Special Topic Study

Influence of acupoint-injection on TXB₂ and 6-keto-PGF_{1a} in patients with pseudobulbar palsy: a randomized controlled trial

穴位注射对假性延髓麻痹患者 TXB2和 6-keto-PGF1a 的影响的随机对照试验

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Abstract

Objective: To prove the feasibility and validity of *Xing Nao Jing* acupoint-injection (XNJ-AI) at Fengchi (GB 20) for pseudobulbar palsy caused by ischemic stroke (PBP-IS).

Methods: An assessor-blinded, two-parallel-group, randomized controlled trial was conducted, and the patients with PBP-IS were recruited and randomly divided into two groups. Patients in the control group received oral aspirin (100 mg per day for 2 weeks). In addition to oral aspirin; patients in the treatment group received XNJ-AI at Fengchi (GB 20), once a day, for two weeks. The primary outcome was assessed by the water-swallowing test (WST). Thromboxane B_2 (TXB₂) and 6-keto-prostaglandin F_{1a} (6-keto-PGF_{1a}) in plasma were measured before and after the treatment.

Results: In the treatment group, the percentage of swallowing function no less than grade 3 before and after the treatment was 32% and 88%, respectively; in the control group, it was 28% and 76% before and after the treatment, respectively; the difference after the treatment between the two groups was statistically significant (P < 0.05). There were statistical differences between pre- and post-treatment levels of plasma TXB₂ and 6-keto-PGF_{1 α} in the two groups (both P < 0.05). After the treatment, there were significant differences in the levels of plasma TXB₂ and 6-keto-PGF_{1 α} between the two groups (both P < 0.05).

Conclusion: XNJ-AI at Fengchi (GB 20) can improve the patients' swallowing function and balance the levels of TXB₂ and 6-keto-PGF_{1 α} in plasma.

Keywords: Point, Fengchi (GB 20); Hydro-acupuncture; Acupoint Therapy; Pseudobulbar Palsy; Deglutition Disorders; Brain Ischemia; Thromboxane B₂

【摘要】目的: 证实风池穴注射醒脑静治疗缺血性中风引起的假性延髓麻痹的可行性和有效性。方法: 采用单 盲、平行、随机对照试验, 中风后假性延髓麻痹患者被随机分为两组。对照组患者口服阿司匹林, 每日 100 mg, 连 续 2 星期。治疗组患者在口服阿司匹林的基础上接受风池穴注射醒脑静治疗, 每日 1 次, 连续 2 星期。主要采用 洼田饮水实验评价疗效。治疗前后检测血浆中血栓烷素 B₂(TXB₂)和 6-酮-前列腺素 F_{1α}(6-keto-PGF_{1a})水平。结果: 治疗组中, 患者治疗前后吞咽功能 3 级以上百分率分别为 32%和 88%; 对照组中分别为 28%和 76%; 两组治疗后 差异具有统计学意义(P<0.05)。两组治疗前后血浆 TXB₂和 6-keto-PGF_{1a}含量与同组治疗前比较, 差异均具有统计 学意义(均 P<0.05); 两组治疗后血浆 TXB2 和 6-keto-PGF_{1a}含量差异均具有统计学意义(均 P<0.05)。结论: 风池 穴注射醒脑静可提高患者的吞咽功能并且能平衡血浆中 TXB₂和 6-keto-PGF_{1a}水平。

【关键词】穴,风池;水针;穴位疗法;假性延髓麻痹;吞咽障碍;脑缺血;血栓烷素 B2

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Pseudobulbar palsy (PBP) is caused by bilateral corticobulbar tract damage. PBP includes dysarthria, dysphagia and emotional incontinence. Recent studies point out that it may also induce pseudobulbar affect^[1]. Pseudobulbar affect is an neurological condition

that exerts a significant health burden on patients and care-givers^[2-3], characterized by frequent, sudden, uncontrollable episodes of crying and/or laughing that are greatly exaggerated or contrary to the patient's emotional state^[2,4]. Among these symptoms, dysphagia is the most harmful one. Patients often have difficulty taking food, especially drinking. This situation can cause patients psychological disorders, malnutrition and dehydration, electrolyte disturbances, and aspiration

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pneumonia, which is a great threat to human health. Without timely treatment, it can lead to suffocation which may endanger the life of the patients because of sputum and foreign body obstruction in respiratory tract. At present, modern medicine doesn't provide an effective treatment modality for this disease, but mostly symptomatic treatment such as nasal feeding and infusion to sustain life^[5]. Moreover, it gives patients and their families a lot of heavy economic and social burdens. Its prevention and treatment have become a difficult problem.

