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Research Article

Therapeutic Effect of Panax Notoginseng Saponins (PNS) on Hematoma Absorption Neurological Function Recovery in Hypertensive Intracerebral Hemorrhage Patients

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Abstract

Objective: Hypertensive intracerebral hemorrhage(HICH) leads to high mortality and disability, yet lacking widely approved clinical therapy. Here, we conducted a case-control study in patients with HICH to investigate the effect of panax notoginseng saponins (PNS), a well-known Chinese herbal, on hematoma absorption and neurological function recovery in HICH patients.

Methods: This study enrolled 120 patients which were randomly assigned into control group (n=62, regular treatment) and PNS group (n=58, regular treatment for 3 days, then plus PNS, 0.4g/d, for the following 14 days from the 4th day). Hematoma volume measured was by CT scanning and the National Institutes of Health Stroke Scale (NIHSS) scores, activities of daily living (ADL) were used to evaluate the treatment for both cohorts at the 10th and 17th day.

Results: Hematoma volume of PNS cohort was significantly less than that of the control cohort at the 10th and the 17th day and the neurological deficit scores were lower, while activities of daily living scores were improved.

Conclusion: PNS can significantly promote the absorption of hematoma as well as the recovery of neurological function in patients with HICH, offering novel clinical therapeutics for HICH.

Keywords: Panax Notoginseng Saponins; Hypertensive Intracerebral Hemorrhage; Hematoma Absorption; Neurological Deficit

1. Introduction

Hypertensive intracerebral hemorrhage (HICH) accounts for approximately 10-15% of all strokes that occur in the United States, Europe, or Australia, this ratio is doubled (20-30%) in Asia [1].The mortality rate from onset is 36% within 30 days, and 47% within a year [2]. Even the survivors are more likely to suffer from a great loss of neurological functions.

Currently, there is no effective pharmacologic or surgical therapy for HICH. Surgical treatments, such as Hematoma clearance, craniotomy and ventricular drainage, could effectively remove hematoma and reduce intracranial pressure, however, are far from desirable [3]. With regular medical treatments, such as anti-hypertensive and anhydration therapy, stress ulceration prophylaxis, water-electrolyte balance maintaining, the absorption of hematoma is

quite slow which may lead to severe neurological function disorder. Numerous studies have demonstrated that regional cerebral blood flow was decreased in surrounding tissue and remote area of intracerebral hemorrhage, resulting in a secondary ischemic lesion and a penumbra area, focus of infarct as well as vasogenic brain edema [4-6].Therefore, theoretically, circulation-improving medicine could palliate secondary lesion caused by ischemia and ameliorate prognosis. Panax notoginseng saponins (PNS) are an active ingredient extracted from Sanqi, a Chinese medicinal herb. PNS is well-known for its potent circulation-improving properties, curative effect and safety. Thus, PNS has been widely applied to the treatment of ischemic stroke [13], but seldom to that of acute ICH. Approved by State Food and Drug Administration of China (SFDA) for treatment of patients with some ischemic diseases, XUESAITONG Injection was mainly composed of PNS. This study, by comparing between regular treatment and that plus XUESAITONG injection, was aimed to assess the role of PNS played in hematoma absorption and neurological function recovery in HICH patients.

2. Materials and Methods

2.1. Participants

This study protocol was approved by the Ethical Committee on human research of Clinical Medical College, Yangtze University. Written informed consent was obtained from all patients or their legal guardians. Patients were recruited from May 4, 2012 to August 15, 2014 at Department of Neurology, The First Hospital of Jingzhou. Patients were eligible for screening if ICH was diagnosed by computer tomography (CT) within 2 days onset. Inclusion criteria were: 1) a history of hypertension treated with medication and blood pressure (BP) management (systolic <180mm Hg and diastolic < 100mm Hg) after hospitalization ; 2) 50-80 years old; 3) CT measured hematoma volume 10-30ml; 4) one-side basal ganglia area hemorrhage; 5) muscle power less than IV; 6) consciousness or slight lethargy with cooperation; 7) no heart, liver, kidney and other major organ disease, Exclusive criteria were: 1) cerebellar or brainstem hemorrhage; 2) anticoagulant-related; 3)intracerebral hemorrhage caused by bleeding diathesis, 4) aneurysms, vascular malformation; 5) hemorrhage in ventricle or subarachnoid; 6) multifocal hemorrhage; 7) subtentorial hemorrhage; 8) mixed stroke or hemorrhagic infarct; 9) hematoma volume <10 ml or >30 ml; 10) severe heart disease, therioma, other neurologic diseases, severe renal and hepar insufficiency, severe alimentary tract hemorrhage,shock; 11) hematoma volume expanding or rebleeding to over 40 ml, which was identified by CT; 12) a history of XUESAITONG injection anaphylaxis. Additional exclusion criteria included pregnant women, patients who underwent interventional procedures or neurosurgery, patients with poor compliance, insufficient information and with other contraindication for participation in this study. The physicians (neurologists and radiologists) were blind related to the specific treatment in this study.

