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Angong niuhuang pill improves the neurological function of younger patients with basal ganglia and cerebral lobe intracerebral hemorrhage: A randomized controlled trial

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Abstract

Background & Objective: Spontaneous intracerebral hemorrhage (SICH) is one of the stroke forms with the highest disability and mortality rates and significant differences in prognosis among patients with different locations of SICH. Angong Niuhuang Pill (ANP) 安宫牛黄丸 is one of the most well-known traditional Chinese patent medicines used in the clinical emergency treatment of cardio-cerebrovascular diseases. This prospective study was performed to determine the therapeutic effect of ANP in different locations of SICH. *Methods:* Patients with basal ganglia(n=81) and cerebral lobe (n=67) hemorrhage were randomly assigned into two groups: the standard medical management (SMM) group and the combined ANP as well as medical management group (ANP group). Fisher exact test and Mann-Whitney U test were used for comparing the differences between two groups. Primary and secondary outcomes were the 6-month modified Rankin Scale (mRS) scores and the 2-week Brunnstrom stage ratings. *Results:* For patients with basal ganglia hemorrhage and cerebral lobe hemorrhage, there were no significant differences observed between the ANP group and the SMM group in terms of patient age (53.1±5.3 vs 52.7±6.4; 54.7±4.8 vs 52.7±5.9), sex (male:64.3% vs 53.8%; 63.6% vs 58.8%), body mass index (25.1±2.1 vs 24.2±2.6; 25.6±2.0 vs 25.0±2.4), mean hematoma volume (17.1±6.6 vs 18.6±5.7; 18.4±7.4 vs 18.9±6.0), as well as the proportions of hypertension (88.1%vs71.8%; 90.9% vs 76.5%), alcoholism (40.5% vs 51.3%; 54.6% vs 41.2%), smoking (40.5% vs 38.5%; 36.4% vs 38.2%), and diabetes mellitus (21.4% vs 18%; 12.1% vs 17.7%). The proportion of basal ganglia hemorrhage patients with a 6-month mRS score of 0-2 in the ANP group was significantly higher than that in the SMM group (26.2% vs. 2.6%, *P*=0.004), but it was not significantly improved in patients with cerebral lobe hemorrhage (57.6% vs 38.2%, *P*=0.145). The 2-week Brunnstrom stage ratings of patients with basal ganglia hemorrhage were significant difference (*P*=0.048). But for patients with cerebral lobe hemorrhage, there was no significant difference (*P*=0.164). The incidence of liver dysfunction, renal dysfunction, gastrointestinal dysfunction, hypothermia and allergy in the two groups of patients was not significantly different.
Conclusions: ANP has different therapeutic effects on different locations of SICH, and has the most obvious effect on improving the long-term neurological function of patients with basal ganglia hemorrhage.

Keywords: Intracerebral hemorrhage, neurological function, Angong Niuhuang Pill, basal ganglia, cerebral lobe

INTRODUCTION

Although spontaneous intracerebral hemorrhage (SICH) comprises only 10-15% of cerebrovascular diseases, it is associated with significantly higher mortality and disability rates compared to ischemic cerebrovascular diseases.[1-2] Approximately 32-50% of patients with SICH succumb within the first month following onset. Furthermore, only 20% of patients achieve independent living six months after experiencing an intracerebral hemorrhage (ICH).[3-4] The management of SICH consumes substantial medical resources and

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incurs high costs, thereby imposing a considerable burden on patients, their families, and society as a whole.[5]

Traditional Chinese Medicine (TCM) has been proven to be an effective therapeutic option for cerebrovascular diseases.[6-7] Angong Niuhuang Pill (ANP) 安宫牛黄丸 is one of the most well-known traditional Chinese patent medicines used in the clinical emergency treatment of cardio-cerebrovascular diseases. Originating from the Qing Dynasty, it has a history of several hundred years.[8] The main ingredients of ANP include bovis calculus sativus, pulvis bubali comus concentratus, moschus, margarita, cinnabaris, realgar, coptidis rhizoma, scutellariae radix, gardeniae fructus, curcumae radix and bomeolum syntheticum.[9] Due to its properties of clearing heat, detoxification, sedation, and revival, ANP has been widely applied in the Asian region, particularly in China, for diseases characterized by fever, coma, restlessness, as well as cognitive impairment disorders such as ICH, acute ischemic stroke, viral encephalitis, and traumatic brain injury.[10-11]