Acupoint injection is a therapy by injecting a small dose of drug, saline, or Chinese medicinal injection into an acupoint. It is the combination of the traditional and modern medicine. It follows the meridian theory of traditional Chinese medicine (TCM), and also absorbs the knowledge of Western medicine. Compared with traditional acupuncture that usually punctures multiple points and retains the needles for 20-60 min, acupoint injection is easy to operate, takes less time, and is easy to be standardized and repeatable^[6]. It can excite multiple neural receptors by stimulating one acupoint, which is similar to the action of acupuncture^[7]. And the stimulation of drug to the involved meridians also can nourish the nerves and promote blood circulation^[7]. It produces a dual effect of both meridian and drug, acting faster on human body, in order to achieve the purpose of treating diseases.

This study is to prove the feasibility and validity of *Xing Nao Jing* acupoint-injection (XNJ-AI) at Fengchi (GB 20) for PBP caused by ischemic stroke (PBP-IS).

1 Clinical Materials

Heilongjiang University of Chinese Medicine Committee on Human Research and Clinical Research Center reviewed and approved all study procedures.

1.1 Trial design

An assessor-blinded, two-parallel-group, randomized controlled design was taken.

1.2 Diagnostic criteria of PBP

Dysarthria and swallowing difficulties; the pathological brainstem reflection showed positive, such as sucking reflection and palm-jaw reflection; emotional obstacles; disappearance of soft palate reflex and gag reflex weakened or normal; PBP was confirmed by item 1 plus anyone of the items 2-4.

1.3 Eligibility

1.3.1 Inclusion criteria

Aged 56 to 68 years old with PBP-IS (both male and female participants); all patients with PBP-IS were confirmed by head CT scan or MRI examination for bilateral cerebral hemisphere lesions; conforming to the above diagnostic criteria of PBP; attack within 3 months.

1.3.2 Exclusion criteria

Complications of serious systemic diseases, such as kidney disease and digestive system disease; massive cerebral infarction with consciousness disorder; rejection or afraid of acupoint injection; failure to finish the clinical treatment; intolerance to aspirin or allergy to *Xing Nao Jing* (XNJ) injection.

1.4 Statistical analysis

All analyses were finished by a statistician blinded to the group allocation using the SPSS 17.0 version software. The intention-to-treat principle was used to analyze the data of primary and secondary outcomes. For normally distributed variables, two independent samples were compared by the *t*-test. For abnormally distributed variables, the Wilcoxon rank-sum test was performed. For the counting data, Chi square test was used. A statistical significance was indicated by P < 0.05.

2 Methods

2.1 Treatment group

2.1.1 Medication

Oral aspirin was given to the patients (100 mg per day for two weeks).

2.1.2 Acupoint-injection

In addition to the medication, XNJ-AI was used for two weeks. The two trained doctors performed all injections in this study.

Acupoint: Fengchi (GB 20).

Method: After the location of the acupoint was affirmed, the skin around Fengchi (GB 20) was sterilized with alcohol solution. Then used a 1 mL injector to draw 0.5 mL XNJ injection, and then inserted the needle obliquely into the acupoint by a 45° angle for 1.0-1.2 cm deep. After the needling sensation arrived, XNJ was injected. At last, the needle was removed, and the acupoint was covered with a piece of gauze.

2.2 Control group

The patients in the control group only received the medication treatment; the dosage, usage and the course were the same as those in the treatment group.

3 Observation on the Efficacy

3.1 Outcome measures

3.1.1 Primary outcome measurement

The classification standard of dysphagia was taken as the premise of treatment. While the water-swallowing test (WST) is frequently used in clinical practice as a kind of evaluation criteria to estimate the swallowing function. It has been 30 years since Kubota first described the 30 mL WST^[8]. Thus this test was used in this study.

