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Original Article

Efficacy of ginaton combined with mouse nerve growth factor in treating patients with sudden hearing loss

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Abstract: Objective: This study aimed to analyze the efficacy of Ginaton combined with mouse nerve growth factor (MNGF) in treating patients with sudden hearing loss. Method: A total of 93 patients diagnosed with sudden hearing loss in our hospital were retrospectively analyzed and divided into the Group A (GA, n=48, routine treatment + MNGF retroauricular mastoid subperiosteal injection) and Group B (GB, n=45, routine treatment with ginkgo biloba leaf extract (Ginaton), alprostadil and hormones). The pure tone thresholds (PTT), symptoms, blood lipids, blood rheology, and neutrophil-to-lymphocyte ratio (NLR) were compared between the two groups. Results: The total effective rate of aural rehabilitation was 91.67% in GA and 75.45% in GB (P<0.05). At 7 d and 14 d after treatment, GA exhibited lower PTT, scores of tinnitus and ear stuffiness, TC, TGF and LDL-C levels, high/middle/low shear viscosity, number of neutrophils and lymphocytes as well as NLR and higher HDL-C than GB (P<0.05). Conclusion: Compared with the routine treatment, Ginaton combined with MNGF in the treatment of patients with sudden hearing loss is more effective and can significantly mitigate symptoms and can effectively control blood lipids, blood rheology and NLR.

Keywords: Sudden hearing loss, ginaton, mouse nerve growth factor

Introduction

Sudden hearing loss, also known as sudden deafness, is an unexplained acute disease seen in the E.N.T. Department that usually occurs within 72 hours, and manifests as sensorineural hearing loss, with a loss of 20 db or more in hearing awareness in 2 sequential frequencies [1]. The disease progresses rapidly after attack, and some patients have symptoms such as ear stuffiness, tinnitus and abnormal sensations of periarticular skin and vertigo, while some other patients suffer from psychological stress, leading to mental and psychological symptoms [2].

Most sudden hearing loss occurs in one ear and is thought to be associated with irregular work and rest, overstrain and long-term psychentonia, and its incidence is gradually rising in recent years because of an accelerated pace of life and increased pressure, and it is showing a younger trend [3]. In view of the rapid progress of the disease, timely treatment is necessary after diagnosis. Otherwise, it may develop into permanent deafness, seriously affects the quality of life of the patients [4]. However, clinical researches on the nosogenesis of sudden hearing loss are not comprehensive, leading to the failure of developing targeted and specific therapies. The therapies of this disease are mainly focused on nerve nutrition, circulation improvement, application of hormones, and drugs commonly used in routine therapies that include alprostadil, ginkgo biloba leaf extract (Ginaton) and glucocorticoids [5]. However, routine treatment is associated with a high recurrence rate and unsatisfactory long-term effects [6].

Further studies have gradually revealed the application values of mouse nerve growth factor (MNGF) in disease treatment. Domestic studies have found that the application of

Table 1. Intergroup comparison of general materials (mean ± SD)/[n (%)]

Materials		GA (n=48)	GB (n=45)	t/X^2	*P*
Gender	Male	26 (54.17)	25 (55.56)	0.018	0.893
	Female	22 (45.83)	20 (44.44)		
Age (year)		38.75±12.67	39.51±13.40	0.281	0.779
Time from attack to visit (d)		6.82±2.13	6.43±2.19	0.870	0.386
Hearing loss degree	Low frequency	31 (64.58)	25 (55.56)	0.754	0.649
	High frequency	13 (27.08)	15 (33.33)		
	Full frequency	4 (8.33)	5 (11.11)		
Affected side	Unilateral	45 (93.75)	41 (91.11)	0.232	0.630
	Bilateral	3 (6.25)	4 (8.89)		

MNGF in the treatment of deafness can rapidly alleviate the degree of deafness so as to effectively improve the quality of life of patients. Foreign studies have shown that compared with glucocorticoids in the treatment of deafness, MNGF can reduce adverse reactions and ensure higher safety. This study summarized the results of 93 patients with sudden deafness using MNGF to provide a reference for the best choice of treatment for sudden hearing loss.