ANP has been shown to have neuroprotective and cardiovascular protective effects[11-12], improving the overall effective rate and neurological functional deficit scores of patients with acute cerebral infarction (ACI) and acute intracerebral hemorrhage (AIH).[13] The hematoma locations of SICH include cerebral lobe, basal ganglia, thalamus, ventricles, cerebellum and brainstem. Different locations of SICH have significant differences in occurrence rates and long-term neurological function.[14-15] The prognosis of lobe and cerebellar hemorrhage is significantly better than that of brainstem and basal ganglia hemorrhage, with the highest proportion of coma and mortality observed in brainstem hemorrhage patients.[15-18] Currently, it remains unclear whether ANP has the same therapeutic effect on SICH in different locations. The purpose of this study was to investigate different locations of SICH separately, randomly assigning patients into two groups: the standard medical management (SMM) group and the combined ANP as well as medical management group (ANP group) to comparing the outcomes of these two management approaches.

METHODS

Participants

This randomized controlled study screened patients with SICH diagnosed by head computed tomography (CT) who were admitted to the emergency department of Haining people's Hospital from January 2021 to December 2022. This data collection site was approved by the local Institutional Review Board, and written informed consent was obtained from all participants or their representatives.

Inclusion and exclusion criteria

The inclusion criteria were: Age 40-60 years, within 6 hours of onset and was diagnosed as SICH by emergency head CT, hematoma volume < 30ml and no emergency surgical treatment required.

The exclusion criteria were: progressive brain illness (Dementia, Parkinson disease, multiple sclerosis, seizure disorder, brain tumor), history of brain injury or stroke without full recovery, unable to complete or cooperate with the neurological function test.

Randomization and blinding

Eligible participants were divided into six categories according to the location of the hematoma (cerebral lobe, basal ganglia, thalamus, ventricles, cerebellum and brainstem), and each category of participants were randomly assigned to either the ANP group or the SMM group with a 1:1 ratio. Random numbers were generated by a computerized random number generator. For allocation concealment, we used closed envelopes containing random numbers and patients with odd numbers were assigned to the ANP group. The participants, clinical researchers, outcome evaluators, data manager, and statisticians were blinded to the treatment allocations during the study.

Interventions

Patients in the ANP group were administered oral or nasogastric ANP (3g) after early enteral nutrition was given on the second day of hospital admission. This was given once daily for a duration of 14 days. Patients in the SMM group received a matched placebo (3g once daily for 14 days). The remaining treatment protocols were the same between the two groups. The placebo was matched to ANP in terms of appearance, weight, and taste. Both ANP and the corresponding placebo were produced by Tongrentang Pharmaceutical Factory of Beijing Tongrentang Co., Ltd., China. The production processes of the study drug and placebo followed the standards of Good Manufacturing Practice. The drug extraction and hierarchical analysis methods have been patented in China.

SMM included maintaining airway through endotracheal intubation or, when necessary, tracheostomy, providing oxygen through a mask or ventilator, elevating the head by 30°, monitoring daily fluid balance, controlling blood pressure, using mannitol and diuretics to reduce intracranial pressure, prophylactic antiepileptic treatment to prevent seizures, prophylactic antibiotics, appropriate nutrition, and management of any associated conditions.

Outcome measures

The primary outcome was the modified Rankin Scale (mRS) scores[19] at 6 months after onset, and the secondary outcome was the Brunnstrom stage ratings[20] at 2 weeks. Each patient's test was performed by trained staff in a quiet environment. Taking ANP may lead to adverse reactions such as liver dysfunction, renal dysfunction, gastrointestinal dysfunction, hypothermia, and allergies. Safety outcomes referred to the incidence rates of these adverse reactions between the ANP group and the SMM group.

