Journal of Hainan Medical University

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Effect of batroxobin combine with ginkgo−damole injection on hemodynamics, coagulation function, fibrinolytic function and related factors in patients with sudden deafness

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ARTICLE INFO

Article history:
Received 2 Nov 2017
Received in revised form 9 Nov 2017
Accepted 12 Nov 2017
Available online 28 Nov 2017

Keywords:
Sudden deafness
Batroxobin
Ginkgo-damole injection

ABSTRACT

Objective: To study the effects of combined use of Batroxobin and Ginkgo Leaf Extract and Dipyridamole Injection on hemodynamics, coagulation function, fibrinolytic function and related factors in patients with sudden deafness. **Methods:** A total of 94 patients with sudden deafness in our hospital were selected, and divided them into control group and observation group randomly, 47 cases in each group. All patients were given 10BU batroxobin injection intravenous drip after admission every other day; And the patients of observation group were given intravenous drip of 30ml ginkgo-damole injection, 1 time a day. The hemodynamics, coagulation function, fibrinolytic function and related factors were detected and compared between the two groups before and after treatment. **Results:** Before treatment, there was no statistical difference in hemodynamics, coagulation function, fibrinolytic function and related factors between the two groups; After treatment, the levels of WBV and PV in the control group was (5.21±0.58) mPa/s and (1.78±0.32) mPa/s, and the observation group was (4.13±0.47) mPa/s and (1.31±0.26) mPa/s, compared with the same group before treatment, there were statistical difference, and there was also statistical difference between the two groups; The levels of PT, APTT, TT and PF was (19.22±3.98) s, (43.57±9.88) s, (15.64±3.27) s and (58.22±10.58) μg/L, and the observation group was (23.97±4.82) s, (52.49±10.38) s, (20.59±4.15) s and (41.03±8.46) μg/L, compared with the same group before treatment, there were statistical difference, and there was also statistical difference between the two groups; The levels of Fib, D-dimer and FDP was (4.52±0.93) g/L, (6.53±1.88) mg/L and (8.17±2.34) μg/mL, and the observation group was (3.13±0.75 g/L, (9.75±2.14) mg/L, (13.52±2.58) μg/mL, compared with the same group before treatment, there were statistical difference, and there was also statistical difference between the two groups; The serum levels of ET, NO and SOD was (66.92±5.87) ρ g/mL, (48.75±7.61) μmol/L, (95.01±12.38) NU/mL, and the observation group was (63.97±5.24) ρ g/mL, (43.11±6.83) μmol/L, (104.79±13.15) NU/mL, compared with the same group before treatment, there were statistical difference, and there was also statistical difference between the two groups. **Conclusion:** The treatment of patients with sudden deafness using batroxobin combine with ginkgo-damole injection, can improve the hemodynamics, coagulation function, fibrinolytic function of patients, decrease the serum levels of ET and NO, improve the levels of SOD, the effect is curative, it's worthy of clinical application.

1. Introduction

Sudden deafness refers to sudden sensorineural hearing loss without sudden cause, clinical showed unilateral hearing loss, tinnitus, dizziness, nausea and other symptoms, earplugs. In recent years, the population of sudden deafness has a younger trend, so it is more widely concerned. The etiology of this disease is not fully understood, and the most commonly recognized are viral infection, circulatory dysfunction, immune theory and so on. The clinical diagnosis should be based on the symptoms, physical

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Fund Project: Hubei Provincial Health Bureau project (Hubei health 2016-18).

examination and hearing examination results, and the judgment of hearing loss caused by other diseases should be ruled out. At present, the clinical treatment of sudden deafness patients generally adopt comprehensive treatment plan, but the prognosis is often related to the time of receiving treatment, therefore, the earlier treatment and early treatment, the higher the efficiency. It was found that plasma fibrinogen levels and plasma viscosity were significantly increased in patients with sudden deafness, suggesting that blood viscosity plays an important role in the occurrence and development of the disease[1–3]. In this study, the combined use of Batroxobin and Ginkgo Leaf Extract and Dipyridamole Injection in the treatment of sudden deafness patients was conducted to study the effects of combined use of drugs on hemodynamics, coagulation function, fibrinolysis function and related factors.