Materials and methods

Materials

A total of 93 patients diagnosed with sudden hearing loss in our hospital were retrospectively analyzed and divided into Group A (GA, n=48, 18-63 years old) and Group B (GB, n=45, 20-66 years old). Patients above 18 were eligible to enroll in the study if they met the diagnosis criteria of sudden hearing loss enacted by the China Association of Chinese Medicine ENT Branch [7], were treated for the first time and provided informed consent prior to participating in any study procedure. The study was approved by our hospital. Patients were excluded if they had hypertension, diabetes, coronary heart disease, mental disorders or hemorrhagic diseases, or if they were pregnant, or if their physical conditions were not good enough to withstand the treatments. The two groups were not statistically different in mean age, mean time from attack to visit, proportions of male and female patients, proportions of hearing loss degrees (low-frequency loss, high-frequency loss and full-frequency loss) and proportions of affected sides (unilateral or bilateral) ($P>0.05$) (**Table 1**).

Methods

GB received routine treatment with drugs including Ginaton (specification: 5 ml: 17.5 mg * 10 pieces, approval document No.: HC20090014, manufacturer: Taiwan Chi Sheng Pharma & Biotech Co., Ltd.), alprostadil (specification: 1 ml:5 μg, GYZZ No.: H20084565, manufacturer: Harbin Pharmaceutical Group Bioengineering Co., Ltd.) and methylprednisolone (a synthetic hormone, specification: 40 mg * 1 bottle, approval document No.: H20080284, manufacturer: Pfizer Manufacturing Belgium NV). Also, 105 mg Ginaton was dissolved in 250 ml normal saline, and 10 mg alprostadil injection was mixed with 100 ml normal saline. Both solutions were administered to patients via intravenous drip for 7 d. Methylprednisolone was administered daily via intravenous drip at 80 mg in the first 4 days and 40 mg in the last 3 days. After 7 d, a new course of 7 d was started if patients' hearing was not rehabilitated. In the second course, methylprednisolone was withdrawn and other drugs were used continuously as before. The entire treatment lasted 14 d.

The treatment for the GA was the routine treatment described above, combined with MNGF (Sutaisheng, specification: 30 μg (15000 U)/bottle, GYZZ No. S20060023, manufacturer: Staidson (Beijing) Biopharmaceuticals Co., Ltd.). During the treatment, patients sat down. After disinfecting the mastoid bone and dissolving 20 μg MNGF in 1 ml normal saline, a puncture needle was placed into the postauricular subcutaneous mastoid tissue for subperiosteal injection once daily for 7 d. After audiometry, patients who were not cured continued to receive treatment for another 7 d, during which,

methylprednisolone was withdrawn and other drugs were used continuously as before. The entire treatment lasted 14 d.

Both groups were required to rest in peace and actively cooperate with treatment of underlying diseases as well as auxiliary acupuncture therapy and hyperbaric oxygenation. Psychological intervention was performed if necessary.

Observation indicators

General materials: age, gender, time from attack to visit, and degree of hearing loss were recorded for all patients.

Criteria of therapeutic effects with hearing: the diagnosis criteria of sudden hearing loss enacted by China Association of Chinese Medicine ENT Branch were referred to [8]. Patients were cured if their hearing rehabilitated to a normal level or the previous level before the attack. The treatment was markedly effective if, compared to the level before treatment, the hearing was 30 db higher, or effective (upturn) if the increase in hearing was 15 to 30 db, or ineffective if the increase was less than 15 db. The total effective rate of aural rehabilitation= (cured subjects + markedly effective subjects + upturn subjects)/total subjects × 100%.

Pure tone thresholds (PTT): PTT was measured with the TD-5000 pure tone audiometer produced by Beijing Pitopita before and at 7 d and 14 d after treatment.

Symptoms: symptoms included tinnitus and ear stuffiness. The severity of tinnitus was divided into 6 grades [9], i.e., grade 1 for occasional tinnitus without pain, grade 2 for persistent tinnitus which worsens during rest, grade 3 for persistent tinnitus in noisy environment, grade 4 for persistent tinnitus resulting in distraction and sleep disorders, grade 5 for persistent tinnitus affecting work, and grade 6 for tinnitus leading to suicidal tendency. The 6 grades were assigned with a point from 1 to 6 accordingly. Ear stuffiness is graded by the Visual Analogue Scale (VAS) [10] as mild: >0 and ≤2; moderate: >2 and ≤4; significant: >4 and ≤6; severe: >6 and ≤8; and extremely serious: >8 and ≤10. Both evaluations were performed before and at 7 d and 14 d after treatment.

Blood lipids: before and at 7 d and 14 d after treatment, 5 ml of blood was drawn from patients in a fasting state and centrifuged at 3000 rpm at room temperature for 3 min. The serum was recycled and tested with the Roche Cobas C501 automatic biochemistry analyzer for total cholesterol (TC), triglyceride (TG), high density lipoprotein-C (HDL-C) and low density lipoprotein-C (LDL-C).