The patients were asked to be seated straight and drink 30 mL warm boiled water. The time cost and frequencies of choking cough were recorded.

Grade 1, the patient could swallow water once thoroughly without a choke; grade 2, it took the patient 2 or more times to swallow all water, but without a choke; grade 3, the patient took all water once thoroughly, but with chokes; grade 4, it took the patient 2 or more times to swallow all water with chokes; grade 5, choke happened frequently, and the patient could not finish swallowing.

3.1.2 Secondary outcome measurement

The thromboxane B₂ (TXB₂) and 6-keto-prostaglandin F_{1a} (6-keto-PGF_{1a}) in plasma were measured to estimate the effect of prevention and treatment of cerebral ischemiareperfusion injury. The doctors collected fasting venous blood 2 mL in the morning respectively before and after the treatment. The blood sample immediately was centrifuged to isolate the plasma and stored in the -20 °C refrigerator. The TXB₂ and the 6-keto-PGF_{1a} in plasma were detected by the radioimmunoassay (RIA) method, and the kit was produced by the Northen Biotechnology Research Institute of Beijing.

3.1.3 Adverse events

Any adverse events which were relevant to XNJ would be reported to and recorded by the doctors at every visit. Possible adverse events related to XNJ-AI were bleeding, dizziness, and needle sickness during the treatment. Subjects received appropriate intervention if any adverse events occurred^[9]. Serious adverse events were reported to the doctors instantly, and the participants were withdrawn from the research. The details on adverse events would be recorded: data of occurrence; time lost; treatment for adverse events.

3.2 Results

Fifty-one patients were enrolled and allocated into a treatment group and a control group by randomization at 1:1 in this study. Fifty cases completed the research, one case dropped because of his personal affairs (Figure 1).

There were no significant inter-group differences in general data between the two groups (all P > 0.05), indicating the comparability (Table 1).



Table 1. Comparison of the general data between the two groups

Cassia	n	Gender (case)		Average age	Average duration	
Group		Male	Female	$(\overline{x} \pm s, year)$	$(\overline{x} \pm s, day)$	
Treatment	25	11	14	60±5	28.3±2.9	
Control	25	13	12	59±8	29.7±6.0	

3.2.1 Primary outcomes

For the percentage of grade 3 and above, it was 88% in the treatment group after the treatment, versus 76% in the control group, and there was a significant difference between the two groups ($P \le 0.05$). There were significant intra-group differences in the two groups (both $P \leq 0.05$), (Table 2).

3.2.2 Secondary outcomes

After the treatment, there were significant intra-group differences in TXB₂ and the 6-keto-PGF_{1a} in the two groups (all $P \le 0.05$); there were significant inter-group differences between the two groups (both $P \le 0.05$), indicating a more significant effect in the treatment group (Table 3).

Table 2. Con	nparison of V	WST gi	rade be	tween the	two group	s (case)

Tuble 2. Comparison of 1151 Grade between the two Groups (cuse)								
Group	п	Time	Grade 5	Grade 4	Grade 3	Grade 2	Grade 1	Percentage of grade 3 and above (%)
т., ,	25	Before treatment	0	0	8	8	9	32.0
Treatment 25	After treatment	5	8	9	2	1	88.0 ¹⁾	
Control 25	Before treatment	0	0	7	8	10	28.0	
	After treatment	4	7	8	3	3	76.0	

Note: Inter-group comparison after the treatment, 1) P<0.05

and area the distance (10 ===, pg m2)								
Group	п	Time	TXB ₂	6-keto-PGF $_{1\alpha}$				
Treatment	25	Before treatment	249.39±72.20	25.22±7.50				
		After treatment	$152.71{\pm}44.46^{1)2)}$	$35.84{\pm}6.38^{1)2)}$				
Control	25	Before treatment	234.52±40.78	24.97±5.35				
		After treatment	$181.70{\pm}21.93^{1)}$	$30.80{\pm}4.30^{1)}$				

Table 3. Comparison of plasma TXB₂ and 6-keto-PGF_{1a} before and after the treatment ($\overline{x} \pm s$, pg/mL)

Note: Intra-group comparison, 1) P<0.05; inter-group comparison after the treatment, 2) P<0.05

4 Discussion

In recent years, there has been a great interest in eating and swallowing disorders, and rehabilitation hospitals and care facilities have taken a proactive approach toward dysphagia^[10-11].