2. Information and methods

2.1. General information

A total of 94 patients with sudden deafness treated in our hospital from May 2014 to April 2017 were randomly divided into the control group and the observation group, 47 cases in each group. In the control group, 21 cases were male, 26 cases were female, aged 19-66 years old, the average age was (48.9 ± 9.2) years old.In the observation group, 23 cases were male, 24 cases were female, aged 18-69 years old, the average age was (47.6 ± 8.7) years old. The basic data of the two groups were statistically analyzed, there was no significant difference (P>0.05).

2.2 Case selection criteria

(1) met the diagnostic criteria of sudden deafness[4]; (2) no efficacy similar drugs were used for treatment before the treatment; (3) informed treatment, agreed to accept the relevant research and signed informed consent.

2.3 Case exclusion condition

(1) patients with serious diseases such as heart, liver and kidney; (2) imaging scans showed intracranial or internal auditory canal lesions and a clear cause of hearing loss; (3) there were obvious contraindications to the use of drugs in this study; (4) patients who need to change treatment before the ending course of treatment; (5) pregnant or lactating women; (6) patients with severe psychiatric disorders.

2.4 Treatment methods

All patients were given 10 BU Batroxobin Injection intravenous drip after admission every other day; Patients in the observation group were given intravenous drip of 30 mL Ginkgo Leaf Extract and Dipyridamole Injection on this basis for 1 time a day; All patients were evaluated after 10 d of treatment.

2.5 Evaluation index

Fasting venous blood was extracted from all patients before and after treatment, and related tests were carried out.

2.5.1Hemodynamics

Blood viscosity (WBV), hematocrit (HCT) and plasma viscosity (PV) were detected in two groups by using a blood rheometer

2.5.2 Thrombin function

The prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and platelet factor (PF) were detected by Automatic Coagulation Analyzer in two groups

2.5.3 Fibrinolytic function

Fibrinogen (Fib), D-two and fibrinogen degradation products (FDP) were measured in two groups by Automatic Coagulation analyzer

Table 1.

Comparison of hemodynamics before and after treatment in two groups.

Group	Time	n	WBV (mPa/s)	HCT (%)	PV (mPa/s)
Control group	Before treatment	47	6.17±1.03	47.55±7.23	2.80±0.42
	After treatment	47	5.21±0.58*	46.74±6.88	1.78±0.32*
Observation group	Before treatment	47	6.21±1.22	47.68±7.56	2.75±0.41
	After treatment	47	4.13±0.47$^{*\#}$	46.60±6.79	1.31±0.26$^{*\#}$

Note: compared with before treatment, $^{*}P$<0.05; compared with the control group, $^{\#}P$<0.05.

Table 2.

Comparison of thrombin function before and after treatment in two groups.

Group	Time	n	PT (s)	APTT (s)	TT (s)	PF (μg/L)
Control group	Before treatment	47	14.25±4.12	35.34±8.59	11.34±2.18	74.64±11.15
	After treatment	47	19.22±3.98*	43.57±9.88*	15.64±3.27*	58.22±10.58*
Observation group	Before treatment	47	14.03±4.01	35.41±8.25	11.57±2.36	74.97±11.94
	After treatment	47	23.97±4.82$^{*\#}$	52.49±10.38$^{*\#}$	20.59±4.15$^{*\#}$	41.03±8.46$^{*\#}$

Note: compared with before treatment, $^{*}P$<0.05; compared with the control group, $^{\#}P$<0.05.

Table 3.

Comparison of fibrinolytic function before and after treatment in two groups.

Group	Time	n	Fib (g/L)	D-Dimer (mg/L)	FDP (μg/mL)
Control group	Before treatment	47	5.85±1.23	0.31±0.12	2.93±0.56
	After treatment	47	4.52±0.93*	6.53±1.88*	8.17±2.34*
Observation group	Before treatment	47	5.81±1.34	0.38±0.13	3.12±0.63
	After treatment	47	3.13±0.75*#	9.75±2.14*#	13.52±2.58*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

Table 4.

