Clinical efficacy of nerve growth factor in the treatment of blast-induced hearing loss: a pilot study

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Abstract. – OBJECTIVE: There is no effective therapy for blast-induced hearing loss in the clinic. The present report summaries our case series with using nerve growth factor in the treatment of patients with various blast-induced hearing loss.

PATIENTS AND METHODS: This retrospective study analyzed the clinical outcomes of 21 patients (33 ears) seen in our Outpatient Service Clinic who were treated with nerve growth factor (NGF) by intramuscular injection for 10 days. The pure tone audiometry changes before and after NGF treatments were measured for five frequencies.

RESULTS: Among the 21 patients with blast-induced hearing loss (33 ears) treated with 10-d NGF injection, the mean value of pure tone audiometry for the 5 frequencies for all the 33 ears after NGF treatment was significantly improved (p = 0.01). Three patients (6 ears) had hearing improved in different degrees, with average hearing being recovered by 15 dB HL. The total effective rate of the treatment was 18%.

CONCLUSIONS: Nerve growth factor can be used to treat blast-induced hearing loss in clinic. The key to clinical success is early treatment; the efficacy on the patients with late treatment (more than one-month after injury is poor).

Key Words:
Nerve growth factor, Blast injury, Deafness, Hearing loss.

Introduction

Blast-related ear injuries are one of the most common damages to the body after exposure to explosive noises. Extensive studies have demonstrated that the ear is the most vulnerable and typically the first organ to incur injury from a blast (or pressure) wave[1-4]. These injuries can occur to civilian and military personnel. For example, blast-induced hearing loss can be caused by sudden acute detonation of explosives used in various operations such as firing weapon and tunnel construction, which is also called explosive hearing loss, traumatic hearing loss or ear blast injury. It also happens in blasting operations of mountain collapse, building road, mining and so on, and it also can be found in some accidental explosions, such as: boilers, gas, pressure cookers and household TV, fridge and so on; there are also some hearing loss patients caused by fireworks and crackers. Detonation-caused hearing loss also happens in weapon firing in military exercises and war time[4-6]. Recently, the increased use of improvised explosive devices (IEDs) by terrorists and insurgent activities in Iraq and Afghanistan wars has yielded an unprecedented proportion of blast-related casualties compared with previous wars[7,8]. The blasts are responsible for about 75% of U.S. combat casualties in Operations Iraqi and Enduring Freedom[6]. Although hearing protection devices are available to personnel with potential occupational exposure to explosive injury, their effectiveness has not been well documented and sometime the use of such devices is not affirmed. For example, in the combat zones, some troops decline to wear hearing protection for fear of reduced situational awareness on the battlefield[9-11]. However, in many cases, blast-related ear injuries occur unexpectedly, due to sudden exposure to unaware sources of explosion.

The pathogenesis of blast-induced hearing loss demonstrates that the disease is sensorineural hearing loss due to cochlea and nerve injury caused by detonation[1,2,12]. Blast-related ear injuries often present as damage to the sensitive structures of the inner and middle ear, such as the cochlea, ossicular chain, tympanic membrane (TM), and vestibular system[1,12,13]. Damage to these components of the auditory system may result in transient or permanent impairment, such as hearing loss and tinnitus (ringing in the

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ears)[1,12,14]. The total annual expense to deliver hearing healthcare services and compensations for hearing impairment has been increasing[15,16]. As such, the prevention, identification, and treatment of blast-related ear injuries are critical to the healthcare for civilians and armed forces. Unfortunately, there are no effective treatments in the clinic, especially for those patients with delayed treatment. Early treatment and prevention of worsening damage to injured nerve may hold the key to success.

