Effectiveness of Nicergoline in Preventing Acoustic Trauma

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Research

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Abstract

Background: In Thailand, military personnel attending the annual firing practice are at risk for acoustic trauma (AT). Presently, hearing protection devices have been approved to prevent AT. Furthermore, N-acetyl-cysteine or magnesium were proved to be beneficial for hearing protective effect. However, the study of the effectiveness of nicergoline on preventing AT is limited. The study aimed to demonstrate the effectiveness of nicergoline in preventing AT.

Methods: The study employed a randomized controlled trial design. Two hundred twenty-four participants were evaluated for general physical status, hearing threshold level and blood chemistry. The inform consent form was explained and signed, and participants were allocated to 2 groups. The study group (n=118) was prescribed nicergoline 30 mg twice daily for 2 weeks before the firing practice and 1 week after firing practice while the controlled group (n=106) was prescribed placebo. All participants had to wear the silicone ear plugs. The postfiring practice audiograms were measured within 48 hours. Aural symptoms (tinnitus and aural fullness) and the side effects of the medication were also recorded.

Results: The incidence of AT was detected in 14 ears, 10 ears from the placebo group ($p=0.075$). The postfiring practice audiograms showed the average hearing threshold level of the study group significantly improved than that of the control group across all frequencies ($p<0.05$). Moreover, the audiograms from the placebo group worsened at 250Hz and 6,000 Hz ($p<0.05$). The presence of tinnitus and aural fullness in the study group occurred over a shorter period than that in the placebo group.

Conclusion: The incidence of AT occurred in both groups. The effectiveness of nicergoline from this study demonstrated reduced tinnitus after firing practice. Furthermore, the hearing threshold significantly improved in the study group.

Trial registration: Registered 16 October 2019 – Retrospectively registered, TCTR20200519002.
<http://www.clinicaltrials.in.th>

Background

At present, approximately 10% of people are affected from hearing loss and one half of cases results from noise exposure¹. 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 two most common problems causing disability among military personnel are NIHL and tinnitus².

The mechanism of the injury to the inner ear consists of 1) the direct injury of the cochlear, 2) metabolic stress affecting the outer hair cells, 3) free radicals and 4) oxidative stress reducing cochlear blood flow. Acoustic trauma (AT) refers to temporary sensorineural hearing loss usually occurring postexposure to loud noise over a short period. This condition is divided in temporary threshold shift (TTS) which usually resolves spontaneously within 48 hours and permanent threshold shift (PTS) leading to permanent hearing loss². Currently, researchers are interesting in the TTS because this condition is preventable.

Furthermore preventing TTS can also reduce the disability caused by PTS². Several medications have proved to be beneficial in preventing TTS.

In 1994, Attia J³ demonstrated that magnesium had a protective effect on NIHL among military personnel. Furthermore, Wu L, et al.⁴ proved the protective effective of N-Acetyl-cysteine (NAC), antioxidant against NIHL. In animal models, glutathione, D-methionine and ebselen also showed NIHL attenuation². Moreover, nicergoline, an anti-oxidant derivative of ergoline, provides neuroprotective effect and increases inner ear circulation^{5, 6, 7}. The clinical use of nicergoline such as in treating dementia, vascular and balance disorders, vertigo and tinnitus, is well recognized⁵. One study investigated the clinical use of intravenous nicergoline in cochleo-vestibular syndrome⁸. At present, the studies of nicergoline on preventing NIHL are limited. Consequently, our study aimed to demonstrate the effectiveness of nicergoline in preventing acoustic trauma or TTS among military personnel attending the annual firing practice.

