly improved than that of the control group across all frequencies ($p<0.05$). Moreover, the audiometry from the control group worsened at 250 and 6K Hz ($p<0.05$). The duration of tinnitus and aural fullness in the study group occurred over a shorter period than that in the control group.

Conclusion: The TTS was found in both groups without statistical significant differences. The effectiveness of nicergoline from the study demonstrated tinnitus reduction after the firing practice. Furthermore, the hearing threshold significantly improved in the study group.

Background

Approximately 10% of the population worldwide suffer hearing loss, and about half of them can be attributed to exposure to intense noise(1). The two most prevalent disabilities among veterans in the United States at the end of fiscal year 2012 remain tinnitus and hearing loss, with tinnitus affecting 115,638 veterans (9.7%) and hearing loss affecting 69,326 veterans (5.8%)(2). In addition, military personnel are also affected from noise induced hearing loss (NIHL) as a consequence of the annual firing practice or other military training programs.

The noise causes damage to the inner ears by two mechanisms. First, the intense noise can damage the cochlea mechanically by decoupling the organ of Corti from the basilar membrane(3). Second, long term exposure to lower levels of noise causes metabolic stress and hair cell death. As a result of noise exposure, the increased levels of reactive oxygen species (ROS) were demonstrated. Moreover, many

studies have reported the use of antioxidants such as Magnesium, N-acetyl-cysteine or Cyanocobalamin (Vitamin B₁₂), to scavenge and eliminate the damaging ROS(4).

The noise-induced hearing loss (NIHL) refers to injury to the inner ears after exposure to noise. NIHL is divided into temporary threshold shift (TTS) and permanent threshold shift (PTS). TTS generally recovers within 24–48 hours. Additionally, persistent TTS may result in permanent hearing loss which promotes permanent threshold shift(5). These two conditions (TTS and PTS) are still not well understood(6).

In 1994, Attia J(7) demonstrated that magnesium had a protective effect on NIHL among military personnel. Furthermore, Wu L, et al.(8) proved the protective effectiveness of N-Acetyl-cysteine (NAC), antioxidant against NIHL. In animal models, glutathione, D-methionine and ebselen also showed NIHL attenuation(6). Many studies reported the effectiveness of medications in preventing TTS but there is much controversy about it. Moreover, nicergoline, an anti-oxidant derivative of ergoline, provides neuroprotective effects and increases inner ear circulation(9-11). The clinical use of nicergoline such as in treating dementia, vascular and balance disorders especially in vertigo and tinnitus, is widely recommended(5). Nowadays, the studies of nicergoline on preventing NIHL are limited. Consequently, the primary objective of this study is to investigate the effectiveness of nicergoline in preventing TTS. Additionally, the secondary objective is to determine the duration of tinnitus among the military personnel attending the annual firing practice.

Methods

A randomized controlled trial (RCT) was conducted and the protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department. Two hundred and thirty-eight male conscripts from The Royal Thai Navy, aged 20 to 25 years were informed about the aims and methods of the study then signed their written consent to participate in the study. All participants obtained a physical examination including an otoscopic examination of the ear canal, tympanic membrane and baseline hearing thresholds (Pure-tone air-conduction audiometry) before the firing practice. Besides, the complete blood count (CBC), blood urea nitrogen (BUN), creatinine, uric acid and liver function test were required. Participants were excluded if they were diagnosed as having any disease consisting of perforated tympanic membrane, infected or inflamed ear disease, abnormal audiometry, abnormal blood chemistry and allergy to nicergoline. The participants consisting of 224 conscripts were divided into two groups by using the cluster randomization method. The participants in the study group and the control group were 119 and 105 respectively. After the physical examination, 4 participants from the study group and 10 participants from the other group were excluded from the study (Figure 1). The trial was registered at the Thai Clinical Trials Registry (TCTR20200519002).

Noise exposure

From April 2019 to July 2019, all subjects participated in basic military training in The Royal Thai Marine Corps, Chonburi Province, Thailand and then attended the annual firing practice conducted on 31 August

2019. All participants used M16 rifles and each person was to fire 30 shots in a row. They were reminded to use ear plugs during firing practice. The approximated noise intensity level of M16 rifle is 157 decibel (dB)(12), while the ear plugs attenuated the noise level by 18 to 20 dB(13).

Nicergoline administration and dosage

The blinded labels of nicergoline (30mg) and placebo were attached to aluminum blisters. Furthermore, these packages were allocated to both groups. The participants were to take 1 tablet after meals twice daily for 3 weeks, and then they were observed for side effects such as nausea, drowsiness, diarrhea, fainting, headache and vertigo(14) on their own. At the end of the second week of taking medication, they had to attend the firing practice.

