Continual Transcranial Doppler in the Monitoring of Hemodynamic Change following Aneurysmal Subarachnoid Hemorrhage

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Keywords

Aneurysm; Hemodynamics; Subarachnoid hemorrhage; Transcranial Doppler sonography; Vasospasm.

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SUMMARY

Aims: To analyze and compare the value of different treatment methods for acute aneurysmal subarachnoid hemorrhage (aSAH)-related vasospasm. Cerebral hemodynamic variables' changes were evaluated by transcranial Doppler (TCD) in aSAH patients within 14 days after onset. **Methods:** Thirty aSAH patients were enrolled in the study within 72 h after onset. Baseline CT and TCD were used for assessment. Patients were divided into three groups according to SAH severity and patients' discretion: nonsurgical group, endovascular coiling, and neurosurgical clipping. TCD hemodynamic parameters were measured and Lindegaard index was calculated daily from onset to 14th day after SAH. The group mean cerebral blood velocity (MBFV) and Lindegaard index were compared using repeated measures analysis of variance (reANOVA). Least Significant Difference (LSD) test was used for *post hoc* comparison. All 30 patients were followed for 90 days after onset for outcome assessment. **Results:** The values of MBFV and Lindegaard index of anterior cerebral artery (ACA)/middle cerebral artery (MCA) from high to low is nonsurgical group, clipping and coiling (ACA: $P = 0.0001/P = 0.006$; MCA: $P = 0.243/P = 0.317$). **Conclusions:** These results indicate that both neurosurgical clipping and endovascular coiling management may relieve the severity of cerebral vasospasm in acute aSAH.

Introduction

Subarachnoid hemorrhage (SAH), because of ruptured intracranial aneurysms, accounts for approximately 5% of all strokes, but its impact is relatively greater because it tends to affect younger adults in good health, often with devastating consequences [1–3]. Cerebral vasospasm (CV) is the most frequent complication after aneurysmal SAH (aSAH). CV occurs in 70% of patients with aSAH, causes symptomatic brain ischemia in 36% of patients, and is correlated with a 1.5- to 3-fold increase in mortality [4]. The diagnosis of CV may be suspected on the basis of clinical examination and transcranial Doppler (TCD) results, and can be confirmed with cerebral angiography. The measurement of cerebral blood flow (CBF) velocities with TCD has provided a way of detecting developing vasospasm after SAH [5]. Meanwhile, the sensitivity and specificity of TCD for the detection of both angiographically and clinically defined vasospasm are high. Therefore, TCD usually be used as a noninvasive tool to evaluate cerebral hemodynamics variables' changes of different treatments after aSAH.

American Heart Association Guidelines for the management of aSAH have recommended that neurosurgical clipping or en-

dovascular coiling should be performed to reduce the rate of re-bleeding after aSAH [2]. There is ongoing debate regarding the best modality to repair a given aneurysm according to current international clinical trials [6–8]. Furthermore, there are limited data using TCD to assess the efficacy of different treatments, particular for those who will undergo medical interventions because of any of surgical contradictions. To evaluate and compare the efficacy of different treatments for acute aSAH-related vasospasm, using TCD, we continually monitored and analyzed cerebral hemodynamic variables in patients daily for 14 days after onset.

Subjects and Methods

Patient Population

The identified population included thirty patients admitted to the Neurology Department within 72 h after SAH onset from April 2008 to January 2009. All the patients had definitively diagnosed SAH, verified by cranial computed tomography (CT). All patients were diagnosed with an intracranial aneurysm revealed through

intra-arterial angiography and confirmed independently by two experienced interventional neuroradiologists. TCD was carried out within the first 72 h after SAH to establish a baseline for each patient. Patients were included according to the following criteria: (1) 18 to 75 year old; (2) diagnosis with International Classification of Diseases, 9th Revision (ICD-9), diagnostic code 430.0 (SAH); (3) ruptured aneurysm confirmed by digital subtraction angiography (DSA) and treated (if done) within 72 h; (4) favorable temporal acoustic bone window. Patients were excluded if any of the following applied: (1) nonaneurysmal SAH; (2) unclear time for the onset of symptoms or over 72 h when admission; (3) deficient temporal acoustic bone window; (4) TCD and/or DSA found stenosis in extracranial and/or intracranial arteries; (5) severe comorbidities. The design of this research was approved by the ethics committee of the hospital and patients or their legal representatives gave written consent to participate.