PBP-IS is a difficult health problem which has not been solved so far. It is an added burden to patients who may be disabled or experience a reduced quality of life due to their underlying neurological disorder^[12]. The outcomes of this pilot study focused on ischemic stroke patients with PBP and assessed if XNJ-AI at Fengchi (GB 20) is a potential and effective therapy for remission of this kind of disease.

Aspirin, an acetylated salicylic acid, is classified as one of the nonsteroidal anti-inflammatory drugs (NSAIDs)^[13]. Meanwhile, it is internationally recognized as an antithrombotic drug and its mechanism of preventing platelet aggregation is achieved by inhibiting the production platelet prostaglandin of and cyclooxygenase to prevent the formation of thrombus alkanes A2. In a previous study, low-dose aspirin has been shown useful for the prevention of stroke recurrence^[14]. Furthermore, low-dose aspirin can also reduce the mortality rate of stroke patients^[15]. Therefore, as a basic drug, aspirin is not only good for subjects' health, but also conductive to the experiment.

Fengchi (GB 20) belongs to the Gallbladder Meridian of Foot Shaoyang. The name of the acupoint literally means a pool of wind. Acupuncture at Fengchi (GB 20) can promote the flow of qi and blood, calm the liver, and normalize secretion^[16]. Previous studies have found that needling at Fengchi (GB 20) could increase blood supply to the brain^[17]. Therefore, this acupoint can cure some diseases caused by the wind such as ischemic stroke.

XNJ is an effective Chinese medicinal preparation which is extracted and purified by modern biotechnology according to *An Gong Niu Huang Wan* [a classic traditional prescription, first documented in *Wen Bing Tiao Bian* (*Systematized Identification of Warm Diseases*), a classic of TCM written in Ming dynasty]^[18]. It consists of four Chinese herbs: *She Xiang (Moschus)*, Yu Jin (Radix Curcumae); Zhi Zi (Fructus Gardeniae) and Bing Pian (Borneolum Syntheticu)^[19]. Previous studies have reported that XNJ could reduce brain injury and enhance functional recovery after stroke^[20]. Pharmacological trials also had demonstrated that XNJ had neuroprotective effects in cells and animal models of stroke^[21-22]. For XNJ, it has a broader prospect on treating stroke.

Acupoint injection therapy emerged in China in 1950s. It originated from intra-muscular injection in Western medicine and was gradually integrated into TCM^[23]. It is an acupoint-stimulating technique in which a liquid agent is injected to prevent and/or treat disease^[24]. Acupoint injection therapy is widely used for various diseases such as joint pain, urinary retention, hiccups, optic atrophy and stroke. Therefore, XNJ at Fengchi (GB 20) can unite the effects of drug and acupuncture point to enlarge the clinical efficacy.

Prostaglandin I₂ (PGI₂) and thromboxane A₂ (TXA₂) are important intermediate metabolites mediated by cyclooxygenases (COXs) in the amino acid (AA) metabolic pathway, but unstable and quickly degrade to 6-keto-PGF_{1α} and TXB₂, respectively^[25]. Under normal conditions, the two ingredients are in a state of relative balance. But in cases such as hypoxia, balance can be easily destroyed, resulting in thrombosis. Some studies have shown that TXB₂ in plasma of patients with cerebral infarction increases and 6-keto-PGF_{1α} decreases, which will promote the occurrence of cerebral infarction^[26-27].

This pilot study aimed to evaluate the effectiveness and feasibility of XNJ-AI at Fengchi (GB 20) for patients with PBP-IS. This experiment proved that XNJ-AI at Fengchi (GB 20) could improve the patients' swallowing function. Besides, it could decrease TXB_2 and increase 6-keto-PGF_{1a} to balance their relationship. So, it can produce some positive effects on patients with PBP-IS.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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Statement of Informed Consent

Informed consent was obtained from all individual participants included in this study.

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