The Effect of Cerebrovascular Stenosis on Peri-Hematoma Cerebral Perfusion and Clinical Outcomes in Patients with Supratentorial Spontaneous Intracerebral Hemorrhage

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Background: Many factors are associated with the cerebral hypoperfusion after spontaneous intracerebral hemorrhage (sICH), however, the effect of cerebrovascular stenosis on peri-hematoma cerebral blood flow (CBF) and 90-day poor outcomes in patients with spontaneous intracerebral hemorrhage is still unclear.

Material/Methods: From September 2016 to March 2017, we prospectively collected data on adults with supratentorial spontaneous intracerebral hemorrhages. Using the Propensity Score model, we compared the peri-hematoma CBF and 90-day poor outcomes (mRS ≥3) in the stenosis group and the control group.

Results: Before matching, a total of 116 patients were included in this study, 25 patients in the stenosis group and 91 patients in the control group. After matching, the patients in the stenosis group had a higher absolute decrease of CBF (p=0.003), higher relative decrease of CBF (p=0.016), and higher incidence of 90-day poor outcomes (p=0.041) than the control group. With subgroup analysis, the patients with Glasgow Coma Scale from 13 to 15 (p=0.035), hematoma in the cerebral lobe (p=0.003), mean arterial pressure lower than 120 mm Hg (p=0.003), absolute decrease of CBF higher than 15 mL/100 g per minute (p=0.007), and relative decrease of CBF higher than 30% (p=0.020) had poorer outcomes.

Conclusions: In our series, the stenosis of main cerebral vessels decreased the peri-hematoma CBF and increased the rate of 90-day poor outcomes. Despite higher Glasgow Coma Scale, the evaluation of cerebral perfusion in patients with sICH is needed, especially for the patients with hematoma in the cerebral lobe and lower mean arterial pressure; and treatments to keep adequate cerebral perfusion are needed.

MeSH Keywords: Intracranial Hemorrhages • Perfusion Imaging • Propensity Score • Stroke

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Background

Almost one million patients suffer from spontaneous intracerebral hemorrhage (sICH) every year, worldwide [1,2]; sICH is the second cause of strokes and is associated with high mortality [3] and morbidity [1,4]. Brain ischemia is the major complication of sICH, and has a high incidence of 23–41% during the first weeks after onset. [5,6] The ischemic penumbra refers to the area surrounding the hematoma, which has a high incidence of brain ischemia or infarction due to its high sensitivity to decreased cerebral blood flow (CBF) [7]. Furthermore, brain ischemia or infarction is associated with the poor outcomes in patients with sICH [5,8].

Some factors are associated with brain ischemia after sICH, such as cerebrovascular stenosis, microbleeds, leukoaraiosis, and blood pressure (BP) reduction [5,8]. A prospective study [6] of 97 cases showed the microbleeds increased new ischemic lesions on diffusion-weighted imaging; and a randomized controlled trial [9] found that relative CBF had no obvious changes after BP reduction in patients with sICH. However, the effect of cerebrovascular stenosis on the peri-hematoma CBF and clinical outcomes in sICH patients had not been previously discussed in the literature.

Cerebrovascular stenosis has a high incidence in patients with sICH, about 20–50% [10], including intracranial cerebrovascular stenosis and extracranial cerebrovascular stenosis [11]. The main intracranial cerebral vessels include posterior circulation (basilar artery and vertebral artery) and anterior circulation including posterior cerebral artery, middle cerebral artery, anterior cerebral artery, and internal carotid artery. The patients with stenosis of main cerebral vessels had a hypoperfusion in ischemic penumbra [12,13] and had a higher risk of ischemic stroke with decreased CBF [14,15]. A previous study [16] showed CBF significantly decreased when the severity of cerebrovascular stenosis was higher than 50%. Theoretically, the stenosis of main cerebral vessels would result in a decrease of cerebral perfusion. Meanwhile, the lager hematomas tend to aggravate the decrease of CBF in ischemic penumbra [17,18]. When the decrease of peri-hematoma CBF is more than 34% [19,20] compared with the contralateral homologous reign, the patients have a high risk of ischemic stroke and 90-day poor outcomes.

Thus, to provide evidence for clinical practice, we performed a study based on prospective data to verify the effect of cerebrovascular stenosis on the peri-hematoma CBF and 90-day poor outcomes in sICH patients.

