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Efficacy and safety of penetration acupuncture on head for acute intracerebral hemorrhage

A randomized controlled study

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Abstract

Background: Acupuncture, especially acupuncture treatment on head for acute intracerebral hemorrhage (ICH), has long been disputable. The aim of this study was to evaluate the efficacy and safety of penetration acupuncture on head in patients with acute ICH.

Methods: Eighty-two patients with acute ICH were randomized to receive penetration acupuncture treatment on head combined with conventional treatment (treatment group [TG]) or conventional treatment only (control group [CG]). Acupuncture treatments were given in 24 sessions over 4 weeks, with 3-month follow-up period. Measures included Clinical Neurological Function Deficit Scale (CNFDS), Barthel Index (BI), vital signs (respiration, heart rate, blood pressure, and oxygen saturation), and hematoma absorption ratio.

Results: Both groups showed a progressively improvement in CNFDS and BI scores from day 7 to 90. The TG showed a significantly greater improvement in CNFDS than CG over time ($P < 0.05$). However, BI failed to show significant difference between the 2 groups ($P > 0.05$). The vital signs were stable and no expansion of hematoma occurred over the course of acupuncture treatment.

Conclusion: Penetration acupuncture treatment on head appeared to be safe over the course of treatment on acute ICH and may result in additional functional improvements detected in the CNFDS but not reflected in the BI. A larger-scale clinical trial with longer follow-up assessments is required to confirm these findings.

Abbreviations: BI = Barthel Index, CG = control group, CNFDS = Clinical Neurological Function Deficit Scale, HAR = hematoma absorption ratio, ICH = intracerebral hemorrhage, TG = treatment group.

Keywords: acupuncture, acute stroke, cerebral hemorrhage, randomized controlled trial, safety

1. Introduction

Primary intracerebral hemorrhage (ICH), the most devastating subtype of stroke, accounts for 10% to 15% of all strokes.[1] Compared with ischemic stroke, it has higher mortality and disability rate, causing up to 80% survivors functionally dependent at 6 months.[2] Early interventions for acute ICH are important to promote absorption of hematoma, so as to alleviate secondary damage it might cause.[3] For those unnecessary for surgery, with small hematoma and no significantly increased intracranial pressure, conservative medication treatment is to stop bleeding and decrease hematoma growth. However, some medication treatments, such as factor VIIa, come with an increase in some complications.[4] To date, the evidence showing effective therapeutic approach to improve the clinical outcome of acute ICH remains insufficient.[3] The increasing burden on family and society following the aging population warrants more investigation on the treatment of acute ICH.

Incidence of ICH in China is relatively higher than in Western countries.[5] Acupuncture treatment, as a major therapeutic method in China, has been used in stroke therapy since ancient times and is extending to Western countries nowadays. Some studies have shown the possibility of clinical efficacy and functional improvement in ischemic stroke treated by acupuncture and are underpinned by other mechanism studies.[6,7] However, there are few studies focusing on the safety and efficacy of acupuncture on acute ICH. Acupuncture, especially acupuncture treatment on head for acute ICH, has long been disputable. Some academics with negative attitude are concerned that as a external stimulus, acupuncture on head might disturb the stability of hematoma and increase the risk of rehemorrhage.[8] As the previous studies being equivocal, we planned a single blind, randomized controlled trial to evaluate the efficacy, and safety of penetration acupuncture therapy on head for acute ICH.

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2. Methods

2.1. Design and setting

This study adopted a prospective, single-blind, randomized control design and was carried out in cerebral surgery department, neurology department, and acupuncture department in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. The study was approved by Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine and registered in the Chinese Clinical Trials Registry (ChiCTR-TRC-08000225). This study is reported in accordance with the CONSORT statement.[9]

2.2. Participants

In this study, 120 patients with acute ICH were recruited from December 2007 to October 2009. Eighty-two patients, aged 18 to 70 years, were enrolled according to inclusion criteria as follows: patients with ICH confirmed by computed tomography (CT) scan according to the diagnosis criteria of the Fourth National Cerebrovascular Academic Conference,[10] patients conscious at onset with a duration of less than 14 days after onset or unconscious at onset with a duration of less than 30 days after onset, neurological deficit score ≧18, patients conscious or with mild conscious disturbance at inclusion, blood pressure below 180/110 mm Hg, hematoma volume less than 30 mL for alba hemorrhage or less than 20 mL for hemispheric thalamus or basal ganglia hemorrhage, and stable vital signs.

