Clinical Study

Whole-brain CT perfusion combined with CT angiography for ischemic complications following microsurgical clipping and endovascular coiling of ruptured intracranial aneurysms

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1. Introduction

Rupture of an intracranial aneurysm causes aneurysmal subarachnoid hemorrhage (SAH), which is a serious clinical condition that occurs without warning [1]. Microsurgical clipping and endovascular coiling are the preferred treatment modalities for aneurysmal patients with SAH. The outcome of postoperative aneurysmal SAH is affected by ischemic complications, including treatment- and disease-associated events [1]. The typical treatment-associated ischemic complications are thromboembolism, injury to the parent vessel and occlusion of arteries as a result of clipping or coiling [2,3]. Delayed cerebral ischemia associated with vasospasm is the main disease-associated complication [4]. The incidence of postoperative ischemic complications associated with treatment and vasospasm in patients with intracranial aneurysms varies widely and ranges from 7.6% to 65% [5–7]. For timely management of ischemic complications, a neuroimaging diagnostic tool is needed to identify patients with acute clinical deterioration.

This study was conducted to determine whether ischemic complications following microsurgical clipping or endovascular coiling of ruptured intracranial aneurysms can be classified and detected early using a combination of whole-brain CT perfusion (WB-CTP) and CT angiography (CTA).

2. Methods

The protocol was approved by the local Ethics Committee and informed consent was obtained from all the patients and/or their legal representatives prior to study enrollment.

2.1. Patients

The study prospectively enrolled 261 consecutive patients who were scheduled for acute treatment of ruptured intracranial aneurysms at our hospital from March 2013 to November 2014.
The diagnosis of SAH was based on clinical presentation and CT scan. The presence of intracranial aneurysms was confirmed by digital subtraction angiography (DSA) or CTA. All patients with SAH underwent surgical treatment for the aneurysm within 72 hours of diagnosis. Patients who had sudden neurologic deterioration or presented with poor grade (Hunt-Hess grade ≥ II), large aneurysm size (>13 mm) and multiple aneurysms (n ≥ 2) after surgery were included in this prospective study. Patients with ischemic lesions as confirmed by unenhanced CT scan before surgery were included in this prospective study. With the same data set, the CTA of the entire intracranial circulation was reconfigured to a thickness of 0.75 mm. The subtraction and presubtraction CTA were reviewed by two neuroradiologists using volume-rendered and multplanar reformatted images. Both CTA images were evaluated for the presence of residual flow in intracranial aneurysms, and the relationship between the clipping or coiling and the parent vessels and perforating arteries, and stenotic changes or vasospasm in the parent or neighboring artery. In case of disagreement, the radiologists re-evaluated the findings until a consensus was reached.

2.4. CTA data processing and analysis

With the same data set, the CTA of the entire intracranial circulation was reconfigured to a thickness of 0.75 mm. The subtraction and presubtraction CTA were reviewed by two neuroradiologists using volume-rendered and multplanar reformatted images. Both CTA images were evaluated for the presence of residual flow in intracranial aneurysms, and the relationship between the clipping or coiling and the parent vessels and perforating arteries, and stenotic changes or vasospasm in the parent or neighboring artery. In case of disagreement, the radiologists re-evaluated the findings until a consensus was reached.

2.5. Determination of ischemic complications

Postoperative ischemic events were identified based on perfusion abnormalities on WB-CTP scans. Infarction was confirmed if new lesions were found on the follow-up CT scan or MRI. We ensured that the new lesion had not been observed on the preoperative CT scan and was not related to intracerebral hemorrhage, ventricular drain placement, or any other nonvascular event. Stenotic change or occlusion in the parent or neighboring artery as a result of clipping or coiling was evaluated by CTA. Vasospasm was defined as evidence of arterial narrowing compared with the parent vessel or baseline examination by CTA. Patients who had atherosclerosis-induced vessel narrowing were excluded. The modified Rankin score [9] was evaluated in patients with infarction at the 3 month follow-up.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as counts and/or frequencies. Owing to the small number of patients in individual groups, descriptive statistical analysis was performed for most parameters. A paired t-test was conducted on groups with a larger number of cases. A p value less than 0.05 was considered to be significant in all tests. Statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Clinical characteristics