Blood rheology: before and at 7 d and 14 d after treatment, 5 ml of blood was drawn from patients in the morning in a fasting state and tested with the BC-5390 CRP automatic blood analyzer produced by Shenzhen Mindray for high shear viscosity, middle shear viscosity and low shear viscosity.

Neutrophil-to-lymphocyte ratio (NLR): neutrophils and lymphocytes were counted and NLR was calculated before and at 14 d after treatment.

Statistical analysis

Statistical analysis was performed with SPSS 23.0. In the case of numerical data it was expressed as mean ± standard deviation (mean ± SD), comparison studies were carried out through *t* test. In the case of nominal data it was expressed as [n (%)], comparison studies were carried out through chi-squared test for intergroup comparison. In the case of comparisons at multiple time points, ANVOA and F test were applied. Figures were drawn in Graphpad Prism 8. For all statistical comparisons, significance was defined as $P<0.05$.

Results

MNGF increases the total effective rate of aural rehabilitation

The total effective rate of aural rehabilitation was 91.67% in GA (14 cured, 18 with marked effectiveness, 8 with upturns and 4 ineffective) and 75.45% in GB (9 cured, 15 with marked effectiveness, 10 with upturns and 11 ineffective) ($P>0.05$) (**Table 2**).

MNGF improves PTT

The two groups exhibited no statistical difference in terms of PTT before treatment ($P>0.05$). This indicator steadily reduced in both groups as treatments continued for 7 d and 14 d ($P<0.05$), and the level in GA was lower than that in GB at 7 d and 14 d after treatment ($P<0.05$) (**Figure 1**).

Table 2. Intergroup comparison of total effective rate of aural rehabilitation at 14 d after treatment [n (%)]

Group	Cured	Markedly effective	Upturn	Ineffective	Total effective rate
GA (n=48)	14 (29.17)	18 (37.50)	8 (16.67)	4 (8.33)	44 (91.67)
GB (n=45)	9 (20.00)	15 (33.33)	10 (22.22)	11 (24.44)	34 (75.45)
X^2					4.457
P					0.035

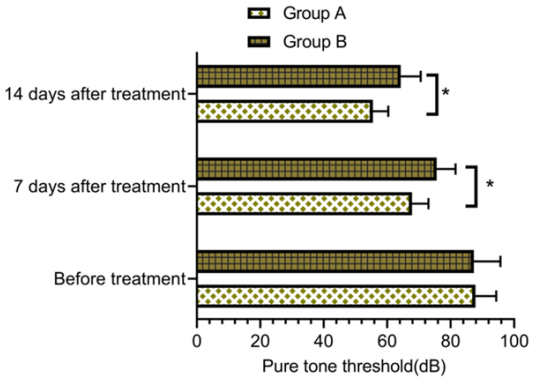

Figure 1. Intergroup comparison of PTT. Before treatment, the two groups were not statistically different (*P*>0.05). At 7 d and 14 d after treatment, PTT was significantly lower in GA (*P*<0.05). **P*<0.05 vs GB.

MNGF alleviates symptoms

The two groups exhibited no statistical difference in the scores of tinnitus and ear stuffiness before treatment (*P*>0.05). At 7 d and 14 d after treatment, the scores of tinnitus and ear stuffiness steadily decreased in both groups (*P*<0.05), and those in GA were lower than those in GB (*P*<0.05) (**Figure 2**).

MNGF improves blood lipid levels

The levels of TC, TG and LDL-C steadily reduced and the level of HDL-C steadily rose in both groups at 7 d and 14 d after treatment (*P*<0.05). GA expressed lower levels of TC, TG and LDL-C and higher level of HDL-C than those in GB (*P*<0.05) (**Figure 3**).

MNGF improves blood rheology

The levels of high shear viscosity, middle shear viscosity and low shear viscosity steadily decreased in both groups at 7 d and 14 d after treatment (*P*<0.05), and the values of each in GA were lower than those in GB (*P*<0.05) (**Figure 4**).

MNGF improves NLR

At 7 d and 14 d after treatment, the count of neutrophils and lymphocytes and NLR steadily reduced in both groups, and those in GA were lower than those in GB (*P*<0.05). In GB, the three indicators changed insignificantly at 7 d after treatment (*P*>0.05) but were significantly reduced at 14 d after treatment (*P*<0.05) (**Table 3**).