Exclusion criteria were patients after surgery, subarachnoid hemorrhage, brainstem or cerebellar hemorrhage, patients with pregnancy, patients with severe primary cardiovascular, liver, kidney or hematopoietic systems diseases or mental illness, and cognitive impairment or communicative disorders that interfered with evaluation.

2.3. Randomization

Each patient signed an informed consent form before allocated to either treatment group (TG) or control group (CG). Randomization was undertaken using prepared opaque-sealed envelopes containing random numbers, which were produced using SPSS software (SPSS Inc., Chicago, IL, USA) by a researcher not involved in data collection. A research assistant opened the envelopes consecutively for each patient enrolled and informed the acupuncturist for treatment if the patient was in the TG.

2.4. Intervention

2.4.1. Conventional treatment. Both the TG and the CG received standard routine internal medicine care during the trial. In the first week, mannitol and furosemide were administrated to reduce intracranial pressure if necessary. Citicoline was given by intravenous infusion, once a day, in the following 3 weeks. Blood pressure was controlled at around 20.0/12.0 kPa (150/90 mm Hg). Antihypertensive drugs were given if the blood pressure was over 26.6/13.3 kPa (200/100 mm Hg). Various complications (lung infections, urinary tract infections, bed sores, etc.) were prevented or treated if necessary. All the medicines should be administrated by blinded physician and based on symptoms of each patient. In addition, each patient received regular care such as good limb position, active and passive activities.

2.4.2. Penetration acupuncture treatment on head. In addition to the conventional therapy, the TG received penetration acupuncture treatment on head. Head and facial points in the affected side of ICH were selected according to different symptoms of each patient. Penetrating Baihui (GV20) to Taiyang (EX-HN5) for paralysis: Baihui was punctured 25 to 30 mm toward Taiyang. Other 2 points at the 1/3 and 2/3 of the distance from Baihui to Taiyang were localized and punctured 25 to 30 mm toward Taiyang. Taiyang was punctured backward and downward (Fig. 1). Penetrating Sishencong (EX-HN1) to Baihui for urinary dysfunction; Penetrating Dicang (ST4) to Jiache (ST6) and Xiaguan (ST7) for facial paralysis; Puncturing Yintang (EX-HN3) obliquely downward for oculomotor apraxia; Penetrating Luoque (BL8) to Chengling (GB18) and Chengling to Xuanli (GB6) for sensory disturbance.

Acupuncture manipulation: In this study, sterile, disposable needles, with a diameter of 0.25 mm and lengths of 40 to 70 mm, were used (Suzhou Hua Tuo Medical Instruments Co., Ltd, Suzhou, China). Each needle was at first punctured perpendicularly until passed galea aponeurotica, then punctured 30-mm obliquely at a 15-degree angle. Needle was twisted rapidly at more than 200 rev/min for 5 min. Manipulation of twisting was repeated 3 times with 2 intervals of 5 min. During the manipulation, the patient obtained a sensation of soreness, numbness, and distention defined as "de qi".

Patients received 6 sessions of acupuncture treatments per week for 4 weeks. The acupuncture treatment protocol was designed by a senior acupuncture expert with more than 30 years'