Methods

A randomized controlled trial (RCT) was conducted and the protocol approved by the Institutional Review Board of the Royal Thai Army Medical Department. Two hundred and thirty-eight conscripts from The Royal Thai Navy, aged 20 to 25 years were informed about the aims and methods of the study then provided their written consent to participate. All participants underwent a physical examination including otoscopic examination of the ear canal, tympanic membrane and baseline hearing threshold (pure-tone audiogram) before the firing practice. Additional blood samples such as complete blood count (CBC), blood urea nitrogen (BUN), creatinine, uric acid and liver function test were obtained. Participants were excluded if they presented perforated tympanic membrane, infected or inflamed ears disease, abnormal audiogram, abnormal blood chemistry and allergy to nicergoline. Furthermore, an audiogram was taken within 48 hours after the firing practice to evaluate hearing threshold and blood chemistry was obtained again. The participants were allocated in two groups using the cluster randomization method. In all, 119 participants were placed in the study group (battalion 1) and 105 participants were placed in the placebo group (battalion 2). Fourteen participants were excluded from the study, namely, 4 participants from the study group and 10 participants from the placebo group (Fig. 1). The trial was registered at the Thai Clinical Trials Registry (TCTR20200519002).

Noise exposure

From April 2019 to July 2019, all participants underwent basic military training in The Royal Thai Marine Corps, Chonburi Province, Thailand then attended the annual firing practice conducted 31 August 2019. All participants used M16 rifles and each person was allowed to fire 30 shots continuously. All participants were reminded to use ear plugs during firing practice. The M16 rifles made the approximated noise level 140 decibel (dB), while the ear plugs attenuated the noise level to 18 to 20 dB^{9,10}.

Nicergoline administration and dosage

The blinded labels of nicergoline (30 mg) were attached to aluminum blisters. Furthermore, these packages were allocated to the study group. However, the packages in the placebo group were also attached to similar aluminum blisters and allocated. The participants had to take 1 tablet after meals twice daily then were observed for side effects such as nausea, drowsiness, diarrhea, fainting, headache and vertigo¹¹.

Statistical analysis

The statistical analysis was performed by a certificated statistician using repeated-measure paired and unpaired Student’s t-tests, Chi-square and Mantel-Haenszel Chi-square and Pearson’s correlation using STATA Software, Version 15. A value of $p < .05$ indicated statistical significance.

Results

Fourteen participants were excluded from this study because they did not meet the inclusion criteria including abnormal blood chemistry and abnormal audiogram. The 224 participants (448 ears) were analyzed. The average age of the participants in the study and placebo groups was 22.31 ± 1.44 and 22.36 ± 1.40 respectively ($p = 0.693$). The incidence of acoustic trauma was detected in 14 ears, 10 ears from the placebo group and 4 ears from the study group ($p = 0.075$), (Table 1).

	Study group	Placebo group	<i>p</i> -value
Number of Participants	119	105	
Age (year)	22.31±1.44	22.36±1.40	
Number of Ears (%)	238 (53.1%)	210 (46.9%)	
Normal Audiogram (%)	234 (98.3%)	200 (95.2%)	
Acoustic Trauma (%)	4 (1.7%)	10 (4.8%)	0.075
Chi-square test			

Table 1
The Incidence of Acoustic Trauma (AT)

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

Group	Frequency (Hz)	Hearing threshold (dB)		p-value
		Pre-exposure	Post-exposure	
Study	250	17.73±7.33	16.81±6.15	0.034*
	500	18.51±6.76	17.37±6.62	0.003*
	1000	18.36±7.13	17.08±6.89	< 0.001*
	2000	18.00±7.68	16.87±7.4	0.002*
	3000	20.67±8.66	18.13±8.54	< 0.001*
	4000	19.47±9.35	17.77±9.36	< 0.001*
	6000	20.44±10.87	19.18±10.19	0.008*
	8000	15.95±10.43	14.29±10.88	< 0.001*
Placebo	250	15.6±6.28	17.45±5.27	< 0.001*
	500	17.81±5.03	17.48±4.99	0.412
	1000	18.1±5.33	17.52±5.18	0.115
	2000	16.86±5.54	16.64±5.67	0.500
	3000	18.52±6.88	17.52±7.14	0.012*
	4000	17.95±8.9	17.48±8.92	0.301
	6000	18.67±10.78	20±11.92	0.027*
	8000	14.76±11.82	15.64±11.6	0.158
Paired t-test				

Table 2

The comparison of the average audiogram between the study and placebo groups

The associated symptoms postexposure to noise were reported such as tinnitus and aural fullness as demonstrated in Fig. 2. Our study was the first to demonstrate the duration of tinnitus. The participants in the study group reported tinnitus in the right ear (n = 6) lasting 9.33 minutes compared with that of the placebo 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 compared with that of the placebo 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 compared with that of the placebo group (n = 16) lasting 273.63 minutes ($p = 0.186$). Additionally, aural fullness occurred in the left ear in the study group (n = 11) lasting 13.82 minutes compared with that of the placebo group (n = 19) lasting 461.63 minutes ($p = 0.459$). Tinnitus and aural fullness presented more in the placebo group but without significance.