Comparison of related factors before and after treatment in two groups.

Group	Time	n	ET (ρ g/mL)	NO (μmol/L)	SOD (NU/mL)
Control group	Before treatment	47	69.82±6.54	56.19±9.25	84.22±10.54
	After treatment	47	66.92±5.87*	48.75±7.61	95.01±12.38*
Observation group	Before treatment	47	69.13±6.18	56.37±8.76	85.18±10.27
	After treatment	47	63.97±5.24*#	43.11±6.83*#	104.79±13.15*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

2.5.4 Correlation factor

Hormone serum endothelin (ET), carbon monoxide (NO), superoxide dismutase (SOD) levels were detected.

2.6 Statistical analysis

SPSS 20.0 data package was used to analyze and process data, Statistical analysis was carried out by (means ± standard deviation), t test and chi square test were used to compare and analyze the differences between the observation group and the control group. And P<0.05 is considered to have statistically significant differences.

3. Results

3.1. Thrombin function

Before treatment, the levels of WBV and PV in the control group were (6.17±1.03) mPa/s, (2.80±0.42) mPa/s, that in observation group were (6.21±1.22) mPa/s, (2.75±0.41) mPa/s, there was no statistical difference between the two groups (P>0.05); After treatment, the levels of WBV and PV in the control group were (5.21±0.58) mPa/s, (1.78±0.32) mPa/s, that in observation group were (4.13±0.47) mPa/s, (1.31±0.26) mPa/s, there were statistically significant differences compared with the same group before treatment (P<0.05), and there was also statistically significant difference between the two groups (P<0.05). see Table 1.

3.2. Thrombin function

Before treatment, the levels of PT, APTT, TT and PF in the control group were respectively (14.25±4.12) s, (35.34±8.59) s, (11.34±2.18) s, (74.64±11.15) μg/L, that in observation group were (14.03±4.01) s, (35.41±8.25) s, (11.57±2.36) s, (74.97±11.94) μg/L, there was no statistical difference between the two groups (P>0.05); After treatment, the levels of PT, APTT, TT and PF in the control group were (19.22±3.98) s, (43.57±9.88) s, (15.64±3.27) s, (58.22±10.58) μg/L, that in observation group were (23.97±4.82) s, (52.49±10.38) s, (20.59±4.15) s, (41.03±8.46) μg/L. Compared with the same group before treatment, there were statistically significant differences (P<0.05), and there was also statistically significant difference between the two groups (P<0.05). see Table 2.

3.3 Fibrinolytic function

Before treatment, the levels of Fib, D-two and FDP in the control group were (5.85±1.23) g/L, (0.31±0.12) mg/L, (2.93±0.56) μg/mL, that in observation group were (5.81±1.34) g/L, (0.38±0.13) mg/L, (3.12±0.63) μg/mL, there was no statistical difference between the two groups (P>0.05); After treatment, the levels of Fib, D- two and FDP in the control group were (4.52±0.93) g/L, (6.53±1.88) mg/L, (8.17±2.34) μg/mL, that in observation group were (3.13±0.75) g/L, (9.75±2.14) mg/L, (13.52±2.58) μg/mL, Compared with the same group before treatment, there were statistically significant differences (P<0.05), and there was also statistically significant difference between the two groups (P<0.05). See Table 3.

3.4 Correlation factor

Before treatment, the serum levels of ET, NO and SOD in the control group were respectively (69.82±6.54) ρ g/mL, (56.19±9.25) μmol/L, (84.22±10.54) NU/mL, that in observation group were (69.13±6.18) ρ g/mL, (56.37±8.76) μmol/L, (85.18±10.27) NU/mL, there was no statistical difference between the two groups (P>0.05);After treatment, the serum levels of ET, NO and SOD in the control group were respectively (66.92±5.87) ρ g/mL, (48.75±7.61) μmol/L, (95.01±12.38) NU/mL, that in observation group were (63.97±5.24) ρ g/mL, (43.11±6.83) μmol/L, (104.79±13.15) NU/mL. Compared with the same group before treatment, there were statistically significant differences (P<0.05), and there was also

statistically significant difference between the two groups (P<0.05), see Table 4.