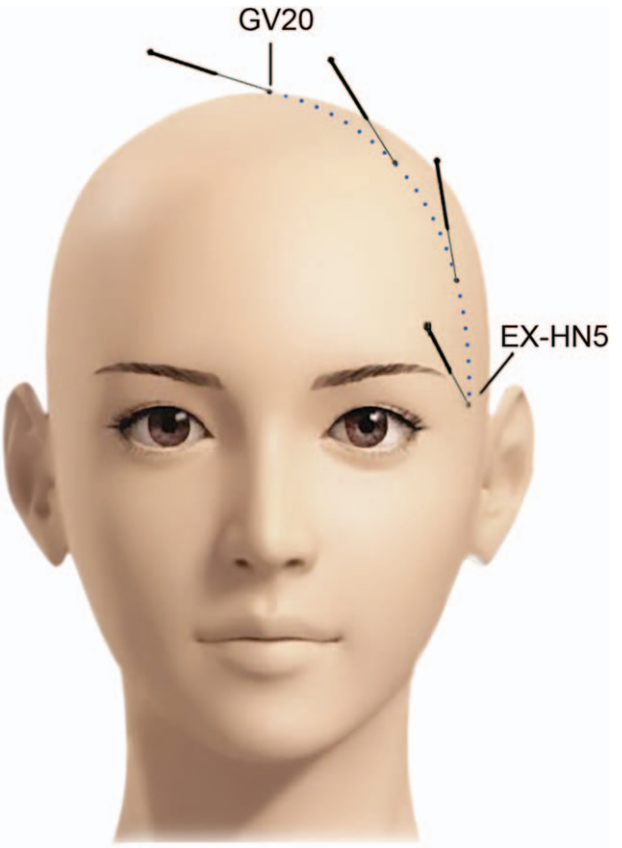

Figure 1. Diagram showing localization of acupuncture points for penetrating Baihui (GV20) to Taiyang (EX-HN5).

experience and administered by 2 acupuncturists with more than 5 years' experience.

2.5. Measurements

2.5.1. Primary outcomes. Neurological deficit was assessed using Clinical Neurological Function Deficit Scale (CNFDS) at day 7, 14, 28, 60, and 90 after enrollment. Barthel Index (BI) assessment was performed to evaluate the activities of daily living (ADL) function at day 28, 60, and90. Adverse events and mortality were both recorded. The assessor performing all the evaluations was qualified and blinded to patients' allocation. She was told not to talk about treatment with the patients, and there was no information regarding the patients' allocation in their case records CNFDS.

CNFDS is a reliable and validated instrument to assess the clinical neurological function of stroke patients and was developed based on the Scandinavian Stroke Scale (SSS) and according to the specific condition in China. The scores include consciousness, horizontal gaze function, facial paralysis level, speech function, upper limbs movements, hands movement, lower limbs movements, and walking ability. The total score is 45, and a higher score means more neurological function deficit.[11]

2.5.2. Barthel Index. BI is a validated instrument for assessing ADL and has been widely used.[12] It has a total score of 100, with 10 personal activities: feeding, bathing self, personal hygiene, dressing, bowel control, bladder control, toilet, chair/bed transfer, ambulation/wheelchair, and stair climbing.

2.6. Secondary outcomes

The patients were carefully examined at baseline. During the first week of treatment, vital signs were documented 2 hours before acupuncture treatment, in the treatment, and 2 hours after the treatment, including respiration, heart rate, blood pressure, oxygen saturation. A CT scan was performed to evaluate the hematoma volume change at baseline and 14 days after enrollment.

2.6.1. Hematoma absorption ratio. Hematoma absorption ratio is calculated using the following formula:[13] hematoma absorption ratio (HAR) = ([hematoma volume at baseline − hematoma volume at d14]/hematoma volume at baseline) × 100%. Hematoma absorption level is classified as substantially absorbed (HAR > 70%), partly absorbed (41% < HAR < 70%), slightly absorbed (10% < HAR < 40%), no absorption (HAR < 10%).

2.7. Statistical analysis

The sample size was calculated using repeated-measure analysis module. With significance level set at 5% ($\alpha = 0.05$) and statistical power at 90% ($\beta = 0.1$), 32 patients per group were required to detect a difference of 5 points and standard deviation of 5 points for CNFDS, and 33 patients per group were required to detect a difference of 20 points and standard deviation of 20 points for BI. Therefore, a sample size of 66 patients was chosen. Given a 20% dropout rate, 82 patients were included in this study.

The t test or χ^2 test was used to analyze demographic characteristics before the study. The rank sum test was used to analyze significance of the differences of HAR between groups. Repeated-measure analysis of variance model was carried out by using "Time" as a within-group factor and "Group" as between-group factor. Post-hoc comparisons were carried out by using an independent-samples t test to assess the significance of the differences between groups for each assessment. The Bonferroni (equal variances assumed) or Dunnett T3 (equal variances not assumed) correction was used in multiple comparisons. The level of significance was set at 5% for all comparisons (2-tailed). Analyses were performed with SPSS software for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 82 Chinese patients were enrolled and randomized to TG (n = 42) and CG (n = 40) in the present study. Fourteen patients dropped out during the trial, accounting for a 17% dropout rate. Subjects tolerated treatment well, and there were no adverse effects reported in TG. One patient in CG was transferred to other hospital as a result of hematoma expansion at day 2. There were no deaths during the trial (Fig. 2).