The side effects of the medication were reported (Fig. 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 placebo 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 level in blood serum, our study demonstrated increased uric acid level in both groups without significance. The comparison of uric acid level in blood serum is shown in the Table 3.

Uric acid (3.4-7.0 mg/dL)	Baseline (mg/dL)	2 weeks (mg/dL)	<i>p</i> -value
Study group	6.17±1.17	6.26±1.31	0.378
Placebo group	6.16±1.32	6.25±1.17	0.345
Paired t-test			

Table 3
The comparison of the serum uric acid level

Discussion

This study demonstrated not only the attenuation in NIHL from hearing protection devices but also proved the effectiveness of nicergoline on preventing acoustic trauma (AT). Furthermore, all the participants used the same silicone ear plugs; consequently, the incidence of AT was only detected in 14 ears and in only 4 ears from the study group (Table 1). Although the incidence of AT showed no significant difference between the 2 groups, participants using hearing protection devices and taking nicergoline obtained more protective effect from AT.

The audiograms pre- and postexposure to noise between the two groups were compared. The participants in the study group showed significantly improved average hearing threshold level, postfiring practice at all frequencies (250, 500, 1K, 2K, 3K, 4K, 6K and 8K Hz). However, the average hearing threshold level, postfiring practice in the placebo group worsened at 250 and 6K Hz. These interesting results represented that nicergoline affected the inner ears. Furthermore, the worsening hearing threshold level at 250 Hz and 6K Hz found in the placebo group might have been associated with TTS.

Not only producing neuroprotective effect, anti-oxidant benefits and increased inner ear circulation⁵ but nicergoline also showed indirect effects. Using the animal model, Robert A, et al.¹² indicated that nicergoline was an effective cognitive enhancer in a learning model of age related deficits. In addition, participants taking nicergoline regularly may have exhibited enhancing intention and concentration to listen to the signal noise while performing the pure-tone audiogram.

The study conducted by Boismare F and Lefrancois J¹³ demonstrated the effect of nicergoline on the cardiovascular system. Intravenous nicergoline (5 mg) sustained lowered blood pressure, bradycardia, and elevated cardiac output. As a result, more participants from the study group reported side effects such as dizziness, fainting, nausea, diarrhea, vertigo and headache. Moreover, no statistical significance was observed between the two groups.

Another side effect of nicergoline elevated serum uric acid level. This study compared the serum uric acid level between the two groups pre- and postexposure to noise. The serum uric acid level was elevated in both groups but without significance.

Our study demonstrated the effectiveness of nicergoline in preventing NIHL and enhancing the hearing threshold. As well as the beneficial results from magnesium³ or N-acetyl-cysteine⁴, military personnel may use nicergoline before participating in any military training having a high risk of NIHL. Furthermore, the nicergoline tablets are contained in an aluminum blister which is durable and easy to carry.

Limitations were encountered in this 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 this study. The duration of drug administration was relatively short (3 weeks). For this reason military personnel regularly working as trainers should participate in another long duration study. The study design involved conducting an RCT with a cross over between the study and placebo groups to eliminate any selection bias. The measurement of hearing threshold level by audiogram may not represent accurate results. Moreover, measuring hair cells function in the inner ear such as the otoacoustic emission test (OAE) could be performed and compared with the audiogram.

Conclusion

The incidence of AT occurred in both groups; however, no statistically significant difference was found. The effectiveness of nicergoline from this study demonstrated reduced tinnitus after firing practice. Furthermore, the hearing threshold 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

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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 Nicergoline compared to the placebo.

Supplementary Files

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