Material and Methods

Patient selection

The study was approved by the Biological and Medical Ethics Committee of West China Hospital and was performed in the Department of Neurosurgery in West China Hospital, Sichuan University. This study was based on the early stage data of ATICHST trial and prospectively included the consecutive patients with sICH between September 2016 and March 2017. The inclusion criteria were as follows: the adult (>18 years of age) diagnosed with supratentorial sICH by non-contrast computed tomography (NCCT). The exclusion criteria were as follows: secondary ICH caused by intracranial aneurysm, arteriovenous malformation, tumor stroke, or anticoagulant correlation hemorrhage; Glasgow Coma Scale (GCS) ≤3; with operation indication of evacuation of intracranial hematoma; disabled or severe medical comorbidities (kidney failure, severe cardiac insufficiency, malignant tumor) before sICH; contraindication to computed tomography (CT) perfusion (CTP) imaging.

Clinical data

The baseline data of patients were collected by a special researcher in department of emergency, including gender, age, GCS, admission BP, history of hypertension, diabetes, stroke, medications, location and volume of hematoma, location and level of stenosis. The technician who was blinded to this research evaluated the peri-hematoma CBF by CTP and brain ischemia using the last NCCT before discharge. By telephone follow-up, two neurosurgeons who were not involved in the study design and assignment evaluated the 90-day clinical outcomes, including 90-day poor outcomes and 90-day mortality. The poor outcomes were defined as modified Rankin Scale (mRS) ≥3 and the death was mRS of 6.

Imaging data and analysis

The NCCT and CT angiography (CTA) were performed on a 64-slice CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector, Forchheim, Germany). Upon admission, NCCT (5-mm slice, 120 kvp, 340 mA) was performed on the whole brain of patients and CTA scans were triggered after infusion of 100 mL contrast at a speed of 4.8 ml/second (1-mm slice, 80 kvp, 110 mA and pitch 1: 1). Cerebrovascular stenosis was evaluated by the three-dimensional reconstruction of CTA scans and the two-dimensional gray-scale MPR images with window level and window width of 500 and 1,000 HU [21]. Although the definition of cerebrovascular was the reduction of diameter ≥50% [22–24] detected by Digital Subtraction Angiography (DSA), the cutoff value of reduction of diameter was 30% on CTA to detect the reduction ≥50% on DSA [25]. The patients were assigned to the stenosis group when the stenosis of the
main cerebral vessels was more than 30% [23,26] on CTA, while the patients with cerebrovascular stenosis lower than 25% were assigned to the control group. As for the reduction from 25% to 30%, another technician evaluated the severity of stenosis again and assigned the patients to a group. After 24 hours from admission, the CTP were conducted to assess the peri-hematoma CBF. The scans of CTP (1-mm slice, 70 kvp, 150 mA) were collected every 1.5 seconds with at least 50 second-delay after infusion of 42 mL contrast. The region of 1 cm from the circumference of parenchymal hematoma was defined as the peri-hematoma penumbra [18]. The blood vessels, subarachnoid and intraventricular space were excluded from the region [27–29]. We calculated the mean decrease of peri-hematoma CBF of all voxels and the relative decrease to the contralateral homologous regions.

Statistical analysis

All of the data were analyzed using IBM SPSS Statistics, version 13.0 (IBM, Armonk, NY, USA). The continuous variables were analyzed by Student t-test and the categorical variables were examined by the Pearson’s chi-squared test. Stenosis group and control group were matched one by one based on the estimated propensity scores of each patient, using nearest neighbor matching with no replacement [30]. With the Propensity Score (PS) model, the following variables were considered as the covariates: age, gender, time from onset to initial treatment, Glasgow Coma Scale, medical history, location of hematoma, baseline hematoma volume, systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), heartbeat, left hemisphere site of hematoma and intraventricular extension. The clinical outcome was divided into good outcome (mRS <3) and poor outcome (mRS ≥3). The subgroup analysis were performed by age, Glasgow Coma Scale location of hematoma, baseline hematoma volume, MAP, left hemisphere site of hematoma, intraventricular extension, absolute decrease of CBF, and relative decrease of CBF (relative decrease=1-(peri-hematoma CBF/contralateral homologous regions CBF)). Statistical significance was defined as $p<0.05$.

Results

From September 2016 to March 2017, a total of 116 patients meet the inclusion criteria: 25 patients (22%) were assigned to stenosis group (among them 20 patients (17.2%) were diagnosed with extracranial cerebrovascular stenosis, and five patients (4.3%) had intracranial cerebrovascular stenosis), and 91 patients (78%) were assigned to the control group. The demographic data upon admission are summarized in Table 1. Before PS matching, there was a significant difference between the two groups in age, Glasgow Coma Scale, history of stroke, and smoking.