Characteristics of the patients at baseline were comparable between the 2 groups (Table 1). No significant differences were found in baseline values between the 2 groups in gender, age, or duration from stroke onset (all Ps > 0.05).

Changes in CNFDS scores over the course of treatment are demonstrated in Table 2. No significant difference was found at baseline between TG and CG ($P < 0.05$). Repeated measurements analysis showed a group × time interaction ($P = 0.004 < 0.05$). Both groups got a progressively improvement in CNFDS scores from day 7 to 90. However, the TG showed a significantly greater improvement than CG over time ($P < 0.05$). Figure 3 shows the CNFDS trajectory.

Table 2 also summarizes the BI scores over the course of treatment. No significant difference was found at baseline between groups ($P > 0.05$). Repeated measurements analysis showed a significant effect of time ($P = 0.000 < 0.01$). Both groups showed a progressively increase in BI scores over time. However, no significant group × time interaction ($P = 0.062 > 0.05$) was found.

In the TG, improvement in the second month (M_{2-1}) was significantly greater than that in the first month (M_{1-0}) ($P < 0.05$). However, improvement in the third month (M_{3-2}) did not significantly differ from that in the second month ($P > 0.05$). In the CG, no significant difference was found in the improvement between first and second month ($P > 0.05$). However, improvement in the third month was significantly greater than that in the second month ($P < 0.05$). Figure 4 shows the BI trajectory.

The oxygen saturation showed no significant change in the acupuncture treatment compared with that 2 hours before treatment ($P > 0.05$). However, the heart rate, respiration, and blood pressure showed significant improvement 2 hours after treatment, compared with those 2 hours before treatment ($P < 0.05$) (Table 3).

After 14 days of treatment, hematoma was absorbed significantly in both TG and CG. No patient with hematoma expansion was found in both groups. The percentage of patients with substantial and part HAR in TG was 76.47%, which was significantly greater than 55.88% in CG ($P < 0.05$) (Table 4).

4. Discussion

Acupuncture is commonly considered a viable complementary treatment for poststroke patients. As reported by a survey in Canada, 87% of poststroke patients were willing to be given acupuncture treatment, and 98% were willing to learn more regarding acupuncture as a treatment on stroke rehabilitation.[14]

