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Effect of local mild hypothermia on regional cerebral blood flow in patients with acute intracerebral hemorrhage assessed by ^{99m}Tc-ECD SPECT imaging

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Abstract.
OBJECTIVE: This study aimed to observe the effect of local mild hypothermia on regional cerebral blood flow (rCBF) after acute intracerebral hemorrhage (ICH) and to evaluate its relation to clinical outcome in patients with ICH.
METHODS: 36 CT proven ICH patients with Glasgow coma scale (GCS) score of 5 or more were randomly assigned to 2 group: local mild hypothermia with conventional mannitol (Group A) or conventional mannitol (Group B). SPECT study was performed at day 7 after therapy. The SPECT images were semi-quantitatively analyzed, and the radioactivity ratios of lesion to normal tissue (L/NT) were calculated. National Institutes of Health Stroke Scale (NIHSS) were used in evaluation at days 14 and 21 after therapy.
RESULTS: There were significant differences in NIHSS score at days 14 and 21, and the L/NT ratios between the groups A and B ($P < 0.05$). Based on GCS, more patients in the group A showed favorable outcomes than patients in the group B ($P < 0.05$). Furthermore, the L/NT ratios significantly increased in patients with favorable outcomes compared to poor outcomes. Changes in NIHSS score at days 14 and 21 were closely negatively correlated with the L/NT ratios in the groups A and B ($r = -0.58$, -0.61, and -0.52, -0.75, respectively, $P < 0.05$).
CONCLUSION: Local mild hypothermia could significantly increase rCBF and improve clinical outcome in ICH patients as evaluated by ^{99m}Tc-ECD SPECT study.

Keywords: Local mild hypothermia, regional cerebral blood flow, intracerebral hemorrhage, SPECT imaging

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1. Introduction

Acute intracerebral hemorrhage (ICH) accounts for 10 to 15% of all strokes and is associated with poor outcome and high mortality [1]. The 1-month mortality rate accounts up to 40% [2]. Major factors contributing to secondary damage and worsened outcomes are hematoma expansion and edema [3]. Although the mechanisms that lead to hematoma growth and edema remain unclear, they commonly increase strongly during the first week and reach their maximum during the second week after ICH onset [4].

Although a variety of treatment strategies have been tested for ICH such as the surgical removal of the hematoma, and treatment of raised intracranial pressure, the prognosis of ICH is poor, because the efficacy of surgical and anti-edematous treatment strategies is limited [5]. However, recent experimental and clinical studies have demonstrated that mild hypothermia is useful for neuroprotection [6,7] and the treatment of cerebral edema [8,9] after acute brain injury, including brain trauma, ischemic stroke, and ICH. Mild hypothermia may reduce cerebral metabolism, decrease levels of excitatory amino acids, stabilize the blood-brain barrier, and account for membrane stabilization [10–12]. In mild hypothermia, systemic mild hypothermia is difficult to achieve in clinical practice due to its potential adverse effects, including pneumonia, shivering, and metabolic derangements [8,9], local mild hypothermia can achieve target temperature quickly, and overcome possible adverse effects [13], thus, its efficacy is superior to systemic mild hypothermia in neuroprotective therapies.

The regional cerebral blood flow (rCBF) is a useful surrogate marker of neuronal activity. Accurate measurement of rCBF is important for clinical evaluation of neurological diseases. The rCBF imaging with single-photon emission computed tomography (SPECT) is a noninvasive, simple, sensitive and specific functional imaging method, which has been widely used for predicting outcome in a variety of diseases including cerebrovascular disease [14], ischaemic stroke [15], ICH [16], migraine [17], and neurodegenerative diseases [18]. To the best of our knowledge, few studies about the effect of local mild hypothermia on rCBF in ICH patients was performed by SPECT. Therefore, we assessed consecutive ICH patients following the treatments of combined local mild hypothermia with mannitol or mannitol alone by ^{99m}Tc-ethyl-cysteinatedimer (^{99m}Tc-ECD) SPECT. We attempted to observe the characteristics of rCBF occurring in ICH patients after treatments, and its relation between changes of rCBF and neuro-function recovery as a means of assessing the value of SPECT for predicting clinical outcome in ICH patients after treatments.