Discussion

Most studies on the nosogenesis of sudden hearing loss revolve around the theory of viral infection, the theory of microcirculatory disturbance, the theory of autoimmunity disorders and the theory of RWM (round window membrane) rupture [4]. However, the nosogenesis of sudden hearing loss is a complex process that cannot be fully explained by a single theory, and these theories are variously questioned [11]. A summary study of the nosogenesis revealed that sudden hearing loss was caused by different pathogenic factors, which jointly resulted in microcirculatory disturbance, hypoxia and ischemia in the inner ear, and damage of bristle cells [12]. Therefore, the rehabilitation quality in case of sudden hearing loss directly depends on the degree of recovering the microcirculation in the inner ear.

In the light that microcirculatory disturbance is highly recognized as the nosogenesis of sudden hearing loss, clinical treatments emphasize the improvement of microcirculation, and a number of studies have reached a consensus on the application values of microcirculatory drugs [13, 14]. The application values of hormones in this disease have been clearly defined in the diagnosis criteria in 2015, while studies on the application of drugs on nerves in the treatment of sudden hearing loss are increasing with efficacies being proved constantly [15, 16]. In the present study, ginaton, alprostadil and glucocorticoids were used as treatment for

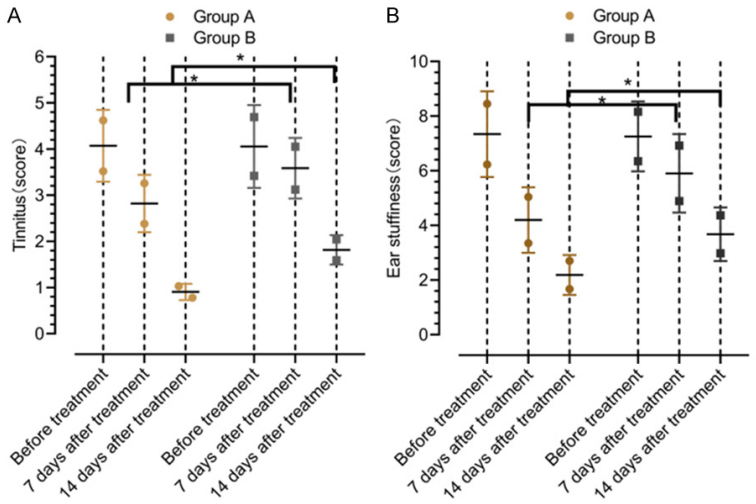

Figure 2. Intergroup comparison of changes in symptoms. The two groups expressed no statistical difference in the scores of tinnitus (A) and ear stuffiness (B) before treatment. At 7 d and 14 d after treatment, the scores of tinnitus and ear stuffiness were significantly lower in GA ($P<0.05$). *$P<0.05$ vs GB.