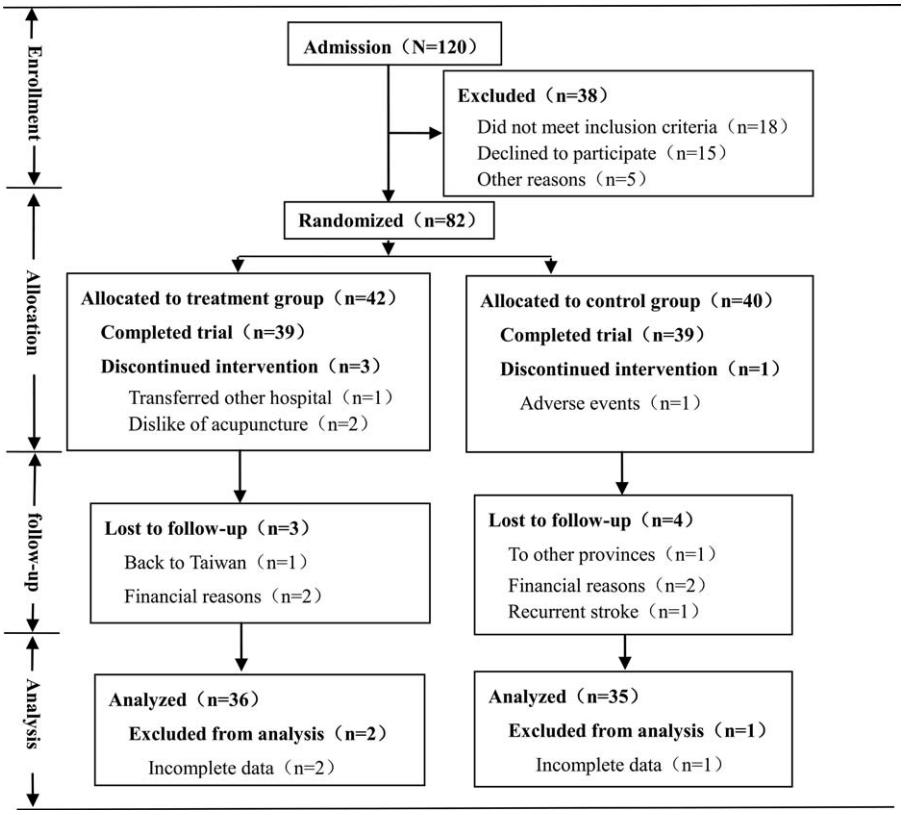

Figure 2. Trial flow diagram.

However, the benefit of acupuncture for stroke is still controversial.[15,16] Previous studies investigating efficacy of acupuncture treatment on stroke patients have presented varied results,[17–20] even though many acupuncturists and patients believe in the efficacy of acupuncture on stroke. Heterogeneity of patients recruited is one of the important reasons for these discrepant results. Most of the previous studies recruited both cerebral hemorrhage and ischemia patients.[17–20] This probably is due to the difficulty to recruited enough patients with the same type of stroke, especially the hemorrhagic stroke. In a previous study investigating efficacy of scalp and penetration acupuncture for stroke, Jungchul Seo thought that the negative results in their study may be changed if hemorrhagic stroke patients were targeted.[21] Our study focused on the cerebral hemorrhage patients, which may partly reduce the heterogeneity of subjects, despite it took a long time to recruit all the patients.

In Traditional Chinese Medicine, penetration acupuncture on head is a special acupuncture skill by penetrating the needle at 1 acupoint toward another acupoint and is frequently employed to treat ischemic stroke patients. It can help patients obtain the needling sensation "De qi" easily and achieve a good effect by employing few points. Based on modern findings regarding the

Table 1

Baseline characteristics of the acute ICH patients (mean ± standard deviation).

Characteristics	TG (n = 34)	CG (n = 34)	*P*
Gender			
Female	12	14	0.618
Male	22	20	
Age, y	57.74 ± 8.76	54.94 ± 10.53	0.239
Duration (after onset)	7.88 ± 6.73	5.44 ± 4.29	0.080

CG = control group, TG = treatment group.

Table 2

Comparison of CNFDS score and BI score (mean ± standard deviation).

	CG	TG
CNFDS score		
Baseline	26.76 ± 5.88	24.24 ± 5.74
7 d	23.00 ± 6.16*	18.65 ± 6.91*,†
14 d	20.50 ± 6.43*	14.44 ± 7.85*,†
28 d	16.79 ± 7.14*	10.79 ± 7.59*,†
60 d	13.12 ± 7.09*	8.56 ± 7.02*,†
90 d	9.32 ± 6.19*	5.41 ± 5.03*,†
BI score		
Baseline	14.41 ± 12.54	19.12 ± 13.73
28 d	45.00 ± 22.73*	56.32 ± 28.93*
60 d	65.88 ± 24.10*	74.56 ± 22.31*
90 d	75.74 ± 23.00*	84.85 ± 20.06*
M_{1-0}	30.59 ± 18.04	37.21 ± 23.75
M_{2-1}	20.88 ± 15.20	18.24 ± 19.54‡
M_{3-2}	9.85 ± 7.44§	10.29 ± 10.51

M_{1-0}, day 28 versus baseline; M_{2-1}, day 60 versus day 28; M_{3-2}, day 90 versus day 60. BI = Barthel Index, CG = control group, CNFDS = Clinical Neurological Function Deficit Scale, TG = treatment group.

* $P < 0.01$, compared with baseline within-group.

† $P < 0.05$, compared with CG.

‡ $P < 0.05$, compared with M_{1-0} in TG.

§ P, compared with M_{2-1} in CG.