The baselines of the two groups were well matched. The mean age of the two groups was 66.12 years, ranging from 38 to 86 years. Forty-one patients were admitted within 24 hours after onset and nine patients were admitted within 72 hours. Five patients had coma (GCS ≤8) upon admission and the consciousness of 27 patients was affected slightly by sICH (GCS ≥13). Three patients had a history of ischemic stroke and the rest three patients underwent hemorrhagic stroke previously. The hematoma was located in the basal ganglia (46%), thalamus (16%), and cerebral lobe (18%) respectively. The mean hematoma volume was 17.51 mL, and 36 hematomas (72%) were between 10 mL and 30 mL. The MAP was 117.65 mm Hg, 38 MAP values (76%) were from 100 mm Hg to 135 mm Hg. Nineteen patients (38%) coexisted with the intraventricular extension.

After PS matching, the absolute decrease of peri-hematoma CBF and relative decrease of peri-hematoma CBF was significantly higher in the stenosis group than the control group ($p=0.003$ and $p=0.016$, Table 2). Nine patients during hospitalization, six of the nine patients (67%) were in the stenosis group. Five patients died within 90 days after discharge, and four of the five patients (80%) were in the stenosis group. A total of 31 patients (62%) had poor outcomes, of which 19 patients (76%) were in the stenosis group and 12 patients (48%) were in the control group. There was a significant difference between the two groups in 90-day poor outcomes ($p=0.041$). After subgroup analysis of 90-day poor outcomes (Table 3), we found that patients in the stenosis group had worse outcomes, especially in patients with GCS from 13 to 15 ($p=0.035$), hematoma in the cerebral lobe ($p=0.003$), MAP lower than 120 mm Hg ($p=0.003$), absolute decrease of peri-hematoma CBF higher than 15 ($p=0.007$), and relative decrease of peri-hematoma CBF higher than 30% ($p=0.020$).

Discussion

This study was based on the prospective data of ATICHST trial [31], which was a randomized clinical trial and discussed the effect of anti-hypertensive treatments on the outcomes of sICH patients with cerebrovascular stenosis. From this study, we found that stenosis decreased peri-hematoma CBF, which would increase the risk of 90-day poor outcome, especially in patients with hematoma in cerebral lobe, lower MAP, and substantial reduction of peri-hematoma CBF.

To the best of our knowledge, this study was the first study to discuss the effect of stenosis on the peri-hematoma CBF and clinical outcomes in sICH. Brain perfusion was influenced by the cerebrovascular stenosis. One study [12] included the patients with stenosis of the opposite internal carotid artery 50–60%, and found that peri-hematoma CBF decreased about...
### Table 1. Characteristics of subjects with supratentorial spontaneous intracerebral hemorrhage before and after Propensity Score Matching by cerebrovascular stenosis or not.