In total, 73 intracranial aneurysms were identified in 58 patients (25 men and 33 women; mean age, 52 ± 11 years). Thirty-six patients developed clinical deterioration after treatment, including headache (n = 21), aphasia (n = 5), hemiplegia (n = 7), and loss of consciousness (n = 3). The other 22 patients presented with Hunt-Hess grade ≥ III, aneurysm size >13 mm and multiple aneurysms, without any definite clinical symptoms. The clinical characteristics of the patients and aneurysms are shown in Table 2. Of the 58 patients, 44 were treated with microsurgical clipping and nine with endovascular coiling; five with multiple aneurysms were managed with both treatments. The complications of the studied patients and the modified Rankin score at 3 month follow-up in patients with cerebral infarction are summarized in Table 3.

3.2. WB-CTP and CTA results

3.2.1. Treatment-associated ischemic complications

Of the 58 patients, 15 (26%) had perfusion abnormalities indicative of treatment-associated vascular injuries, as identified by WB-CTP and CTA. Among these 15 patients, the diameter of the parent vessels was reduced in six patients as a result of clipping...
woman with a ruptured anterior communicating artery aneurysm (Hunt-Hess grade II) and was treated by microsurgical clipping. Unfortunately, she developed right hemiparesis 10 hours after the procedure. CTA showed that her left anterior communicating artery was compressed as a result of the clipping, and the diameter of the parent vessel was reduced as well (Fig. 1A, B). Furthermore, WB-CTP demonstrated reversible impaired perfusion in her left cerebral hemisphere (Fig. 1D–I). Twelve hours later, repeated CT scan identified infarction in her left frontal lobe (Fig. 1C).

3.2.3. Occlusion of the parent vessels or perforating arteries

CTA revealed that two patients had occlusion of the parent vessels or perforating arteries as a result of clipping. WB-CTP revealed decreased ipsilateral CBF and CBV, and increased TTP, TTD and MTT compared to the contralateral side. Follow-up CT scan identified cerebral infarction. For example, one patient was a 44-year-old man with a ruptured bifurcation aneurysm of the middle cerebral artery (MCA) (Hunt-Hess grade II) (Fig. 2A) who was treated by microsurgical clipping. He developed confusion after the procedure. CTA showed that the perforating arteries of the MCA were ligated as a result of the clipping (Fig. 2B). WB-CTP demonstrated irreversible impaired perfusion in his left cerebral hemisphere (Fig. 2C, 2E–N). Twelve hours later, repeat CT scan identified a stroke in the left temporal and occipital lobes in this patient (Fig. 2D).

3.2.4. Unexplained or indistinguishable vascular injury

CTA clearly demonstrated that the parent vessels or perforating arteries close to the site of the clipping or coiling were preserved in 6 patients, but it failed to demonstrate vascular injury due to coil-related artifacts in one patient. WB-CTP revealed decreased ipsilateral CBF (affected versus contralateral side: 37.03 ± 10.83 versus 52.63 ± 5.62 ml/100 ml/minute, \( p = 0.01 \)), decreased normal CBV (affected versus contralateral side: 2.38 ± 0.70 versus 3.26 ± 0.35 ml/100 ml, \( p = 0.02 \)), and increased TTP, TTD and MTT (affected versus contralateral side: TTP 14.28 ± 3.74 versus 11.09 ± 3.99 seconds, \( p = 0.001 \); TTD 7.96 ± 1.41 versus 4.40 ± 0.36 seconds, \( p = 0.001 \); MT 5.45 ± 1.01 versus 4.02 ± 0.36 seconds, \( p = 0.01 \)) in all the seven patients. Furthermore, all the patients developed cerebral infarction. For example, one patient was a 47-year-old man with a ruptured aneurysm of the right anterior choroidal artery and unruptured aneurysms of the left anterior choroidal artery and paracerebral internal carotid artery (Hunt-Hess grade III), who was treated by microsurgical clipping and endovascular coiling. He developed left hemiplegia after the procedure. CTA failed to demonstrate his vascular injury due to coil-related artifacts (Fig. 3A, B). However, WB-CTP showed an irreversible ischemic lesion in his left cerebral hemisphere (Fig. 3C–H). Twelve hours later, repeat CT scan confirmed the presence of multiple anterior cerebral artery territory infarcts (Fig. 3I).