Pure-tone air-conduction audiometry

This auditory sensitivity test was used to evaluate the hearing threshold. The procedure was usually performed in both ears. Results of audiometry were displayed on a graphic plot called an audiogram. Besides, the audiometry was measured at the frequencies of noise at 250, 500, 1K, 2K 3K, 4K, 6K and 8K Hz. Thresholds that fall into the range between 0 to 25 dB are considered normal, whereas thresholds above 25 dB represent various levels of hearing loss(15). The TTS was diagnosed as well as the threshold above 25 dB at any level of the frequencies among 3K, 4K, 6K and 8K Hz after participants exposed to rifle noise(5).

Regarding, the Navy military training units set the buddy system defined as a procedure in which two individuals, the "buddies", operate together so that they are able to monitor and help each other. Moreover, the buddy system helped the researcher to monitor the participants taking the pills and wearing ear plugs.

Measurement of tinnitus

A portable self-recording form with necessary details was given to each qualified participant in order to record the side effects of medication in their own during 3 weeks of the protocol. Additionally, at the end of the firing practice, the participants would record the time when tinnitus and hearing loss began until the symptoms were resolved.

Statistical analysis

The statistical analysis was performed by a certificated statistician using STATA Software. Descriptive statistics such as number, percentage, mean, standard deviation, minimum and maximum were reported. Categorical data were analyzed by using Chi-squared test while continuous data were analyzed by using independent t-test. The average difference between the study and the control one was analyzed by using Paired t-test, and statistical significance was inferred at $p < 0.05$.

Results

Fourteen participants were excluded from the study because they did not meet the inclusion criteria including abnormal blood chemistry and abnormal audiometry. The information of 224 participants consisting of 448 ears was analyzed. The average age of the participants in the study group and the control group was 22.31 ± 1.44 and 22.36 ± 1.40 respectively ($p=0.693$). The incidence of TTS was detected in 14 ears comprising 10 ears from the control group and 4 ears from the study group ($p=0.075$), shown on Table 1.

The comparison of pre- and post-noise exposure audiometry between the two groups is shown in Table 2. The study has demonstrated the post firing practice hearing threshold levels from the study group was significantly better than that of the control group across all frequencies. Moreover, the hearing threshold levels in the control group worsened at the frequencies 250 Hz and 6,000 Hz whereas at 3,000 Hz the hearing threshold significantly improved.

The associated symptoms from post-exposure to noise such as tinnitus and aural fullness were reported and demonstrated on Figure 2. The participants in the study group reported tinnitus in the right ear ($n=6$) lasting 9.33 minutes which was much shorter than that of the control group ($n=6$) lasting 244.17 minutes ($p=0.463$). Furthermore, tinnitus occurred in the left ear in the study group ($n=8$) lasting 6.13 minutes which was far shorter than that of the control group ($n=9$) lasting 326.44 minutes ($p=0.808$). Moreover, aural fullness was reported in the right ear in the study group ($n=11$) lasting 14.73 minutes which was much shorter than that of the control group ($n=16$) lasting 273.63 minutes ($p=0.186$). Additionally, aural fullness was detected in the left ear in the study group ($n=11$) lasting 13.82 minutes which was far shorter than that of the control group ($n=19$) lasting 461.63 minutes ($p=0.459$). Tinnitus and aural fullness presented more in the control group but without significance.

The side effects of the medication were reported on Figure 3. The participants in the study group reported dizziness ($n=11$), fainting ($n=8$), nausea ($n=1$), diarrhea ($n=1$), vertigo ($n=3$) and headache ($n=11$). However, the participants from the control group reported dizziness ($n=8$), fainting ($n=3$), nausea ($n=2$), diarrhea ($n=2$), vertigo ($n=8$) and headache ($n=10$). More participants in the study group experienced side effects of the medication.

Although nicergoline might increase the uric acid levels in blood serum, the study demonstrated increased uric acid levels in both groups without significance. The comparison of uric acid levels in blood serum is shown on Table 3.

Discussion

According to the results demonstrated on Table 1, the TTS was only detected 14 ears from both groups and only 4 ears from the study group. The results are unclear whether nicergoline prevented TTS, since the number of the participants who sustained TTS in both group was not significant. Additionally, the long term follow up would be necessary to be investigated.