4. Discussion

Most of the sudden hearing loss patients were hearing loss in unknown reason, and the hearing loss of the patients decreased sharply within three days. Although its etiology is not fully understood, the theory of inner ear microcirculation and viral infection has been widely recognized by many scholars. The labyrinthine artery of the body is the main source of blood in the inner ear, but this artery has no collateral circulation. After the occurrence of vasospasm, thrombosis and other diseases, it directly affects the blood supply of the inner ear, resulting in ischemia, hypoxia and microcirculatory disturbance, resulting in inner ear injury. If not treated promptly and effectively, it will cause permanent deafness. Glucocorticoids are the first choice for the treatment of this disease in the United States guidelines for the treatment of sudden deafness, However, some patients have poor prognosis and poor prognosis. Many studies have shown that in the development of sudden deafness, vascular lesions play a very important role, coagulation, fibrinolysis, anticoagulation and other disorders of the final results of the system further evoked sudden deafness. Therefore, improving the inner ear microcirculation is helpful to improve the curative effect[5–7].

Batroxobin is a single component protease extracted from snake venom. It is a new thrombolytic agent, which has the effect of reducing blood viscosity, inhibiting thrombosis and dissolving thrombus. Batroxobin can selectively act on FiB, inhibit and dissolve thrombus by protein removal, and inhibit aggregation of red blood cells and platelets. In addition, batroxobin can reduce blood viscosity, reduce vascular resistance and increase vascular permeability, improve blood supply and inner ear microcirculation,so as to further restore hearing function. And studies have shown that batroxobin has free radical scavenging and anti-lipid peroxidation effect[8,9]. Ginkgo biloba extract and dipyridamole is a drug composed mainly of Ginkgo flavone, ginkgolide, dipyridamole, it can achieve the effects of anti-vasospasm, dilating cerebral blood vessels and improving microcirculation by exerting the functions of vasodilation, reducing blood viscosity and improving hemorheology. Therefore, the inner ear ischemia state can be improved, so as to further help the patients with sudden hearing loss to recover their hearing[10,11].

WBV is a comprehensive manifestation of serum viscosity, hematocrit, erythrocyte deformability and aggregation ability, platelet and leukocyte rheological properties. The determination of its level can provide reference for many diseases in clinic, especially for the diagnosis and treatment of thrombus like and thrombotic diseases[12]. PV is an important factor affecting the whole blood viscosity, mainly depends on the concentration of plasma proteins, especially fibrinogen, and its level increases, WBV will increase[13]. In this study, Batroxobin and Ginkgo biloba extract were used in the treatment of sudden deafness,The reduction of WBV and PV levels was significantly greater than that of batroxobin alone, indicating that combination therapy can dilute the plasma of patients and improve hemodynamics, thereby improving the hearing of patients.

PT refers to the time when prothrombin is converted into thrombin and plasma coagulation is made by adding sufficient tissue factor into the plasma without platelet. Determining the level of PT can determine whether the abnormal coagulation system exists in the body, and it is also an important indicator of anticoagulant therapy[14]. APTT is a relatively sensitive screening test for endogenous coagulation system, and its level mainly reflects the abnormality of endogenous coagulation[15]. TT refers to the time of blood clotting after the addition of standardized thrombin in plasma. Studies have shown that the level of thrombin is a screening test for fibrinolytic system, reflecting whether there is abnormal anticoagulation in the common pathway[16]. PF is a specific substance containing platelet itself,when the blood vessel is injured, platelets contact with collagen tissue to adhere and accumulate, and release PF after rupture, so as to participate in the coagulation process[17]. The results of this study showed that when patients with sudden deafness treated by combined application of Batroxobin and ginkgo dipyridamol, the PT, APTT, TT, PF improvement were significantly greater than with batroxobin alone, it suggests that combination therapy can improve the hypercoagulable state and improve the hearing level of the patients.