2.2. Patient cohorts and treatment

Patients were randomly assigned into two cohorts according to the results of coin-flipping, heads or tails. Control cohort (n=62, regular treatment) and PNS cohort (n=58, regular treatment for 3 days, then plus PNS, 0.4g/d, for the following 14 days from the 4th day).

Regular treatments included dehydration therapy, obviation of stress ulceration, management of blood pressure, water-electrolyte balance maintaining according to the 2010 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. PNS cohort was given regular treatment for the first 3 days. Brain CT was re-scaned at the 4th day; PNS cohort was then given regular treatment plus XUESAITONG injection, 0.4 g in 250 ml saline, once a day for 14 days. Supportive therapy, such as physical cooling, nutritional support, fluid, was provided as needed to both cohorts.

2.3 Measurement of hematoma by CT scanning

Hematoma was determined by CT scanning and calculated according to this equation: hematoma volume (ml) = $\prod$/6×length (cm) ×width (cm) ×height (cm). All the CT scans analyzed respectively by two experienced neuroradiologists who were blinded to clinical information.

2.4 Assess of neurological function

For both cohorts, The National Institutes of Health Stroke Scale (NIHSS) scores, Activities of Daily Living (ADL), were measured at the 1st, 4th, 10th, 17th day respectively. Patient information (age, gender, weight, body weight index), vital signs (temperature, heart rate, respiratory rate, arterial pressure) and disease history (cardiovascular disease, diabetes) were collected.

2.5 Statistical analysis

Data were analyzed with SPSS 16.0. Continuous values were expressed as a mean ± SD (range). Paired-samples were compared by t-test. Significance was defined as $P<0.05$ in the model.

3. Results

No statistical significance was observed in age, sex, height, weight, temperature, heart rate, respiration rate and arterial pressure between the two cohorts ($P<0.05$,

data not shown).

3.1 Hematoma volume

Hematoma volume is a critical index and closely related to patient prognosis. From table 1, it can be seen that, for PNS cohort, hematoma volume enlarged at the 4th day, but decreased at the 10th day, at the 17th, indicating hematoma absorption accelerated and hematoma volume decreased obviously. For the control cohort, hematoma volume incresed at the 4th day and decreased thereafter but with a slower rapidity. There was no statistical difference between the two cohorts at the 4th day (P>0.05). Both volume figures decreased at the 10th and 17th day, but PNS cohort was significantly different from the control group (P<0.05), suggesting PNS was helpful in hematoma absorption.

3.2 NIHSS scores and Barthel index

For the NIHSS scores and Barthel index, no significant difference existed for the pre-treatment results (P>0.05). After one week treatment, there was a significant decrease for PNS cohort in NIHSS score or Barthel index (P<0.05), but control cohort remained the same. Meanwhile, Barthel index was increased for both cohorts (P<0.01). Two weeks later, NIHSS score of PNS group declined conspicuously while Barthel index increased obviously (P<0.01). Comparing the two cohorts' NIHSS score, the PNS one was noticeablely lower (P<0.01). Regarding Barthel index, PNS was distinguishedly higher (P<0.01).

	1st day	4th day	10th day	17th day
PNS Cohort（*n*=58）	25.58±9.14	26.36±11.42	18.52±10.32 *	10.24±7.35*
Controlcohort (*n*=62)	25.24±9.52	25.47±10.04	22.75±9.85	16.16±7.62

Table 1 Comparison of hematoma volume between PNS cohort and control cohort

* means that the figure has statistical significance, compared with control cohort, P<0.05.