We have been interested in exploring the potential use of nerve growth factor (NGF) for the treatment of blast-induced hearing loss. As one of the most important neurological bioactive molecules[17], NGF is one of the most typical neurotrophic factors that affect the survival and differentiation of neurons in the periphery and central nervous system. NGF is often synthesized and secreted by the target histocytes dominated by related neurons. After it binds to the corresponding receptors in the nerve ending, it enters into axon, through retrogrades axoplasm to transfer to soma, leading to a series of biological effects, such as inducing enation and promoting the synthesis of some proteins and enzymes needed for various neurological functions[17]. Studies have also shown that NGF is the critical factor in the development, maturation, proliferation, differentiation and activation of auditory epithelium and neurons for peripheral auditory system and plays an important role in the recovery after damage, the regeneration of remaining neurons[17]. Considering that NGF has nutritious effects on the peripheral nervous and central nervous auditory system, we treated the patients with blast-induced hearing loss with by neurotrophic factor, and initial results indicated that NGF is effective for a subset of patients. This retrospective study was designed to examine the effectiveness of this treatment in our consecutive cases seen in our clinic and explore the clinical factors that affect the out of the treatment.

Patients and Methods

Patients

Ethics Committee of the General Hospital of Chinese People's Liberation Army approved this retrospective study and prior to analysis patient information was anonymized and de-identified. As shown in Table I, there were 21 patients (33 affected ears) consecutively seen in our outpatient clinic from July 2009 to July 2012. There were 15 males and 6 females, with average age of 41 years old (ranging from 13 to 70 years old). Among them, 12 patients had both ears affected and 9 had only single ear affected. The reasons of detonation that resulted the hearing loss included firecrackers injury (20 ears), rifle shooting in target practice (3 ears), detonation noises when working in a tunnel (2 ears), explosive detonation in cutting into mountains (4 ears), and high pressure steam pipeline crackle (4 ears). The duration between the injury and first visit to our clinic varied from 1 week to 6 months; the majority of the patients were seen in our clinic, 3 months after detonation injury.

Clinical Data Collection and Review

The clinical data of each patient were collected and analyzed, including demographic information, and contact information. The 21 patients included in this analysis had no history of hypertension, diabetes mellitus, trauma or injury, and no other treatment history that may be related to or caused hearing loss. Patients with history of ear diseases or injury before the denotation injury were excluded from the analysis. All patients completed the scheduled treatment and clinical examination before, during, and after the treatment. Therefore, all the patients selected were included in the final analysis.

Pure Tone Audiometry (PTA)

All the 21 patients completed the pure tone audiometry (PTA) in the audiometric room at outpatient clinic. The audiometry instrument was American GSI 61, the audiometric room met national 1640 test standard. They did 500 Hz, 1 KHz, 2 KHz, 4 KHz, 8 KHz, five frequencies pure tone audiometry, after took medicines for 10d, they did 500 Hz, 1 KHz, 2 KHz, 4 KHz, 8 KHz, five frequencies pure tone audiometry again. The test method was applied with pure tone auditory threshold audiometry method-Hughson-Westlak method (rising method) recommended by Hearing protection committee of American Academy of Eye-Otolaryngology, firstly, a acoustical signal that could be heard was given to receptors, sound intensity 10dB was one level, then reduced in sequence until the receptors could not hear. Then took 5dB as one level, rose until the receptors just could hear. Repeat the above steps until three times response were

Table I. Patients' characteristics and clinical outcomes.

No.	Gender	Age	Injured ear	Causes of injury	Admission time after injury	Clinical efficacy
1	Male	13	Bilateral	Firecrackers explosion	1 wk	Yes
2	Male	28	Bilateral	Firecrackers explosion	1 m	Yes
3	Male	32	Bilateral	Firecrackers explosion	2 m	No
4	Female	38	Bilateral	Firecrackers explosion	3 m	No
5	Female	46	Bilateral	Firecrackers explosion	3 m	No
6	Female	70	Bilateral	Firecrackers explosion	6 m	No
7	Female	53	Bilateral	Firecrackers explosion	2 m	No
8	Male	42	Bilateral	Firecrackers explosion	2 m	No
9	Female	31	Bilateral	Firecrackers explosion	3 m	No
10	Male	54	Bilateral	Firecrackers explosion	1 m	Yes
11	Female	43	Bilateral	Steam pipe crackle	3 m	No
12	Male	46	Unilateral	Steam pipe crackle	3 m	No
13	Male	23	Unilateral	Shooting (target practice)	3 m	No
14	Male	28	Unilateral	Shooting (target practice)	3 m	No
15	Male	46	Unilateral	Tunnel explosion	3 m	No
16	Male	45	Unilateral	Tunnel explosion	3 m	No
17	Male	26	Unilateral	Explosive detonation (Cutting into mountains)	2 m	No
18	Male	34	Bilateral	Explosive detonation (Cutting into mountains)	2 m	No
19	Male	52	Unilateral	Explosive detonation (Cutting into mountains)	2 m	No
20	Male	60	Unilateral	Shooting (Target practice)	5 m	No
21	Male	51	Unilateral	Steam pipe crackle	5 m	No