3.2.5. Disease-associated ischemic complications

Fifteen of the 58 patients (26%) had perfusion abnormalities indicative of vasospasm, as identified by WB-CTP and CTA. Of these, 11 were treated with microsurgical clipping and three with endovascular coiling; one patient with multiple aneurysms was treated with both methods. The follow-up CT scan revealed that six of the 15 (40%) patients had vasospasm-related cerebral infarction.

3.2.6. Focal vessel vasospasm

We found that nine patients had CTA abnormalities related to focal vessel vasospasm. In two out of the nine patients, WB-CTP revealed increased TTP, TTD, and MTT, decreased CBF, and decreased or normal CBV; the follow-up CT scan also found infarction. However, in the other seven patients, we found increased TTP,
TTD, and MTT (affected versus contralateral side: TTP 12.44 ± 1.74 versus 11.07 ± 1.77 seconds, $p=0.001$; TTD 6.14 ± 0.59 versus 4.8 ± 0.33 seconds, $p=0.001$; MTT 4.93 ± 0.51 versus 3.72 ± 0.87 seconds, $p=0.003$), and normal CBF and CBV (affected versus contralateral side: CBF 56.49 ± 6.97 versus 56.94 ± 6.70 ml/100 ml/minute, $p=0.13$; CBV 3.48 ± 0.45 versus 3.45 ± 0.39 ml/100 ml, $p=0.74$); no stroke was observed on the follow-up CT scans.

3.2.7. Generalized vasospasm

Six patients had CTA abnormalities, which were indicative of generalized vasospasm. WB-CTP maps were assessed for abnormalities by manual observation and qualitatively compared to the corresponding regional vasospasm detected by CTA. Each abnormality disclosed on the perfusion map corresponded precisely to the vascular territory of the arterial segment that developed vasospasm. Follow-up CT showed that four patients had cerebral infarction.

4. Discussion

Ischemic complications associated with microsurgical clipping and endovascular coiling for cerebral aneurysms can lead to acute worsening of the neurological condition. It should be noted that these complications are not uncommon and should not be overlooked. In our series, a total of 30 ischemic complications (52%) equally associated with both the treatment and the underlying disease were identified by WB-CTP. Seventeen of the 30 (57%) patients had infarction. The majority of ischemic lesions in our patients could be related to the poor grade post-rupture and were detected due to the high sensitivity of WB-CTP. These findings together
indicate that treatment-associated vascular injury and cerebral vasospasm remain leading causes of ischemic complications following aneurysmal SAH.

DSA is the “gold standard technique” to assess aneurysms [10]. CTA and MR angiography are often used for postoperative assessment of the residual aneurysm cavity or aneurysm neck [11,12]. Nevertheless, these angiographic methods only illustrate the anatomy of blood vessels without relevant hemodynamic information. In contrast, CTP provides a series of hemodynamic parameters to identify the presence of an ischemic penumbra following acute cerebral infarction and to evaluate cerebrovascular reserve capacity in cases of chronic ischemia [13,14]. However, because of its limited brain area coverage, infarction in the distal anterior cerebral artery territory and basilar artery or posterior cerebral artery territory may be overlooked by CTP. Subsequently, this problem can increase the likelihood of false-negative findings and thus reduce the accuracy of studies [15,16]. In the present study, WB-CTP was carried out using a dual-source CT scanner with an adaptive four-dimensional spiral scan mode, which enabled total coverage of the brain (15 mm). CTA images were further processed using the same dataset. Such a “one-stop” examination effectively reduced the amount of contrast agent required without significantly increasing the radiation exposure [17].