Fib is an important factor of the body involved in blood coagulation, the increase of its level can increase the coagulation of blood, promote platelet aggregation, and it can cause the abnormal fibrinolytic mechanism by activating plasmin activation inhibitor, and affect the endothelial function. Its level is related to the activity of blood coagulation, and it is an index that can reflect whether the content of the common pathway of internal and external coagulation system is normal[18]. D-two is a specific marker of fibrinolytic process, which is produced by the hydrolysis of the fibrin monomer through the activation of factor XIII, the increase of its level is beneficial to the dissolution of thrombus, which is important for recanalization of the infarction site[19]. FDP is produced by plasmin degradation of Fib, cross-linked fibrin and non crosslinked fibrin, which can prevent fibrin monomer from cross-linking and polymerization, compete anticoagulant and inhibit platelet aggregation of thrombin, and also reflect secondary fibrinolysis[20]. The results of this study showed that after treatment, the Fib of two groups decreased significantly, D-two dimer and FDP increased significantly, and the effect of combination therapy was better than that of single medication. It also indicated that batroxobin combined with ginkgo leaf extract and dipyridamole can improve the activity of fibrinolytic system and prevent thrombosis.

ET is a widely accepted vasoconstrictor factor in the current study, it has a long-lasting effect and is widely distributed in the tissues of human body, and can promote the release of NO, can

cause vasoconstriction, reduce blood flow, resulting in insufficient blood flow in the inner ear and onset[21]. NO is a factor released by vascular endothelial cells. Its oxidation characteristics can react with oxygen to form an oxidant damaging the ear nerve. Therefore, some studies have suggested that the level of NO can reflect the extent of the damage of the ear nerve[22]. SOD is an active substance that can eliminate harmful substances in the body, balance body oxidation and antioxidant reaction, protect cells from damage. When the disease occurs, a large number of free radicals are formed, and the resting state of scavenging and production is broken, thus reducing the activity of SOD[23]. It can be seen from the results of this study that: after treatment, the two groups of patients with ET, NO levels were significantly lower, SOD levels increased significantly, but the efficacy of the combination group was significantly better than the single medication group. It also shows that batroxobin combined with ginkgo leaf extract and dipyridamole in the treatment of sudden deafness patients can improve the body condition of the patients, further improve the inner ear microcirculation, and promote the recovery of hearing.

In conclusion, the treatment of patients with sudden deafness by using batroxobin combine with ginkgo-damole injection, can improve the hemodynamics, coagulation function, fibrinolytic function of patients, decrease the serum levels of ET and NO, improve the levels of SOD, the effect is curative, it's worthy of clinical application.

Reference

[1] Li Ganfeng, Li Zhihai. Evaluation of clinical efficacy and safety of batroxobin in treatment of sudden deafness ginkgo leaf extract and dipyridamole injection. *Chin J Clin Pharmacol* 2016; **32**(8): 675-677.

[2] Sun S, Ma J, Zhang Q. Argonaute proteins in cardiac tissue contribute to the heart injury during viral myocarditis. *Cardiovasc Pathol* 2016; **25**(2): 120-126.

[3] Cheng Z, Li-Sha G, Yue-Chun L. Autonomic nervous system in viral myocarditis: pathophysiology and therapy. *Curr Pharm Des* 2016; **22**(4): 485-498.

[4] Editorial board of Chinese Journal of Otolaryngology Head and neck surgery, Branch of Otolaryngology Head and neck surgery of Chinese Medical Association. Guidelines for the diagnosis and treatment of idiopathic deafness (2015). *Chin J Otorhinolaryngol Head Neck Surg* 2015; **50**(6):443-446.

[5] Hu Huayong. Clinical observation of electroacupuncture combined with Ginger Moxibustion in the treatment of sudden deafness. *Chin Med Clin Res* 2017; **9**(20): 122-123.