The audiometry of the pre-exposure and the post-exposure to noise between the two groups were compared. The participants in the study group significantly improved the average hearing threshold levels at all frequencies. However, the average hearing threshold levels of the participants in the other group significantly worsened at 250 and 6K Hz. These interesting results represented that nicergoline might affect the inner ears indirectly. In addition, the worsening hearing threshold levels at 250 and 6K Hz found in the placebo group might have been associated with TTS.

Although the fact that these results may be statistically significant, they may not be clinically significant, since the limits of audiometry are 5 dB, and it is considered within normal limits for a person to vary in their audiometric responses by 5 dB per frequency over different days. Furthermore, the improvement of audiometry post-exposure to noise, in the study group, was probably caused by the attention of individuals in order to listen to the signals while measuring the audiometry.

The individuals participate in the audiometry test have to listen to the signal, as a single click tone, stimulated by the operator. Each signal represents the hearing threshold from different intensity and frequencies. When the participants hear the random click tone, they have to push the button immediately. Therefore, the errors of audiometry may be attributed to the loud noise environment, the unintended behavior of the participants or the experience of the operator. Accordingly, the results show that the average hearing thresholds in the study group would significantly decrease after they attended the firing practice, maybe associated with the enhancing attention of participants. The results could imply that participants in the study group might obtain the indirect effects of nicergoline. Whereas some of participants in the control group suffered from a severe degree of hearing loss. Based on the results from animal experimentation, McArthur R A, et al.(16) indicated that intake of nicergoline for 11 weeks was an effective cognitive enhancer in a learning model of age related deficits. Due to the limitation of the research regarding the effect of nicergoline in young adults, this unclear results should be investigated by the crossover study. However, the duration of protocol was relatively short.

In the literature reviews, there were limited data which reported the duration of tinnitus. According to the results from the study, the duration of aural symptoms such as tinnitus and aural fullness lasted longer in the control group but without significance. It is difficult to record or measure tinnitus post exposure to noise since tinnitus is individual subjective perception. The drug intake was prolonged for one week after the firing practice in order to observe the effectiveness of nicergoline.

According to the study conducted by Boismare F and Lefrancois J(17), the effect of nicergoline on the cardiovascular system was demonstrated. Intravenous nicergoline (5 mg) made the patients sustain lowered blood pressure, bradycardia, and elevated cardiac output. Consequently, more participants from the study group reported the side effects of nicergoline such as dizziness, fainting, nausea, diarrhea, vertigo and headache. Another side effect of nicergoline is asymptomatic hyperuricemia which is characterized by an increased serum uric acid levels without clinical presentation. Additionally, the normal range of serum uric acid levels of Thai population is referred to 3.4-7.0 mg/100ml (18). In the

study the serum uric acid levels of both groups were compared. We found that the serum uric acid levels was elevated in both groups but without significance.

The study has demonstrated the effectiveness of nicergoline in preventing NIHL and enhancing the hearing thresholds. Another advantage of nicergoline is that the tablets are contained in an aluminum blister which is portable and durable. Military personnel can take it instantly as well.

There are some limitations of the study. Participants comprised males so the safety profiles of nicergoline dosage are limited for women with pregnancy or lactation. Therefore, female participants were not enrolled in the study. The duration of drug administration was relatively short (3 weeks). There was the limitation of the audiometry.

Conclusion

The TTS was found in both groups without statistically significant differences. The effectiveness of nicergoline from the study demonstrated the tinnitus reduction after the firing practice. Furthermore, the hearing thresholds significantly improved in the study group.

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Institutional Review Board of the Royal Thai Army, Medical Department. Informed consent was obtained from all participants according to the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the person for publication of this review and any accompanying images.

Availability of data and materials

All the relevant data and materials are presented in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Pana Klamkam is a primary investigator and corresponding author of this article. Rongrat Pagcharoenpoland is a co-investigator. Treewit Treesaranuwattana and Pichayen Silpsrikul are co-researchers. Pariyanan Jaruchinda and Piyalarp Wasuwat are research consultants. All authors have read and approved the final manuscript.

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Conflict of Interest Disclosure

None reported

Trial registration:

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<http://www.clinicaltrials.in.th/index.php?tp=regtrials&menu=trialsearch&smenu=fulltext&task=search&task2=view1&id=5375>

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Tables

Please see the supplementary files section to view the tables.

Figures

Figure 1

Flow diagram according to the CONSORT 2010 statement shows participants flow in this study.

Figure 2

The duration of associated symptoms (tinnitus and aural fullness)

Figure 3. The side effects of the medication

Figure 3

The side effects of the medication

Supplementary Files

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