	NIHSS score			
	1st day	4th day	10th day	17th day
PNScohort（*n*= 58）	22.60±3.42	20.46±3.37	13.27±3.55△	9.64±2.65△△
Controlcohort (*n*=62)	21.45±3.35	20.28±3.48	18.54±3.62	14.75±2.59

Table 2 Comparison of the NIHSS scores between PNS cohort and control cohort

△ comparing PNS cohort with control cohort, the figure has statistical significance, P<0.05.

△△ means P<0.01.

	Barthel index			
	1st day	4th day	10th day	17th day
PNS cohort（*n*= 58）	36.58±3.66	33.76±3.74	44.82±3.60▲	58.46±4.57▲▲
Control cohort (*n*=62)	35.82±3.58	36.26±4.61	37.42±4.73	46.84±5.12

Table 3 Comparison of the Bathel indexs between PNS cohort and control cohort

▲comparing PNS cohort with control cohort, the figure has statistical significance, P<0.05.

▲▲ means P<0.01.

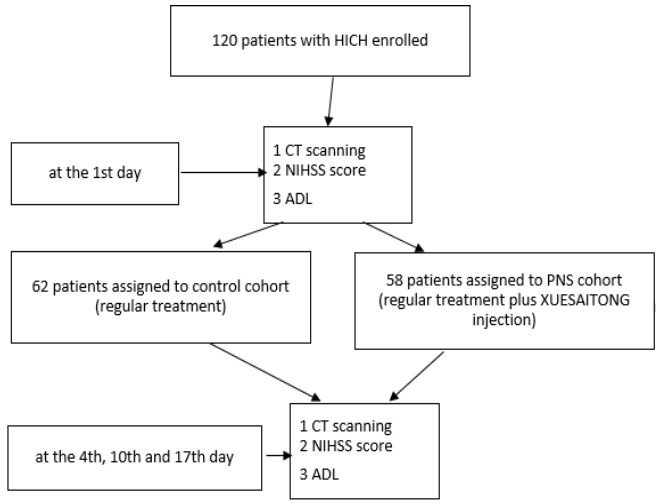

Fig. 1. Schematic of clinical study design.

4. Discussion

Previous studies indicated that cerebral blood flow hypoperfusion occured in the surrounding tissue of hematoma, brain mantle away from the hematoma, contre-hemisphere as well as cerebella, resulting in a series of ischemic cerebral lesion [4,5,7]. By single-photon emission computerized tomography (SPECT) scanning, a previous study confirmed the presence of ischemia around ICH and demonstrated that some of the ischemic perilesional brain could be recovered later. This zone of reversible penumbra points to the presence of sublethal injury in the vicinity of the ICH [5]. Another study concluded that regional cerebral blood volume (rCBV) and mean transit time (MTT) of perihematoma region decreased remarkably comparing to the contralateral side, and the decline would last over 3 weeks. Quantitative research suggested edema intensity was closely related with rCBV. The reduced regional blood flow of perihematoma contributes to the secondary ischemic

injury of perihematoma tissue [4]. It was confirmed that new ischemic lesions (NILs) frequently occured during the acute phase of ICH and were mainly associated with small-vessel pathogenesis. Forty-nine asymptomatic NILs were observed in 26.8% patients, with 75.5% of NILs located in subcortical white matter or brainstem. Microbleeds and moderate to severe white matter leukoaraiosis were independently associated with NILs. NILs were independently associated with the composite of clinical cerebrovascular events or vascular death. 35% of patients with primary ICH had active cerebral ischemia in Ipsilateral and contralateral hematoma in acute intracerebral hemorrhage. At both the baseline and 1 month timepoints, approximately 1/3 of patients had DWI lesions ipsilateral to the primary hematoma, 1/3 contralateral, and 1/3 had bilateral lesions. Independent predictors of DWI lesions included larger hematoma volume, intraventricular hemorrhage, microbleeds, and importantly, large reductions in mean arterial blood pressure [6].