Data collection

Demographic and clinical characteristics were collected during hospitalization, including age, sex, past medical history (hypertension, alcoholic, smoker and diabetes mellitus), height and weight (used to calculate Body Mass Index, BMI), SICH location, mean hematoma volume, Brunnstrom stage ratings at admission and 2 weeks, mRS scores at 6 months after onset.

Statistical analysis

After calculation, the sample size was 58 (two-sided significance level=95%, power=80%, percent of unexposed with outcome=40). All statistical analyses were performed using GraphPad Prism 9.5.0 (GraphPad Software, San Diego, CA, USA). A value of $p < 0.05$ with a two-tailed test was considered statistically significant. Categorical data are presented as frequency or percentage and compared by Fisher exact test. Continuous data are presented as the average and standard deviation, ordinal scales are presented as the median and interquartile range (IQR) and were compared by the Mann-Whitney U test.

RESULTS

Demographic and clinical characteristics

Three hundred and fifty-five SICH patients who met the inclusion criteria were enrolled during the study period. At 6 months after onset, 79 patients were excluded due to the exclusion criteria, and a total of 276 patients with SICH were included. The numbers of patients with different locations of hematoma were 81 in basal ganglia, 67 in cerebral lobe, 24 in ventricles, 19 in brainstem, 39 in thalamus and 46 in cerebellum(Fig.1). Only the number of participants in basal ganglia and

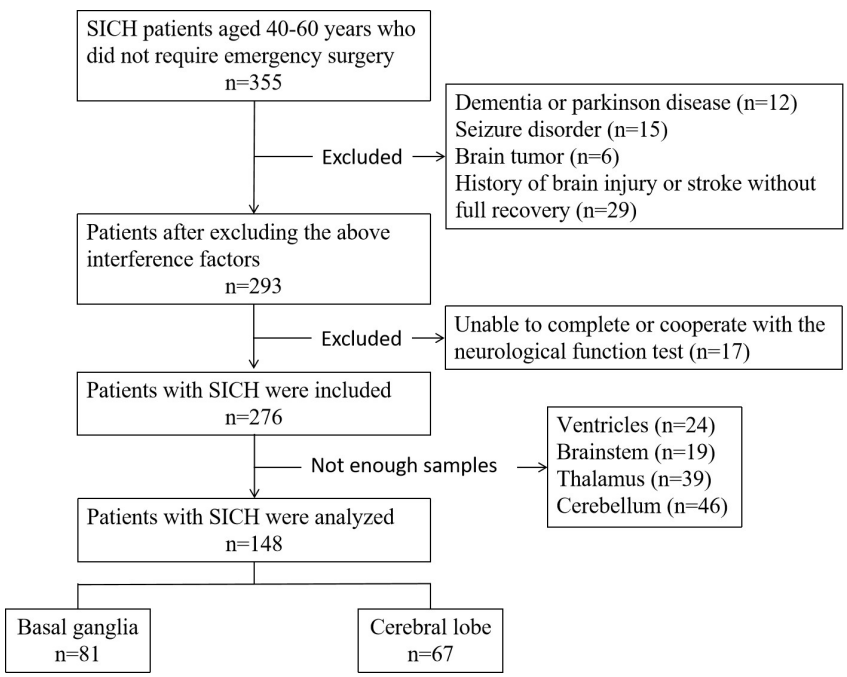

Figure 1. Flowchart of patient enrollment.

Table 1: Clinical and radiological parameters for basal ganglia hemorrhage patients

Parameters	ANP group (n=42)	SMM group (n=39)	*P*
Age (years)	53.1±5.3	52.7±6.4	0.972
Male, n (%)	27(64.3)	21(53.8)	0.373
Hypertension, n (%)	37(88.1)	28(71.8)	0.094
Alcoholic, n (%)	17(40.5)	20(51.3)	0.377
Smoker, n (%)	17(40.5)	15(38.5)	>0.999
Diabetes mellitus, n (%)	9(21.4)	7(18.0)	0.784
BMI (kg/m2)	25.1±2.1	24.2±2.6	0.058
Mean hematoma volume (ml)	17.1±6.6	18.6±5.7	0.384
Admission Brunnstrom grading ratings, median (IQR)	2(2-3)	2(1-3)	0.492

cerebral lobe hemorrhage met the requirements of sample size (n ≥ 58).