got in the same intensity (the weakest intensity), this intensity was threshold value. Then they were given tympanometry to o exclude the external auditory canal and middle ear lesions.

Nerve Growth Factor Treatment

After the 21 patients (33 ears) completed the NGF treatment. The mouse nerve growth factor (30 mg, > 15 000 AU/bottle) was purchased from Staidson BioPharmaceuticals Co., Ltd (Beijing), which was approved by the State Food and Drug Administration (SFDA) of China (authorization document number, S20060023). The NGF (30 ug) was freshly dissolved in 2 ml of physiological saline and given by intramuscular injection, once a day for 10 consecutive days. After the 10-day NGF treatment, all the patients underwent the analyses of pure tone audiometry and tympanometry. No any additional drug treatments were given to any of the patients included in this analysis.

Statistical Analysis

For the analyses of PTA results of 33 ears before and after treatment, each audiometry frequency and the frequency value before and after treatment was compared. SPSS10.0 software package (SPSS Inc., Chicago, IL, USA) was used to perform Student's *t*-test; $p < 0 .05$ was considered statistically significant.

Results

Clinical Outcomes

The individual outcome for each of the patients is shown in Table I. Three patients (6 ears) treated within one month after the injury had almost complete recovery after NGF treatment. However, the hearing recovery of other 18 patients (27 ears) who came to hospital one month or longer after detonation was not good. Therefore, the total effective rate of 21 patients (33 ears) after NGF treatment in this study was 18%.

NGF Efficacy as Measured by PTA

The tympanometry results showed that the 21 patients revealed that most tympanogram was A type and most patients had tympanic pressure and acoustic compliance in normal range (tympanogram was A type in both ear). The pure tone audiometry (PTA) results of each frequency for the 21 patients, 33 ears of blast-induced hearing loss injury before and after the NGF treatment are shown in Table II. After the 10-day NGF treatment, although the improvement for each frequency (500 Hz, 1, 2, 4, and 8 KHz) before and after treatment was seen in these patients, but the differences did not reach the statistically significant level. However, the hearing was improved significantly in 3 patients (6 ears) who were treated within one month after detonation hearing loss, with average recovery being 15 dB HL. The comparison of the means of the 5-frequency combined values among all the 21 patients (33 ears) before and after treatment indicated that the NGF treatment was effective to certain degree (Table III).

Discussion

The present study retrospectively analyzed the efficacy of NGF in the treatment of blast-induced hearing loss. Our results indicated that NGF is generally effective, but depends on the early treatment. As an acute acoustic trauma, blast-induced hearing loss is induced by sudden, short and strong detonation and discontinuity impulse noise. The great changes in detonation sound frequency spectrum peak and jumping lifting can damage inner ear cells and nerves. Noise-induced acoustic loss generally can be classified into mechanical and metabolic inner injury, but blast-induced hearing injury mainly belongs to mechanical injury, which can secondarily become metabolic injury, especially without early treatment. The common lesions of inner ear are cochlea internal hemorrhage, spiral organ structure disorder, inner or outer hair cells damage and deficiency, nerve injury and so on. In the clinic, the main manifestations of blast-induced hearing injury are hearing loss, accompanied with tinnitus or dizziness, which severely affect patients' living quality and social activities.