| Variables                          | Stenosis group (n=25) | Control group (n=91) | P       | Stenosis group (n=25) | Control group (n=25) | P       |
|------------------------------------|------------------------|----------------------|---------|------------------------|----------------------|---------|
| **Before matching**                |                        |                      |         |                        |                      |         |
| Age, years                         | 67.04±11.70            | 57.89±12.08          | 0.001   | 67.04±11.70            | 65.19±13.84          | 0.543   |
| Male                               | 19                     | 71                   | 0.830   | 19                     | 16                   | 0.355   |
| Time from onset to initial treatment | 10.48±12.95           | 11.97±13.04          | 0.613   | 10.48±12.95           | 11.85±12.41          | 0.704   |
| **Stenosis group**                 |                        |                      |         |                        |                      |         |
| **Control group**                  |                        |                      |         |                        |                      |         |
| Glasgow coma scale                 | 3–8                    | 2                    | 0.150   | 14                     | 13                   | 0.776   |
|                                   | 9–12                   | 2                    | 0.305   | 2                      | 1                    | 0.552   |
|                                   | 13–15                  | 14                   | 0.028   | 12                     | 10                   | 0.567   |
| History                            |                        |                      |         |                        |                      |         |
| Hypertension                       | 14                     | 47                   |         | 14                     | 13                   |         |
| Diabetes                           | 2                      | 3                    | 0.006   | 4                      | 2                    | 0.384   |
| Stroke                             | 4                      | 2                    | 0.061   | 2                      | 1                    | 0.552   |
| Smoker                             | 12                     | 23                   | 0.227   | 12                     | 10                   | 0.567   |
| Alcohol                            | 7                      | 31                   | 0.567   | 7                      | 8                    | 0.758   |
| Location of hematoma               |                        |                      | 0.199   |                        |                      | 0.323   |
| Basal ganglia                      | 14                     | 49                   |         | 14                     | 19                   |         |
| Thalamus                           | 5                      | 8                    |         | 5                      | 3                    |         |
| Cerebral lobe                      | 6                      | 34                   |         | 6                      | 3                    |         |
| Baseline hematoma volume, ml       | 17.99±23.30            | 15.86±21.44          | 0.667   | 17.99±23.30            | 17.02±21.95          | 0.880   |
| Systolic BP, mmHg                  | 162.96±20.52           | 171.43±30.09         | 0.188   | 162.96±20.52           | 164.08±23.24         | 0.857   |
| Diastolic BP, mmHg                 | 94.28±11.61            | 97.50±15.57          | 0.338   | 94.28±11.61            | 95.16±15.42          | 0.821   |
| Mean arterial pressure, mmHg       | 117.17±13.53           | 122.14±19.15         | 0.227   | 117.17±13.53           | 118.13±17.49         | 0.829   |
| Heart beat                         | 86.04±13.96            | 79.21±18.54          | 0.090   | 86.04±13.96            | 82.15±15.61          | 0.262   |
| Left hemisphere site of hematoma   | 7                      | 42                   | 0.104   | 7                      | 9                    | 0.544   |
| Intraventricular extension         | 11                     | 35                   | 0.616   | 11                     | 8                    | 0.382   |

BP – blood pressure; Data are mean ±SD or number of patients.

### Table 2. outcomes analysis.

| Variables                          | Stenosis group (n=25) | Control group (n=25) | P values |
|------------------------------------|------------------------|----------------------|----------|
| Absolute reduce of peri-hematoma CBF | 19.19±9.26             | 11.95±6.88           | 0.003    |
| Relative reduce of peri-hematoma CBF | 0.374±0.148            | 0.267±0.155          | 0.016    |
| Incidence of brain ischemia        | 8                      | 6                    |          |
| In-hospital mortality              | 6                      | 3                    | 0.440    |
| 90-days mortality                 | 10                     | 4                    | 0.058    |
| Poor outcomes at 90-days           | 19                     | 12                   | 0.041    |

CBF – cerebral blood flow; Data are mean ±SD or number of patients.
36% compared with the healthy side. Merckel et al. [13] demonstrated that perfusion CT revealed the decrease of peri-hematoma CBF due to the stenosis in patients with brain ischemia, and the CBF increased from 81% to 93% after treatments, such as carotid endarterectomy (CEA). With the decrease of CBF, asymptomatic brain ischemia can be commonly detected by MRI in sICH [8,14], meanwhile, patients with cerebrovascular stenosis have a potential risk for ischemic stroke [14,15]. In the present study, we found the presence of cerebrovascular stenosis significantly decreased the peri-hematoma CBF (Figure 1) by 7.2% compared with the control group in sICH patients (Figure 2). Previous studies [19,20] have suggested that the brain tissue is ischemic when the relative CBF decreased by 34% compared with the healthy side. We found the mean relative CBF in the stenosis group was about 37.4% (Table 1), which suggested that sICH patients with cerebrovascular stenosis had a higher risk of brain ischemia (Figure 1). However, there was no significant difference between the two groups in incidence of brain ischemia by NCCT, which may be attributed to the fact that some cases with asymptomatic brain ischemia might be detected by MRI [8,14] but not NCCT.

Recently, management of blood pressure was a hot topic in the treatment of sICH. A study [5] of 118 patients evaluated the factors to the prediction of brain ischemia by diffusion-weighted imaging and found the diffusion-weighted imaging was abnormal when MAP was lower by 40%. Another prospective study [8] of 95 patients found the greater BP reduction was associated with decreased diffusion and increased three-months poor outcomes. A randomized clinical trial [9] of 75 patients demonstrated the peri-hematoma CBF in 150 mm Hg group was significantly lower than 180 mm Hg group, while the relative peri-hematoma CBF had no significant difference between two groups. However, they did not discuss the effect of intensive BP lowering on the CBF in sICH patients with cerebrovascular stenosis by subgroup analysis. The ongoing ATICHST trial [25] was supplement for previous RCT and evaluated the effect of intensive BP lowering to sICH patients with cerebrovascular stenosis. In patients with bilateral carotid stenosis, many factors [32,33] affected the prognosis and one study [34] suggested the simultaneous bilateral carotid stenting was more effective and safer compared with medical management, while there was no studies that discussed the treatment of sICH patients with cerebrovascular stenosis for