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Based on a combination of WB-CTP and CTA, patients with treatment-associated ischemic complications were identified and divided into three types according to the relative location of the parent vessel to the site of clipping or coiling. This classification is clinically useful, especially in the implementation of different treatments for patients with different types of ischemic complications. Among six patients with a reduction in the diameter of the parent vessels, infarcts occurred in two and a favorable outcome was observed in the remaining four patients, who underwent regular follow-up examinations. A poor outcome was observed in both patients who had an occlusion of the parent vessels or perforating arteries by clipping and developed infarcts in the area related to the occluded vessels. Appropriate treatment should be implemented as soon as possible in such cases. Bypass treatment can be employed for patients with vascular occlusion in the MCA [18].

More importantly, a poor outcome was observed in seven patients who had normal vessel morphology close to the site of arterial clipping or coiling, or indistinguishable vascular injury due to coil-related artifacts on CTA. These ischemic complications were possibly due to thromboembolism [19] or vein compromise [20]. However, WB-CTP sensitively detected these brain perfusion abnormalities. Cerebral infarction occurred in all these patients. Such patients should be examined by CTA combined with WB-CTP to obtain information about hemodynamic impairments, and thus prevent a missed diagnosis.

With regard to both treatment-associated and vasospasm-related perfusion abnormalities, this study observed three hemodynamic patterns using WB-CTP examination. The first pattern is hemodynamic impairment without cerebral infarction and is characterized by increased TTP, TTD, and MTT but normal CBF and CBV due to activated autoregulation following ischemia. The second

![Fig. 2. Preoperative CT angiography showing a ruptured bifurcation aneurysm of the middle cerebral artery (A). Postoperative CT angiography showing that the perforating arteries of the middle cerebral artery were ligated as a result of the clipping (B). Whole-brain CT perfusion demonstrating irreversible perfusion defects in the left hemisphere (C). Axial whole-brain CT perfusion showed that compared with the region of interest of the right hemisphere, the left hemisphere showed decreased cerebral blood flow (CBF) (E, E’) and cerebral blood volume (CBV) (F, F’) and significantly increased time to peak (TTP) (G, G’), time to delay (TTD) (H, H’), and mean transit time (MTT) (I, I’). Follow-up axial CT scan confirmed infarction in the left temporal and occipital lobes (D).](image-url)
pattern is reversible ischemic lesions characterized by increased TTP, TTD, and MTT in association with a decreased CBF and normal CBV. The third pattern is an irreversible ischemic lesion characterized by increased TTP, TTD, and MTT in association with decreased CBF and CBV. In line with previous reports [21,22], our study demonstrated that time-related parametric maps (MTT, TTP, and TTD) are highly sensitive for postoperative acute brain ischemia screening. Cerebral vascular autoregulation induces normal or increased CBV in ischemic territories. An abnormally low CBV is an indicator of cerebral autoregulation dysfunction and a critical predictor of cerebral infarction.

Previous studies have reported that patients with clipped aneurysms have a higher incidence of neurocognitive deficits compared with patients with coiled aneurysms [23]. We could not confirm this finding in our study because of the small number of patients who underwent endovascular coiling and follow-up WB-CTP examination. Another limitation of this study is that cerebral ischemia can occur bilaterally and in a diffuse pattern in the brain of patients with generalized vessel vasospasm. This was difficult to assess using our methodology for CTP. However, visual evaluation by WB-CTP might be helpful for the identification of hemodynamic injury.

Fig. 3. Postoperative CT angiography showed a coil-related artifact and no distinguishable vascular injury (A, B). Whole-brain CT perfusion showing irreversible perfusion defects in the left hemisphere (C). Axial whole-brain CT perfusion showed that compared with the region of interest of the right hemisphere, the left hemisphere showed decreased cerebral blood flow (CBF) (D) and cerebral blood volume (CBV) (E), and significantly decreased time to peak (TTP) (F), time to delay (TTD) (G) and mean transit time (MTT) (H). Follow-up axial CT confirmed infarction in the distribution of the anterior cerebral artery (I).
5. Conclusion

A combination of WB-CTP with CTA can accurately determine the cause of clinical deterioration and classify ischemia complications associated with aneurysm treatment and vasospasm. The combined use of WB-CTP and CTA may help to assess hemodynamic patterns and monitor operative outcomes following clipping or coiling.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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References