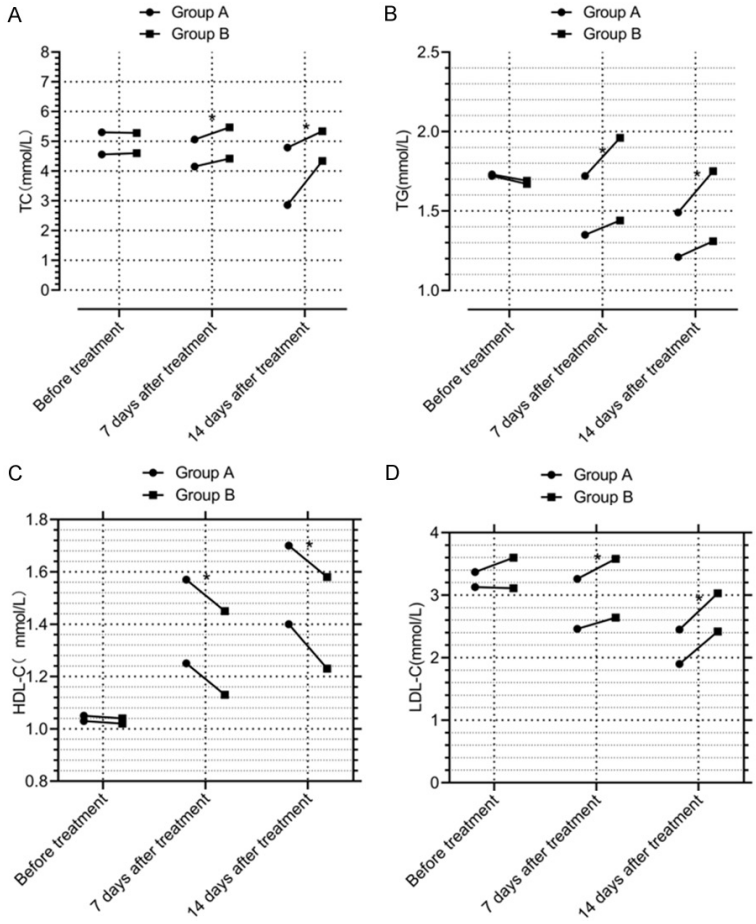

Figure 3. Intergroup comparison of levels of blood lipids. The two groups showed no statistical difference in TC (A), TG (B), HDL-C (C) and LDL-C (D) before treatment ($P>0.05$). At 7 d and 14 d after treatment, the TC, TG and LDL-C levels were significantly lower and the HDL-C level was significantly higher in GA ($P<0.05$). *$P<0.05$ vs GB.

GB and combined with MNGF to treat GA. The functions of alprostadil include heightening the levels of nitric oxide and VEGF to dilate vessels and effectively improve microcirculation. It can not only prevent platelet aggregation, but also stimulate the vascular endothelial cells to produce tissue plasminogen activators that can dissolve thrombi [17]. With prostaglandin E1 as its main active ingredient, alprostadil could dilate spasmodical vessels and promote collateral circulation [18]. Glucocorticoids play a role in promoting vessel dilation by suppressing the production of vaso-excitor materials. It can also reduce the vessels' sensitivity to vaso-excitor materials, accelerate the dilation of spasmodical vessels and recover the blood flow in microcirculation [9]. Other functions of glucocorticoids are to control the inflammation level by regulating genetic transcription through binding with the hormone receptors in cells, and to improve the circulation in the inner ear by suppressing the formation of nitricoxide synthase and mitigating the degree of edema [19]. Ginaton is extracted from ginkgo biloba leaves. Its main active ingredients are Ginkgo biloba flavonoids, Ginkgo biloba amarolide and bilobalide [20]. In patients with sudden hearing loss, Ginaton is a stimulator to produce prostaglandins and endothelium-derived relaxing factors and dilate vessels in the inner ear. It can maintain the tension of veins and arteries, reduce the whole blood viscosity, and increase the plasticity of white and red blood cells, so as to effectively improve the microcirculation of blood in ears [21].

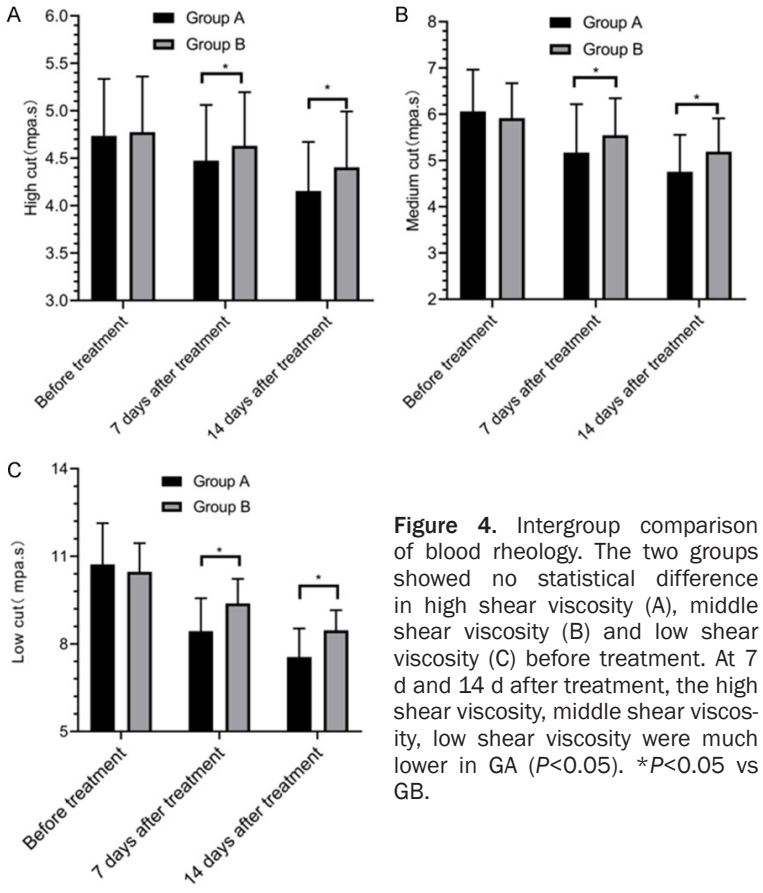

Figure 4. Intergroup comparison of blood rheology. The two groups showed no statistical difference in high shear viscosity (A), middle shear viscosity (B) and low shear viscosity (C) before treatment. At 7 d and 14 d after treatment, the high shear viscosity, middle shear viscosity, low shear viscosity were much lower in GA ($P<0.05$). *$P<0.05$ vs GB.