The final number of patients used for statistical analysis was as following: ANP group (n = 75), including basal ganglia hemorrhage (n = 42), cerebral lobe hemorrhage (n = 33), SMM group (n = 73), including basal ganglia hemorrhage (n = 39) and cerebral lobe hemorrhage (n = 34). The distribution of the baseline characteristics of the ANP group and SMM group were comparable in terms of age, sex, past medical history (hypertension, alcoholic, smoker and diabetes mellitus), BMI, mean hematoma volume, and admission Brunnstrom stage ratings (Table 1 and Table 2).

mRS scores at 6 months after onset

The 6-month mRS scores of patients with basal ganglia hemorrhage were 3 (2.3-4) in the ANP group and 4 (3-4) in the SMM group. The columnar stack chart showed the distribution of mRS scores in patients with basal ganglia hemorrhage. The proportion of patients with a score of 0-2 was significantly higher in the ANP group than in the SMM group (26.2% vs 2.6%, *P*=0.004). (Figure 2). For patients with cerebral lobe hemorrhage at 6 months, the mRS scores were 2 (1-3) in the ANP group and 3 (2-3) in the SMM group. The columnar stack chart showed the distribution of mRS scores in patients with cerebral lobe hemorrhage. The proportion of patients with a score of 0-2 was higher in the ANP group than in the SMM group, although there was no significant statistical difference between the two groups. (57.6% vs 38.2%, *P*=0.145). (Figure 3).

Table 2: Clinical and radiological parameters for cerebral lobe hemorrhage patients

Parameters	ANP group (n=33)	SMM group (n=34)	*P*
Age (years)	54.7±4.8	52.7±5.9	0.211
Male, n (%)	21(63.6)	20(58.8)	0.803
Hypertension, n (%)	30(90.9)	26(76.5)	0.186
Alcoholic, n (%)	18(54.6)	14(41.2)	0.332
Smoker, n (%)	12(36.4)	13(38.2)	>0.999
Diabetes mellitus, n (%)	4(12.1)	6(17.7)	0.734
BMI (kg/m2)	25.6±2.0	25.0±2.4	0.304
Mean hematoma volume (ml)	18.4±7.4	18.9±6.0	0.888
Admission Brunnstrom grading ratings, median (IQR)	4(3-4)	3(2.3-4)	0.114

BMI=Body Mass Index, IQR = (25th percentile–75th percentile).

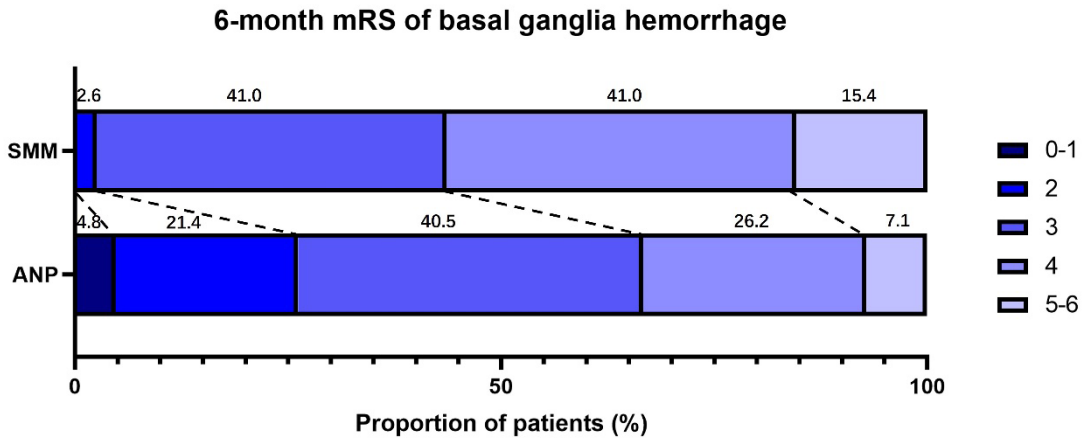

Figure 2. The 6-month mRS scores of patients with basal ganglia hemorrhage. The proportion of patients with a score of 0-2: ANP group(26.2%), SMM group (2.6%). P=0.004.