2. Materials and methods

2.1. Patient selection

This study was based on 36 patients, 19 men and 17 women (age, 35 to 81 years; mean, 58.58 ± 13.69), who had suffered ICH and were admitted to the Neurocritical Intensive Care Unit between December 2007 and September 2008. The protocol was approval by the Ethics Committee of the study hospital, all patients or legally authorized representatives provided written informed consent when enrolling the study. Eligibility was based on clinical (Glasgow coma scale (GCS) score at least 5 or more) and CT evidence of ICH. Exclusion criteria included (1) ICH due to trauma and infections, intracerebral tumor; (2) enrolment $>$ 24 h after symptom onset; and (3) age $<$ 18 years. These patients were randomly assigned to 2 group: local mild hypothermia with conventional mannitol (Group A) or conventional mannitol (Group B). The group A were 19 cases, 11 men and 8 women (mean age, 60.21 ± 12.85). The group B consisted of 17 cases, including 8 men and 9 women (mean age, 58.59 ± 15.11). The average time from onset to therapy was 3.58 ± 1.45 hours, the average ICH volume were 12.51 ± 7.12 ml.

2.2. Basic management

All patients received standard medical treatment according to the Chinese national guidelines for diagnosis and treatment of ICH. Patients were administrated 20% mannitol 100 ml IV bolus infused within 20 min at a dose of 0.33 g/kg, and were mechanically ventilated because of poor level of consciousness or need of airway protection. Furthermore, hypotensive drugs were used for hypertension, balances of electrolyte were kept, and stress ulcer was prevented when necessary. Antipyretics were prescribed if tympanic temperature is higher than 37.5°C.

2.3. Local mild hypothermia therapy

Based on the above basic management, we began to cool 19 patients assigned to the local mild hypothermia using the local mild hypothermia applicator (HDB-01, Hyde Medical Equipment Development Co., Ltd. Harbin) placed on the patient's skull scalp with the lesion. Once the tympanic or nasopharyngeal temperature reached 33∼35°C using a temperature sensor (SL-4, Tongji Medical College, Huazhong University of Science Technology. Wuhan), it was kept between 33∼35°C for 72 hours. During the next 12∼20 hours, the patients were passively rewarmed to a temperature of 36.5 to 37.5°C at a rate no greater than 1°C per 4∼6 hours. No antipyretics were used during local mild hypothermia.

2.4. Image acquisition and reconstruction

A brain SPECT was performed in all patients, with the same camera, and under the same conditions. In patients, this exam was performed at day 7 post-therapy. The patients were injected intravenously at a dose of 740 MBq of ^{99m}Tc-ECD (Wuxi Jinagyuan industrial Technology and Trade Corporation) and were placed at rest for 1 h in a quiet environment with their eyes closed. SPECT imaging acquisition was carried out using a rotating double-head gamma camera (FORTE, Philips) equipped with low energy, high-resolution collimators. Imaging was taken at a rate of 20 seconds per frame through 180° rotation. The data were acquired on a 128 $\times$ 128 matrix with a 20% symmetric window at 140 keV. Images were reconstructed using a Butterworth filter and presented as transaxial, coronal and sagittal slices.

2.5. Image analysis

The evaluation of the images of ^{99m}Tc-ECD was done by two independent, experienced nuclear medical physicians. Regions of interest (ROIs) of lesion were drawn manually on images within transaxial slice recording the lowest lesion uptake. The same size ROI on opposite normal tissue was used as the reference and the radioactivity ratios of lesion to normal tissue (L/NT) were calculated.

2.6. NIHSS scores

The severity of clinical neurological defect in the two groups was assessed using the National Institutes of Health Stroke Scale (NIHSS) by a neurologist on admission, 14 and 21 day post-therapy, respectively.

2.7. Statistical analysis

Statistical tests were performed with the SPSS 16.0 software. The data were expressed as means $\pm$ standard deviation (SD), if not indicated differently. Single comparisons of NIHSS score at different

Table 1
Baseline characteristics on admission

	Group A ($n = 19$)	Group B ($n = 17$)	P
Age, y	60.21 ± 12.85	58.59 ± 15.11	0.11
The average time from onset to therapy, h	3.76 ± 1.48	3.58 ± 1.45	0.19
GCS score	8 (6∼11)	7 (6∼11)	0.12
NIHSS score	15.58 ± 4.43	15.53 ± 5.01	0.70
Hypothermia volume (mL)	14.38 ± 6.54	12.51 ± 7.12	0.56
IVH present	8/19	9/17	0.48

Values are represented as mean ± standard deviation or median and range when appropriate. GCS indicates Glasgow Coma Scale; IVH indicates intraventricular hemorrhage.