Besides Secondary decrease in regional cerebral blood flow after HICH, evidence proved that inflammation reaction surrounding hematoma contributed to the secondary lesion after HICH and was closely related to neurosome death [8, 9]. The inhibition of the adhesion between leukocyte and endothelial cells is one of the crucial steps in the improvement of microcirculatory disturbance which is induced by inflammation [11]. Therefore, it was reasonable to speculate that palliatived lesion and better prognosis can be obtained if we improve cerebral hypoperfusion state and subdue inflammatory reaction induced by hematoma.

Better recovery of HICH patients' neurological function largely depended on higher hematoma absorption rate [3]. This study demonstrated that in the use of XUESAITONG for acute HICH, changes in NIHSS and Barthel index were closely related to that of hematoma volume. Compared with control cohort, PNS cohort had a higher rate in hematoma absorption, more significant decline in NIHSS, and greater growth in Barthel index. These findings suggest that XUESAITONG injection could promote the absorption of hematoma and improve the recovery of neurological functions.

PNS, extracted from traditional Chinese medicinal herb Sanqi, was the main ingredient of XUESAITONG injection. Panax notoginseng saponins are a mixture of more than 20 dammaranetype saponins, including ginsenoside Rg1, Rg2, Rb1, Rb2, Rb3, Rc, Rd, Re, Rh, F2 and notoginsenoside R1, R2, R3, R4, R6, Fa, Fc, Fe. Among these, panax notoginsenoside R1, ginsenoside Rg1, Rd, Re and Rb1 are considered to be the principal active constituents [11]. PNS played a great role in improving circulation, anti-apoptosis and anti-inflammatory action. Therefore, it was widely applied to the treatment of ischemic cerebrovascular and cardiovascular disease [12].

The observed beneficial effect of XUESAITONG injection in promoting hematoma absorption and recovery of neurological functions could be due to several mechanisms. 1) Better cerebral blood circulation, palliate cerebral edema, stabilify blood-brain barrier, and palliate the focal ischemic brain lesion [13]. 2) Haemolyticus. Protopanaxatriol-type saponins, one ingredient of PNS, included 7 compounds which could induce hemoclasis. Among the 7 compounds, the haemolytic activity of Rh1 was higher than that of other six compounds [14]. By promoting dissolution of erythrocyte within the hematoma, PNS could accelerate the decomposition of hematoma and the absorption of hematoma. 3) Anti-apoptotic effects. Neuronal apoptosis is involved in the pathogenesis of intracerebral hemorrhage [15]. PNS could protect myocardial cells from apoptosis induced by ischemia in both the in vitro and in vivo models through activating PI3K/Akt signaling pathway and inhibiting caspases activation [16,17]. 4) Anti-inflammatory effects. When ICH occurs, blood components, including erythrocytes, leukocytes, macrophages, and plasma proteins immediately enter the brain. An inflammatory response follows that involves enzyme activation, mediator release, inflammatory cell migration, glial activation [8]. Activated neutrophils have the ability to impair microcirculatory transit by elevation of endothelial permeabilily, leukocyte adhesion to the endothelium, leukocyte capillary plugging, release of vasoactive products, and capillary deformation and compression [18]. PNS may inhibit the adhesion between leukocyte and endothelial cells [10], and significantly decrease the gene expression of some inflammatory factors, such as integrins, interleukin (IL)-18, IL-1 and matrix metalloproteinases 2 and matrix metalloproteinases 9 [13]. Therefore, it can palliate brain lesion caused by inflammation.

In our research, PNS added into medication since the 4th day rather than the first 3 days, was largely to avoid unfavorable effects caused by hematoma expansion during treatment. Hematoma expansion of HICH patients occurs within 6 hours in the large part, and over 24 hours rarely [19]. It is thus safe and feasible to select patients strictly on the basis of the criteria previously mentioned. This study confirmed that using PNS in the treatment of HICH for 2 weeks after 4th day from onset may promote hematoma absorption and recovery of neurological function rather than cause a hematoma expansion. Our data suggest that it may be feasible to add PNS into the routine medical treatment for acute HICH patients in the early phase.

Consent

The procedures in this study were in accord with the standards of the Committee on Human Experimentation

of the Clinical Medical College, Yangtze University and in accord with the Helsinki Declaration of 1975. Written informed consent was obtained from the patient and his family for publication of this study and any accompanying images. A copy of the written consent is available for review by the Series Editor of this journal.

Competing Interests

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines. None of the authors have any conflict of interest to disclose.

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