Brunnstrom stage ratings at 2 weeks after onset

The 2-week Brunnstrom stage ratings of patients with basal ganglia hemorrhage were 3.5 (3-4) in the ANP group and 3 (2.5-4) in the SMM group. There was a statistically significant difference between the two groups (*P*=0.048). For patients with cerebral lobe hemorrhage at 2 weeks, the Brunnstrom stage ratings were 5 (4-6) in the ANP group and 4 (4-5) in the SMM group. However, there was no statistically significant difference between the two groups (*P*=0.164) (Figure 4).

Safety outcomes

Both groups of patients did not experience hypothermia and allergies. In the ANP group, 16 (21.3%) had liver dysfunction, 6 (8%) had kidney dysfunction, and 8 (10.7%) had gastrointestinal dysfunction. In the SMM group, 12 (16.4%) had liver dysfunction, 6 (8.2%) had kidney dysfunction, and 6(8.2%) had gastrointestinal dysfunction. There were no significant differences observed between two groups.

DISCUSSION

This randomized controlled study indicated that the proportion of basal ganglia hemorrhage patients with a 6-month mRS score of 0-2 in the ANP group was significantly higher than that in the SMM group (26.2% vs. 2.6%, *P*=0.004), and the 2-week Brunnstrom stage ratings were significant difference (*P*=0.048).

SICH accounts for a relatively low proportion of cerebrovascular diseases, approximately 15%. However, it is one of the stroke forms with

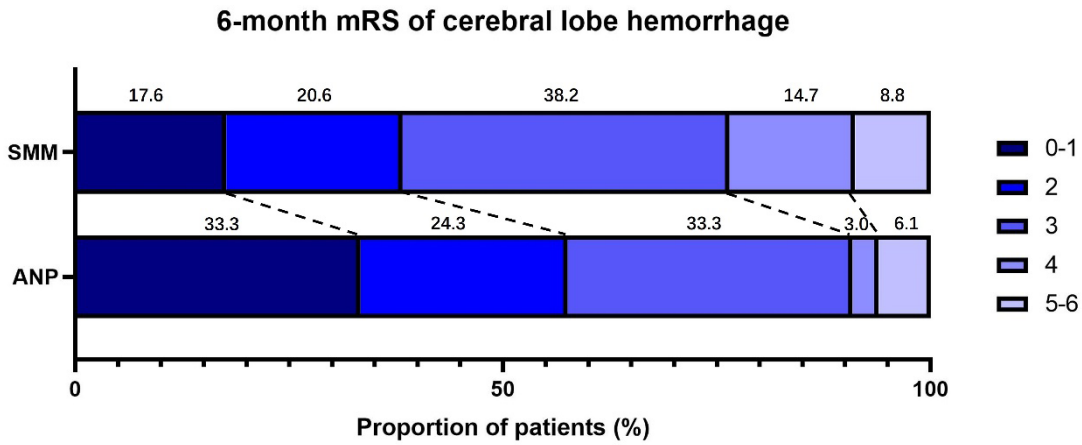

Figure 3. The 6-month mRS scores of patients with cerebral lobe hemorrhage. The proportion of patients with a score of 0-2: ANP group (57.6%), SMM group (38.2%). P=0.145.