After treatment, the scores of tinnitus and ear stuffiness as well as the total effective rate of aural rehabilitation were higher in GA, and PTT at 7 d and 14 d after treatment was lower in GA ($P<0.05$), suggesting that the combination with MNGF could effectively mitigate symptoms and maximally recover the hearing of patients with sudden hearing loss to a normal level. A similar study also showed that the use of MNGF in the treatment of deafness could improve symptoms and hearing more rapidly than patients who did not use the drug [22]. To analyze the mechanism, it may be because NMGF is a nutrient that is homogenous with human nerve growth factor, and its biological role is specific. In patients with sudden hearing loss, MNGF directly enters the histiocytes of the inner ear as a supplement of nerve growth factors that may be in deficiency. In addition to stimulating neuroanagenesis, it can nourish nerves, repair damaged nerves and promote the recovery of bristle cells [23]. Furthermore, compared to GB at 7 d and 14 d after treatment, GA had lower levels of blood lipids, indicators of blood rheology, counts of neutrophils and lymphocytes as well as NLR ($P<0.05$). These results are similar to another study which reported that the serum lipid levels of the combined group treatment with MNGF were all better than those of the single drug group without MNGF [24], indicating that the combination with MNGF could effectively improve the levels of blood lipids, control the blood rheology and mitigate inflammation. Abnormalities in patients with sudden hearing loss may indicate a microcirculatory disturbance, the microcirculation in the body could be evaluated according to blood lipid levels . MNGF can effectively reduce the levels of blood lipids and suppress thrombosis. Along with a rise in blood viscosity, is an increased circulation resistance, as well as reduced flow rate and reduced microcirculation perfusion. Meanwhile, hypoxia and ischemia occur in organs and tissues, affecting the body function and metabolism. After MNGF application, blood viscosity is reduced, platelet aggregation is controlled, vasodilation is promoted and microcirculation is improved [25]. As a novel inflammation marker, NLR is easily tested. It's sharp rise in patients with sudden hearing loss directly reflects the prognosis level. After MNGF application, the capillary permeability is decreased and the inflammatory exudation is inhibited for anti-inflammation [26].

In conclusion, compared to the routine treatment, Ginaton combined with MNGF in the treatment of sudden hearing loss can significantly mitigate symptoms and control blood lipids, blood rheology as well as NLR, which produces evidence for the good application value of MNGF. However, this control study is incomplete, with limited samples divided into only two groups. It is also a retrospective study with possibly biased results. Future studies shall include more samples and be more forward-looking and extensive, so as to obtain more scientific and representative conclusions as refer-

Table 3. Intergroup comparison of NLR changes before and after treatment ($\bar{x} \pm s$)

Group	Time	Neutrophils (*10^9/L)	Lymphocytes (*10^9/L)	NLR
GA (n=48)	Before treatment	7.12±2.13	1.53±0.59	5.30±1.53
	At 7 d after treatment	5.16±1.75*	1.19±0.61*	3.87±1.22*
	At 14 d after treatment	3.86±1.08*,&	0.86±0.75*,&	2.14±1.03*,&
GB (n=45)	Before treatment	7.15±2.16	1.55±0.61	5.32±1.55
	At 7 d after treatment	6.51±1.92	1.50±0.75	4.86±1.43
	At 14 d after treatment	5.12±1.46*	1.25±0.79*	2.96±1.21*
$t/P_{\text{intergroup before treatment}}$		0.067/0.946	0.161/0.873	0.063/0.950
$t/P_{\text{intergroup at 7 d after treatment}}$		3.547/0.001	2.193/0.031	3.599/0.001
$t/P_{\text{intergroup at 14 d after treatment}}$		4.752/0.000	2.442/0.017	3.526/0.001

Note: *P<0.05 vs before treatment, and &P<0.05 vs 7 d after treatment.

ences for the treatment of patients with sudden hearing loss.

Disclosure of conflict of interest

None.

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