Table 2
Comparison of patient's outcome between the two groups (cases)

	Favorable outcome	Poor outcome	Total	Efficacy (%)
Group A	16	3	19	84.21
Group B	8	9	17	47.06
Total	24	12	36	66.67

$x^2 = 5.56$; $P < 0.05$.

Table 3
Comparison of the L/NT ratios in the two groups

	Cases	L/NT ratios
Group A	19	0.77 ± 0.10
Group B	17	0.63 ± 0.06
t		2.45

Values are represented as mean ± standard deviation.

time points in the two groups were performed using the nonparametric Mann-Whitney U test. The differences of NIHSS score and the L/NT ratios in the two groups were compared by t-test. Chi-square test was used for single comparison of GCS score after therapy in the two groups. The relation between NIHSS score and L/NT ratios was evaluated by the correlation coefficient (r). P value below 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

36 patients were randomized in the group A ($n = 19$, 11 male, 8 female) and group B ($n = 17$, 8 male, 9 female). As shown in Table 1, baseline characteristics on admission did not differ significantly between the groups A and B.

3.2. Clinical outcome after therapy

Among 36 patients, 24 had a favorable outcome (NIHSS score was 6.70 ± 2.42 at day 21), whereas 12 had a poor outcome (NIHSS score was 12.83 ± 2.88 at day 21, $P < 0.0001$). In the group A, GCS score improved in sixteen patients (84.21%), worsened in one (5.26%), and remained unchanged in two of the patients (10.53%). NIHSS score significantly decreased from 15.58 ± 4.43 on admission to 9.68 ± 2.66 and 6.89 ± 3.50 at days 14 and 21, respectively ($P < 0.05$). In the group B, on the other hand, GCS score improved in eight (47.06%), remained stationary in seven (41.18%), and deteriorated in two of the patients (11.76%). NIHSS score also decreased from 15.53 ± 5.01 on admission to 13.07 ± 3.43 ($P = 0.72$) and 10.93 ± 3.30 ($P < 0.05$) at days 14 and 21, respectively (Table 2, Fig. 1). As shown in Table 2, there was significant benefit of the group A compared to the group B ($P < 0.05$).

3.3. SPECT date after therapy

SPECT studies revealed that the lesion of hemorrhage could be identified at 1 h after injection with a lower radioactivity as compared with that in opposite normal tissue. In the group A, the radioactivity

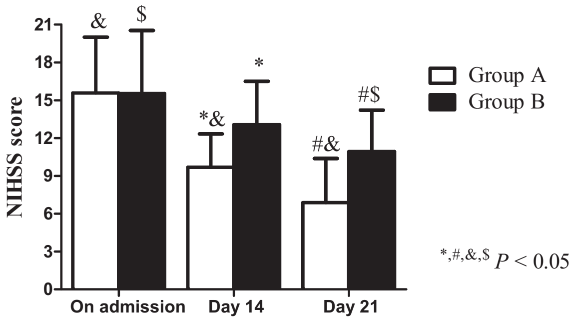

Fig. 1. Comparison of NIHSS score on admission, at days 14 and 21 in the two groups.

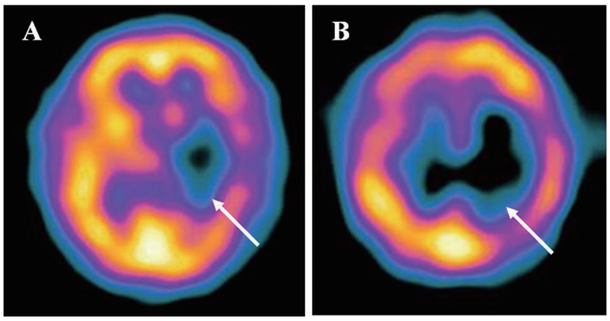

Fig. 2. Comparison of ^{99m}Tc-ECD SPECT imaging in the two groups at day 7 after therapy. A, Group A; B, Group B; White arrow is the hemorrhagic location. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/XST-140473)