The treatment outcome for blast-induced hearing loss in the clinic is not satisfactory. It is challenging to develop effective medicines and methods for the treatment of detonation deafness or hearing loss. In the study, our 21 patients with 33 ears of blast-induced hearing loss were injured by four major causes: firecracker setting off, explosive detonation, tunnel working and sudden detonation accidents (steam pipeline crack). They were treated by nerve growth factor of the mouse for intramuscular injection at outpatient service, one time a day. After 10 days, the hearing of 3 patients (who came to hospital in one week, one month after detonation) recovered to 15dB HL. The hearing recovery of the rest patients (who came to hospital more than two month after detonation) was not satisfactory. Although the differences of the pure tone audiometry results of 5 frequencies were not significant, but there were 3 patients whose hearing had been improved, therefore, the mean comparison of each frequency before and after treatment through statistical treatment had significant differences ($p < 0.05$). This result indicated that NGF has a certain effect on recovering the hearing of the patients with blast-induced hearing loss at early treatment.

NGF is not only the necessary factor in the development, maturation, proliferation and differentiation, and activation of auditory epithelial cells and auditory neurons, but it also has an important effect on repairing auditory system

Table II. Pure tone audiometry analyses before and after NGF treatment (dB HL).

Time	Number of ears	500 Hz	1 KHz	2 KHz	4 KHz	8 KHz
Before treatment	33	30.0 ± 3.3	33.8 ± 3.6	42.8 ± 3.9	56.0 ± 4.0	59.0 ± 3.7
After treatment	33	28.0 ± 3.6	32.0 ± 3.2	41.3 ± 3.7	50.0 ± 3.8	53.2 ± 3.9

Table III. Comparison of mean values of pure tone audiometry before and after treatment (dB HL).

Number of ears	Mean of 5 frequencies before treatment	Mean of 5 frequencies after treatment	*p*-value
33	43.6 ± 1.9	35.1 ± 1.2	0.01

nerve cells after damage, reviving the remaining neuron and functionality and plasticity[17,18]. The mouse nerve growth factor is a new medicine approved by SFDA in 2006; experiments have proven that it has an effect for repairing mouse sympathetic nerve ending and optic nerve injury. In recent years, there have been reports about the treatment effect of acupoint injection on sensorineural deafness[18], but there are no literatures reporting the use of neurotrophic factor to treat blast-induced hearing loss through intramuscular injection. The results of our study using neurotrophic factor to treat blast-induced hearing loss by intramuscular injection show that there are 6 out of 33 ears hearing recovering to 15 dB HL, with the total effective rate being 18%. For those patients without significant improvement after NGF treatment, the major reason may be delayed treatment. If the treatment is delayed after detonation injury, the cochlea cells and nerves of those patients have been degenerated and necrosis occur, resulting in poor treatment outcome. Another reason may be related to the limited uptake of NGF by the neurons. There are limited nerve growth factors and molecules that penetrate blood-labyrinth barrier and the effective concentration of medicine reaching cochlea is low, so the treatment effect is not obvious. There have been animal experiments[17,18] proving that there is little basic fibroblast growth factor that can penetrate blood-labyrinth barrier, but animal experiments show that injecting growth factor by intraperitoneal injection has a recovery effect on blast-induced hearing loss[17,18], indicating that except that nerve growth factor has an effect on hearing recovery through inner ear, it may indirectly play an effect on nerves and cells through neural immune network system. However, this effect is in effect for the patients at early blast-induced hearing loss stage. Otology physicians should pay a close attention to early intervention for blast-induced hearing loss at earlier stage.

Conclusions

This study indicates that in clinic use of nerve growth factor to treat blast-induced hearing loss by intramuscular injection has a certain positive effect to recover hearing for the patients at the early stage of the disease. Therefore, patients and physicians are encouraged to early diagnose the hearing loss, treat early, and monitor the changes in hearing after treatment. We realize the study is limited due to the small sample size and its retrospective nature. Future prospective large-scale studies are needed to confirm our findings. It is hoped that NGF can be developed as a novel treatment blast-induced hearing loss, regardless of actual reasons for the injury.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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