| Variables                                    | Stenosis group (n/N) | Control group (n/N) | P values |
|----------------------------------------------|----------------------|---------------------|----------|
| Age                                          |                      |                     |          |
| ≥65                                          | 12/17                | 7/16                | 0.119    |
| <65                                          | 7/8                  | 5/9                 | 0.149    |
| Glasgow coma scale                           |                      |                     |          |
| 3–8                                          | 2/2                  | 2/3                 | 0.361    |
| 9–12                                         | 7/9                  | 6/9                 | 0.598    |
| 13–15                                        | 10/14                | 4/13                |          |
| Location of hematoma                         |                      |                     |          |
| Basal ganglia                                | 9/14                 | 11/19               | 0.837    |
| Thalamus                                     | 4/5                  | 1/3                 | 0.187    |
| Cerebral lobe                                | 6/6                  | 0/3                 | 0.003    |
| Baseline hematoma volume, ml                 |                      |                     |          |
| <25                                          | 14/19                | 9/17                | 0.086    |
| ≥25                                          | 5/6                  | 3/8                 | 0.196    |
| Mean arterial pressure, mmHg                 |                      |                     |          |
| <120                                         | 12/13                | 6/10                | 0.002    |
| ≥120                                         | 7/12                 | 6/15                | 0.343    |
| Left hemisphere site of hematoma             | 6/7                  | 4/9                 | 0.091    |
| Intraventricular extension                   | 8/11                 | 7/8                 | 0.435    |
| Absolute reduce of peri-hematoma CBF         |                      |                     |          |
| <15                                          | 5/8                  | 9/15                | 0.907    |
| ≥15                                          | 14/17                | 3/10                | 0.007    |
| Relative reduce of peri-hematoma CBF         |                      |                     |          |
| <30%                                         | 3/6                  | 5/10                | 0.463    |
| ≥30%                                         | 16/19                | 7/15                | 0.020    |
maintain the cerebral perfusion. We found the 90-day poor outcomes in two groups was significantly different when MAP was lower than 120 mm Hg, which suggested the BP of sICH patients with cerebrovascular stenosis should be maintain at a higher level to keep the cerebral perfusion.

The peri-hematoma perfusion impairments in some patients needed early treatment to improve the residual function, and lower CBF may result in secondary neuronal injury and poor clinical outcomes [35]. CT perfusion was used to evaluate the delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage and cerebral hypoperfusion was associated with the poor neurologic outcomes [36,37]. We found that lower CBF increased the risk of 90-day poor outcomes in sICH patients with stenosis, and the threshold values were 15 mL/100 g per minute for absolute decrease of peri-hematoma CBF or 30% relative decrease of peri-hematoma CBF. Some studies [38,39] also showed a similar threshold to predict the poststroke hemorrhagic transformation or poor outcome. In China, the patients with ICH are examined by CT and CTA upon admission, while the CTP is not a routine examination after ICH. However, CTP could help to identify patients who need improvement of cerebral perfusion to improve their outcomes. Thus, the CTP would be necessary for sICH patients who coexisted with cerebrovascular stenosis.
Limitation

Although this study was based on prospective data, it was limited to a single institution without a large sample size, which may result in statistical bias. Due to the limited number of patients in the stenosis group, the subgroup analysis of different cerebral arteries in stenosis group could not be performed. With the progress of ATICHST trial results, the effect from different main arteries on the CBF and clinical outcomes will be discussed more fully. In subgroup analysis, the number of patients with GCS from 3 to 8 was too small, and we could not give a conclusion whether the cerebrovascular stenosis had a significant effect on the 90-day outcomes in patients with different GCS. This issue could be discussed with the increasing sample size in our trial.

Conclusions

In the present study, we find that cerebrovascular stenosis will aggregate the ischemia of peri-hematoma area due to decrease of CBF. In addition, patients with cerebrovascular stenosis had a high risk of 90-day poor outcomes. The CTP is necessary for sICH patients upon admission, to identify the patients who have low cerebral perfusion and are prone to ischemic stroke. Especially for the patients with hematoma in cerebral lobe and lower MAP, treatments to keep adequate cerebral perfusion are essential.

Conflicts of interest

None.

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