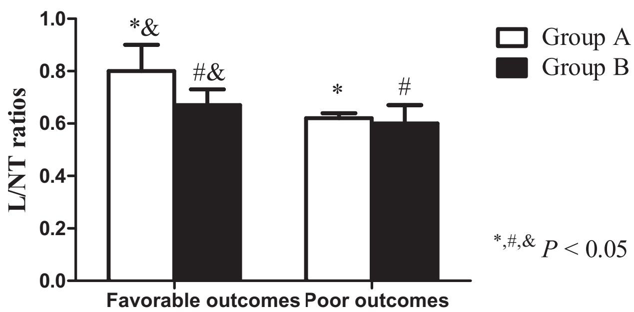

Fig. 3. Comparison of the L/NT ratios between the patients with favorable or poor outcomes in the two groups.

ratios of L/NT (lesion to normal tissue) were 0.77 ± 0.10. In the group B, the radioactivity of primary lesion at 1 h after injection was significantly lower with L/NT ratios of 0.63 ± 0.06. There was a significant difference of the L/NT ratios between the groups A and B ($P < 0.05$, Table 3, Fig. 2).

Figure 3 showed that in the two groups, the L/NT ratios in patients with favorable outcomes were significantly higher than that in poor outcomes (difference significant at $P < 0.05$). Moreover, For patients with favorable outcomes, the L/NT ratios in the group A was significantly higher than that in the group B (difference significant at $P < 0.05$), whereas for poor outcomes, difference of the L/NT ratios was not significant ($P = 0.64$).

3.4. Correlation analysis

As shown in Fig. 4, changes in NIHSS score in group A were closely negative correlated with the L/NT ratios at days 14, and 21 ($r = -0.58$, and -0.61, respectively, $P < 0.05$) (Fig. 4A). Similarly, changes in NIHSS score in group B were also closely negative related to the L/NT ratios ($r = -0.52$, and -0.57, respectively, $P < 0.05$) (Fig. 4B).

4. Discussion

The goal of this study was to evaluate the effect of local mild hypothermia on the regional cerebral

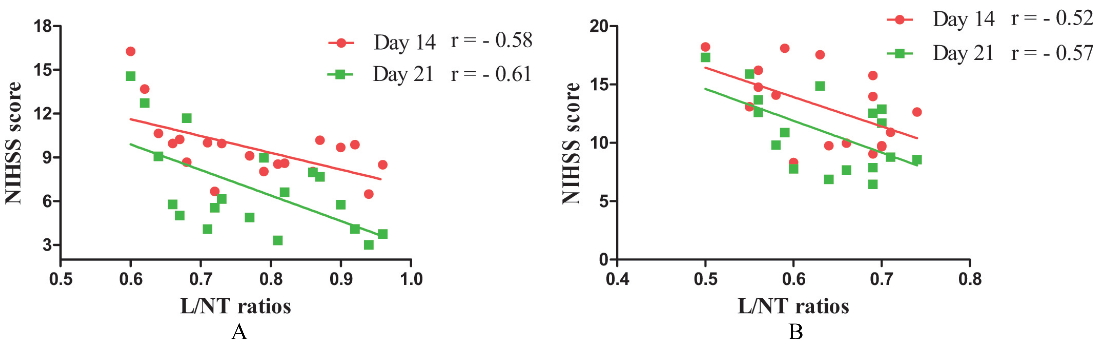

Fig. 4. Correlation between NIHSS score and the L/NT ratios in the two groups. A; Group A, B; Group B. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/XST-140473)

blood flow (rCBF) in patients with ICH via ^{99m}Tc-ECD SPECT imaging. Mean differences in L/NT (lesion to normal tissue) were used to estimate relative changes of rCBF, as previously reported [19,20]. This study showed that local mild hypothermia therapy could significantly increase rCBF as assessed by SPECT imaging at day 7 in ICH patients. The changes in rCBF were also supported by significant chances in GCS and NIHSS score in the two groups. The patients with ICH were performed SPECT imaging at day 7 after therapy, because the patients in acute phase of ICH were too sick to undergo SPECT study. We had therefore randomized those patients who were considered suitable for SPECT study.