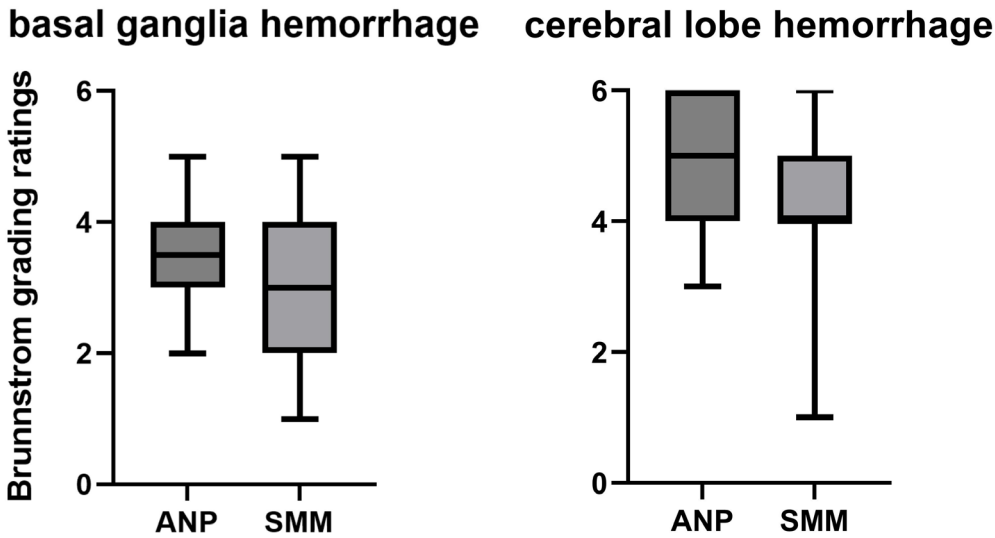

Figure 4. The Brunnstrom stage ratings of patients with basal ganglia hemorrhage and cerebral lobe hemorrhage at 2 weeks after onset.Basal ganglia hemorrhage: ANP group3.5 (3-4), SMM group3 (2.5-4).Cerebral lobe hemorrhage: ANP group5 (4-6), SMM group 4(4-5) .Data were presented as median (IQR).

the highest disability and mortality rates.[21-24] Kearns *et al*. described the secondary injury pathways following ICH, including thrombin-mediated chemotaxis and inflammatory cell migration, disruption of the blood-brain barrier and perihematomal edema, and free radical damage caused by erythrocyte lysis and then explored preclinical and clinical evidence for neuroprotective therapies.[25] In a prospective observational study by Bhatia *et al*., a total of 214 patients with intracerebral hemorrhage were included. During hospitalization, 70 cases (32.7%) resulted in death. Independent predictors of mortality included low Glasgow Coma Scale (GCS) score, high baseline hemorrhage volume, presence of intraventricular hemorrhage (IVH), and the need for mechanical ventilation. Most patients were discharged with disabilities. Surgery did not improve mortality rates or outcomes.[26] Thomas *et al*. conducted an analysis of 43 relevant studies on SICH, which revealed a positive correlation between the presence of complications and the baseline ICH severity with the increased hospital resource use. Intensive care unit (ICU) utilization, length of hospital stay, and the implementation of surgical procedures significantly increased the consumption of hospital resources.[5] Sadaf *et al*. highlighted the importance of rapid neuroimaging evaluation and management of ICH patients in specialized neurosurgical intensive care units or stroke units. Early intervention measures should include controlling systolic blood pressure within the range of 140 mmHg, correcting coagulopathy if indicated, and evaluating the need for surgical intervention.[16] Our study also revealed that in the SMM group of patients with basal ganglia hemorrhage, more than half of the patients remained severely disabled and unable to independently perform daily activities even after 6 months of onset. However, this proportion was relatively lower in patients with cerebral lobe hemorrhage.