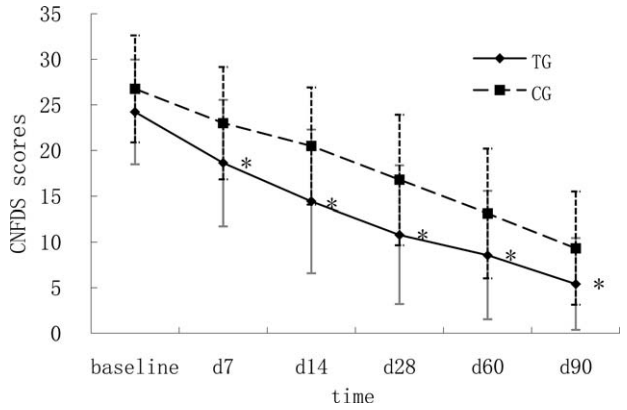

Figure 3. Trends over time for the Clinical Neurological Function Deficit Scale score in the control and treatment groups. $^{*}P<0.05$, compared with control group.

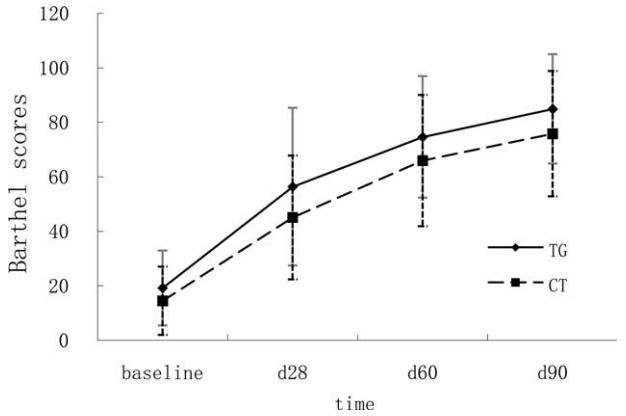

Figure 4. Trends over time for the Barthel Index score in the control and treatment groups. $^{*}P<0.05$, compared with control group.

plastic changes occurring immediately after brain damage, rehabilitation treatment should be more effective if started soon after onset.[22,23] However, due to the rapid onset, high mortality and unstable condition of hemorrhagic stroke, some academics were negative or skeptical about acupuncture on head for acute ICH. The main concern was that external stimulus might influence the stability of hematoma and increase the risks of expansion of edema and hematoma.[8] The present study found no aggravation of cerebral hematoma in patients with penetration acupuncture treatment on head. In fact, significantly more patients among TG got a substantial and part absorption of hematoma, compared with CG. In addition, vital signs in patients with acupuncture treatment were stable or improved during the treatment. The result of acupuncture lowering heart rate and blood pressure is consistent with a previous study investigating acupuncture effects on hypertension patients.[24] Penetration acupuncture on head appeared to be safe for the treatment of acute ICH. Previous experimental studies demonstrated that acupuncture could inhibit the expression of endogenous MMP-9, AQP-4, and PAR-1, which may build the material basis of cerebral edema or play important roles in progression of edema.[25] This may be a potential explanation for our outcomes. Acupuncture has also been found to significantly increase the regional cerebral blood flow, which is the foundation for hematoma absorption, edema elimination, thereby intracranial pressure reduction, providing further support for the hematoma absorption effects attributable to acupuncture stimulation.[26–28]

It is generally believed that the recurrence rate of ICH among patients with first occurrence is higher than the first incidence among ordinary people, about 2% versus 0.3% to 0.53% each year.[15,29] In this study, only 1 patient from the CG was excluded due to the recurrence of cerebral infarction at day 50 in follow-up, accounting for the total recurrence rate of less than 1%. This may be due to the few cases included and short follow-up time.

CNFDS is a wildly used instrument in China for evaluating neurologic impairment of poststroke patients. It was developed based on the SSS with some modification to satisfy the neurologists in daily usage. It explicitly quantificats the extremity strength by the angle between the extremity and the trunk, instead of some vague description such as “normal”, “weakened”. In 20 years usage, it has been testified to be a reliable and valid scale to evaluate the prognosis and severity of acute stroke

Table 3

Change of vital signs over the course of acupuncture treatment (mean ± standard deviation).