Several clinical studies showed a positive effect of mild hypothermia on uncontrollable intracranial hypertension (ICP) after severe head trauma [21,22]. Head-injured patients treated with mild hypothermia between 32°C and 34°C core temperature had a significant reduction in ICP compared with the normothermia-treated control group. Studies indicated better outcome with mild hypothermia and a beneficial effect in limiting secondary brain injury. In most of these studies, mild hypothermia was delivered within the first 6 to 16 hours after head injury. Similar to these clinical studies, mild hypothermia was induced within 12 hours after symptom onset and continued for 72∼96 hours after ICH [8,9]. Mild hypothermia has the most positive effect when applied very early after ICH. Thus, in the study, we chose a relatively long duration of mild hypothermia (72 hours) to overcome maximum brain swelling, which is known to occur between 48 and 120 hours after ICH [23]. Our results are in agreement with Staykov report in which mild hypothermia therapy may improve clinical outcome in these patients [8]. Local mild hypothermia with mannitol can more significantly improve GCS and NIHSS score than mannitol alone, suggesting efficacy of combined Local mild hypothermia with mannitol was superior to conventional mannitol alone in ICH treatment. The improvement following mild hypothermia therapy is attributed to reduction of perihemorrhagic edema which results in aggravation of mortality [9]. Staykov et al. [8] demonstrated that mortality was relatively low in the mild hypothermia group, comprising only 8.3% after 3 months and 16.7% 1 year after symptom onset. Therefore, local mild hypothermia may represent a promising treatment approach for reduction of edema growth and improving clinical outcomes in such patients.

The prediction of clinical outcome after stroke is very important for setting therapeutic goals and minimizing medical costs. Imaging study of rCBF is one of key methods of evaluating the clinical outcome. Imaging study of rCBF includes MRI, CT, digital subtraction angiography (DSA), transcranial doppler (TCD), and SPECT. MRI and CT are structural imaging, and primarily depend on perfusion studies, their specificities and sensitivities for assessing rCBF are relatively low, because their contrast agents are not able to crosses the blood-brain barrier [24]. DSA with the optical flow method (OFM) is a recent developed technology for intracranial blood flow measurements [25], but its invasive nature is often not accepted by patients in clinical settings. TCD is faster and has superior temporal resolution for evaluating intraluminal flow, but it is vulnerable to inter-observer variations and has limited access to the entire intracranial vasculature due to the thickness of the cranial bones [25]. ^{99m}Tc-ECD SPECT imaging, which reflects not only the rCBF but also cellular function, has relatively high sensitivity and specificity, it can be attributed to the ability of ^{99m}Tc-ECD to cross the blood-brain barrier and become trapped in the brain tissue. A number of ^{99m}Tc-ECD SPECT imaging have been discussed to predict outcome during the acute stage of stroke [14–16].

The SPECT imaging before and after therapy in acute phase of ICH is not possible on the same day due to patient's condition. The stay of radiotracer in the circulation does not allow the repeat study on the same day. In the ICH patient, the cerebral edema and the blood flow may change over a period of next few days. Kalita et al. showed that SPECT study in a critically ill patient or deep coma (GCS < 5) is limited by motion artifacts, which render rCBF ratios evaluation invalid [26]. In the study, we excluded patients who were deeply comatose (GCS < 5) and performed SPECT imaging at day 7 after therapy, when the patients were in relatively stable states. Therefore, we had satisfactory SPECT images. Our patient baseline characteristics on admission were homogenous comprising of ICH volume and both the groups A and B were comparable as per GCS score, other clinical, and CT scan parameters. The radioactivity ratios of L/NT of rCBF in the group A were significantly higher than that in the group B. Moreover, more patients in the group A showed favorable outcomes than patients in the group B. The L/NT ratios in patients with favorable outcome also significantly higher than that in poor outcome, demonstrating the L/NT ratios of rCBF may match with clinical outcomes. Correlation analysis also showed that the severity of clinical neurological defect (NIHSS score) after therapy was closely negatively correlated with the L/NT ratios of rCBF. It seems to indicate that the L/NT ratios of rCBF might be useful for predicting clinical outcome in such patients after treatment.

This study is primarily limited by its small sample size, single-blinding, one time point of SPECT imaging, and a semi-quantitative measure of rCBF. In the future, comprehensive studies should be considered, these strategies will cover multiple centers and a large patient population, and include different time points of SPECT imaging, and quantitative measure of rCBF, such as non-invasive Patlak plot method [27], Statistical Parametric Mapping (SPM) [28], and image quality parameters [29].

5. Conclusion

Local mild hypothermia could increase rCBF and improve outcomes in patients with ICH. The results might reflect the physiological model of rCBF recovery at lower head temperature and undermine the use of ^{99m}Tc-ECD SPECT as a rapid and non-invasive method to monitor cerebral hemodynamics during local mild hypothermia treatment.

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