ANP is one of the three major formulas used in traditional Chinese medicine for the treatment of febrile diseases. It is also a well-known Chinese patent medicine used in clinical practice for emergency treatment of cardio-cerebrovascular diseases.[8,12,28] Liu *et al*. identified and analyzed 18 trials involving 1601 patients. The results showed that the combination of ANP and conventional treatment had a significantly higher overall effective rate compared to conventional treatment alone in patients with ACI (RR 1.27) and AIH (RR 1.26). ANP adjunctive therapy also significantly reduced the neurological functional deficit scores and improved the GCS in patients with ACI and AIH.[13] Guo *et al*. discussed the validity and efficacy of ANP in the treatment of different central nervous system diseases.[12] Liu *et al*. further expounded the neuroprotective mechanism, cardiovascular protective mechanism and therapeutic mechanism of ANP on cerebral accidents from the integrative medicine perspective.[28] Chen *et al*. found in animal

experiments that ANP could significantly alleviate blood-brain barrier damage, cerebral edema, hemorrhagic transformation, enhance neurological function, and reduce mortality in ischemic stroke rats treated with tissue plasminogen activator. This effect was achieved by inhibiting the activation of matrix metalloproteinase-9 mediated by peroxynitrite.[11] Through studying the mouse model of acute ischemic stroke induced by middle cerebral artery occlusion (MCAO), Liu *et al*. found that ANP could reverse the dysbiosis of the gut microbiota by regulating bacterial abundance. It inhibited neuronal death, increased Nissl bodies, and reduced cell apoptosis, thereby significantly ameliorated stroke volume, improved neurological functional deficits, and alleviated histopathological damage in the ipsilateral cerebral cortex, hippocampus, and striatum.[10]

Delcourt *et al*. conducted an analysis including 2066 patients with ICH. The conclusion drawn from their study was that ICH involving the posterior limb of the internal capsule, thalamus, and infratentorial regions was associated with poor prognosis. Hemorrhages in the thalamus and posterior limb of the internal capsule had the highest correlation with death or major disability and lower European Quality of Life Scale utility scores.[15] Samarasekera *et al*. selected 128 cases of first-ever primary intracerebral hemorrhage from a population of 695335 adults. Their analysis revealed that the baseline characteristics and prognosis of lobe intracerebral hemorrhage differ from other locations.[29] Eslami *et al*. analyzed the prognosis of patients with severe intraventricular hemorrhage. The results showed that the thalamic location was independently associated with higher mortality rates and worse prognosis in most stroke grading systems. Involvement of the posterior limb of the internal capsule and the globus pallidus/putamen was associated with an increased likelihood of more severe disability. Conversely, injury to the anterior limb of the internal capsule and the tail of the caudate nucleus was associated with reduced mortality rates. Damage to the anterior limb of the internal capsule was also associated with a lower long-term incidence of stroke.[30]

More and more studies have clearly demonstrated significant differences in prognosis among patients with different locations of SICH.[31-34] Therefore, it is necessary and meaningful to classify and compare SICH patients based on the location of hemorrhage. In our study, due to insufficient numbers, patients with hemorrhages in the thalamus, brainstem, ventricles, and cerebellum were not included in the statistical analysis. Ultimately, patients with basal ganglia and cerebral lobe hemorrhage were randomly assigned into two groups. We found that ANP had better improvement in Brunnstrom stage ratings at 2 weeks and mRS scores at 6 months for basal ganglia hemorrhage compared to cerebral lobe hemorrhage, possibly because the baseline Brunnstrom stage ratings and mRS scores were already relatively high in cerebral lobe hemorrhage patients.

There are several limitations in our present study. This is a single centre study, only younger patients were enrolled, no longer term outcome data, no data on non-basal ganglia or non-cerebral lobe haemorrhages. Additionally, the small sample size may have limited the ability to comprehensively evaluate the long-term neurological functional benefits of ANP in patients with SICH.

In conclusion, ANP has different therapeutic effects on different locations of SICH, it has been shown to contribute to the recovery of limb motor function at 2 weeks and the improvement of neurological function at 6 months for basal ganglia hemorrhage patients. It also has a therapeutic effect on patients with cerebral lobe hemorrhage. We hope to have the opportunity to conduct a multicenter study in the future, so that each location of SICH can have a sufficient sample size, and further clarify the therapeutic effect of ANP.

DISCLOSURE

Ethics: Ethical approval for the study was obtained from the ethics committee of Haining People's Hospital.

Data availability: The data during the current study are available from the corresponding author on reasonable request.

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Conflict of interest: None

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