[6] Frasure SE, Siadecki SD, Saul T. Viral myocarditis leading to acuteheartfailure in a young adult. *J Emerg Med* 2014; **46**(3): 75-77.

[7] Wang Y, Gao B, Xiong S. Involvement of NLRP3 inflammasome in CVB3-induced viral myocarditis. *Am J Physiol Heart Circ Physiol* 2014; **307**(10): 1438-1447.

[8] Cai Z, Shen L, Ma H. Involvement of endoplasmic reticulum stress-mediated c/ebp homologous protein activation in coxsackievirus b3-induced acute viral myocarditis. *Circ Heart Fail* 2015; **8**(4): 809-818.

[9] Wang Gang Qiang, Zheng Shanluan.Effect of Batroxobin on coagulation and fibrinolysis in patients with sudden hearing loss. *Int J Lab Med* 2014; **35**(10): 1268-1269.

[10]Li Wenhua, Yang Yingying, Xie Tao. Effects of batroxobin combined with Ginkgo biloba injection on coagulation parameters in patients with sudden deafness. *Strait Pharm* 2015; **27**(10): 169-170.

[11]Pollack A, Kontorovich AR, Fuster V. Viral myocarditis--diagnosis, treatment options, and current controversies. *Nat Rev Cardio*l 2015; **12**(11): 670-680.

[12]Yujun. Effect of batroxobin combined with ginkgo leaf extract and dipyridamole on hearing and blood rheology in patients with sudden deafness. *J Hainan Med Univ* 2016; **22**(21): 2570-2572.

[13]Yao Yikai, Chen Bo, Li Fu. Analysis of Hemorheology and therapeutic effect in patients with sudden hearing loss with different hearing curves. *Chin Contemp Med* 2015; **22**(11): 90-92.

[14]Sandra Margetic, Lvana Celap, Lora Dukic. Interference of M-protein on prothrombin time test – case report. *Biochem Med* 2016; **26**(2): 248-254.

[15]Tom RG, Gordon DL, Debbie AL. A gene-centric analysis of activated partial thromboplastin time and activated protein C resistance using the Human CVD focused genotyping array. *Eur J Hum Genet* 2013; **21**(7): 779-783.

[16]Paul KL, Daniel FB, David MP. A proposal for dose-adjustment of dabigatran etexilate in atrial fibrillation guided by thrombin time. *Br J Clin Pharmacol* 2014; **78**(3): 599-609.

[18]Wang Huifang, Yu Caixia, Wang Jiapo. Clinical significance of changes of coagulation function in patients with sudden deafness treated with batroxobin abeled. *Immunoassays Clin Med* 2014; **21**(6): 698-700.

[19]Aaron RF, Rebecca FG, Duke A. Plasma d-dimer and incident ischemic stroke and coronary heart disease: the atherosclerosis risk in communities study. *Stroke* 2016; **47**(1): 18-23.

[20]Wei-Xin Xiong, Ying Shen, Dao-Peng Dai, et al. Clinical utility of the ratio between circulating fibrinogen and fibrin (ogen) degradation products for evaluating coronary artery disease in type 2 diabetic patients. *Chin Med J* 2015; **128**(6): 727-732.

[21]Wang Li, Guan Shufen, Sun Huizi. Efficacy of batroxobin and extract of Ginkgo Biloba leaves injection in the treatment of sudden deafness in elderly patients. *Chin J Gerontol* 2014; **34**(8): 2103-2105.

[22]Ciorba A, Corazzi V, Bianchini C. Sudden sensorineural hearing loss: Is there a connection with inner ear electrolytic disorders? A literature review. *Int J Immunopathol Pharmacol* 2016; **29**(4): 595-602.

[23]Tang Jianfang, Liu Huiqiao, Fu Jiangtao. Effect of batroxobin combined with Ginkgo Leaf Extract and Dipyridamole Injection on serum levels of ET, NO, SOD and sVCAM-1 in patients with sudden deafness. *Chin J Biochem Drugs* 2017; **37**(4): 210-212.