	Pretreatment	In the treatment	Posttreatment
Respiration, breaths/min	18.01 ± 2.67	18.16 ± 3.46	17.43 ± 2.57*,†
Heart rate, beats/min	76.88 ± 9.56	76.46 ± 8.47	75.23 ± 7.00*
Blood pressure, mm Hg			
Systolic blood pressure	138.66 ± 13.68	136.32 ± 12.26	133.21 ± 11.45*,†
Diastolic blood pressure	84.29 ± 10.52	82.14 ± 9.29	79.44 ± 8.15*,†
Oxygen saturation, %	99.50 ± 1.26	99.53 ± 1.28	99.71 ± 0.86

$^{*}P<0.05$, compared with pretreatment.
$^{\dagger}P<0.05$, compared with in the treatment.

Table 4

Comparison of the hematoma absorption.

Group	n	Substantially absorbed	Partly absorbed	Slightly absorbed	No absorption	Hematoma expanded	Percentage of patients with substantial and part absorption, %
CG	34	4	15	9	6	0	55.88
TG	34	8	18	7	1	0	76.47*

CG = control group, TG = treatment group.
$^{*}P<0.05$, compared with CG.

patients and proved to be significantly correlated with the Canadian Neurological Scale and the NIH Stroke Scale.[30] It excluded some items specified to vertebral basilar artery territory stroke thus suitable for the carotid artery territory stroke. The patients recruited in the present study were all with carotid artery stroke. In addition, due to the unstable condition of patients in the acute phase of ICH, complex and various evaluation measurements were not feasible. Therefore, we used CNFDS and BI during this period, both of which were practicable and time saving.

One key point necessary to discuss is the conflicting results between the CNFDS and the BI. Mechanisms that may physiologically underpin effects of acupuncture for ICH have been specifically investigated by recent work. A number of animal studies demonstrated that acupuncture can affect a variety of factors potentially related with ICH, such as reducing the expression of cytochrome C and p53 protein to decrease neuronal apoptosis, upregulating the expression of brain-derived neurotrophic factor and nerve growth factor to improve nerve regeneration, downregulating neuron-specific enolase expression to keep neuronal cell membrane integrity.[31]

If the mechanism of acupuncture effect for ICH is connected to factors that affect neural plasticity, measures used for acupuncture effect should be more intimately related to neurorecovery. In view of this, our results indicate that CNFDS might be a more responsive instrument that can detect the neurorecovery effect of acupuncture. As CNFDS is a specific assessment focusing on neurological function deficits resulting from the stroke, whereas BI is a globe instrument measuring ADL according to the degree of stroke and covering a wide range of performances, thus insufficient to detect changes in neurological function after stroke and not rationally related with the mechanisms that might account for effectiveness of acupuncture. Due to compensation of the unaffected limb,[32] patients who had poor neurological function may perform well in BI test. As such, there may be subtle improvements detected in the CNFDS that may not be presented in the BI. At this point, this pilot study is consistent with previous studies that have examined acupuncture treatment effects for ischemic stroke, which demonstrated similar result: When global measures are employed, no effects of acupuncture are detected. Conversely, when more sensitive measures are used, effects of acupuncture are obvious.[6] Therefore, we suggest that outcome instruments used in future studies assessing acupuncture effects on stroke should be valid, reliable, and sensitive enough to detect changes following stroke.

Some limitations of this study should be discussed. Although the evaluators in our study were blinded to the allocation of the patients, the patients were not. Using sham acupuncture was not regarded as a suitable control for our study, because it was hard to apply sham acupuncture. The majority of the patients or their families were acquainted with acupuncture; thus, they would easily notice the differences if given sham acupuncture and difficult to get the real feeling. For that reason, we adopted the conventional treatment as the control intervention. The sample size was calculated based on primary outcomes, so it was potentially underpowered for the second outcomes, which are used for safety evaluation. Due to the rigorous inclusion criteria and our choice not to include ischemic stroke patients or patients with previous strokes, we were not able to include enough patients for all the outcomes in a limited time. Therefore, clinical interpretations based on these results should be treated with caution.

In conclusion, the present study demonstrated a significantly greater hematoma absorption and improvement in CNFDS after penetration acupuncture treatment on head combined with conventional treatment compared with conventional treatment alone, whereas no significantly difference was found in BI. Penetration acupuncture treatment on head appeared to be safe over the course of treatment on acute ICH. However, due to the restriction of sample size, a larger trial incorporating a multicenter should be carried out before promoting this treatment widely. Furthermore, longer follow-up time in future work is also needed to assess the long-term effect, mortality and recurrence rate of this treatment.

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