Clinical Management

To compare the impact of different treatments on hemodynamics change after aSAH, we divided patients into three treatment groups based on aneurysm management modality and patients' discretion: a nonsurgical group (nine patients), endovascular coiling group (nine patients) and neurosurgical clipping group (12 patients), the latter two groups of which were combined as surgical group. All patients in our study received nimodipine administration and "Triple H" therapy: hypertension, hypervolemics, and hemodilution after coiling or clipping.

Clinical and Radiographic Assessment

Patient demographics, clinical and radiological severity grades (Fisher grade and World Federation of Neurological Surgeons grading scales) were recorded based on information provided in medical records.

Cranial CT scan was performed on the first day post SAH onset (as soon as possible within 24 h) for every patient. A neuroradiologist who was blinded to the clinical and TCD analyzed all of the CT scans and evaluated Fisher grade.

TCD Hemodynamic Assessment of Vasospasm

TCD hemodynamics monitoring was carried out by a designated professional technician. Within 72 h after onset, baseline data were collected. Four to fourteen days postevent hemodynamics data were measured daily at the same time (5:00 pm to 6:00 pm).

TCD variables were assessed in bilateral middle cerebral artery (MCA) and anterior cerebral artery (ACA) with 2 MHz transducers. Extracranial ICA was measured with 4 MHz transducers by a TCD instrument (Multi-Dop; DWL-Elektronische Systeme GmbH längerach4 D-78354, sipplingen, Germany). MCA and ACA were examined through the temporal acoustic window at a depth of 36–60 mm and 60–70 mm, respectively. The spectra cycles contained in a 6-s frame were analyzed. The segment with the highest mean cerebral blood flow velocity (CBFVMAX) was recorded and used for analysis.

Bilateral MCA and ACA hemodynamic parameters were all collected. Blood diffuses into subarachnoid space after aneurysms ruptures; therefore mean cerebral blood flow velocity (MCBFV) and Lindegaard index (LI) were analyzed on the ipsilateral side of the aneurysm. If the aneurysm was located in midline (e.g., anterior communicating artery aneurysms, basilar artery aneurysms), the side of the surgical or endovascular approach was used. Precision in the diagnosis of vasospasm by TCD may be enhanced by measurements of LI [9]. We use the LI given by MCA/ACA MCBFV/MCBFV extracranial ICA measured by the submandibular approach. Mean CBF velocities more than 120 cm/s but less than 200 cm/s had a high false positive rate, but in most patients, CBF velocities are in this range. In addition, LI greater than 3 is consistent with mild vasospasm. Therefore, MCA-MCBFV (MCBFV of MCA)/ACA-MCBFV (MCBFV of ACA) ≥ 120 cm/s and MCA-LI (LI of MCA)/ACA-LI (LI of MCA) ≥ 3.00 is defined as vasospasm [10, 11].

Outcomes and Follow-Up

Patients were followed for 90 days, and a modified Rankin Scale (mRS) was used to evaluate outcomes. Favorable outcomes was defined as mRS < 3 , whereas poor was ≥ 3 .

Statistical Analysis

A Kolmogorov–Smirnov test for normality and an equal variances test were performed. Chi-square analysis was done to evaluate the relationship between the different treatments and the rate of vasospasm. For the MCBFV and LI trends on baseline and 4–14 days, Repeated measures analysis of variance (reANOVA) were performed to determine differences among three treatment groups. Where significant difference was identified by reANOVA, *post hoc* analysis using LSD test was used to confirm the significant effects. All data were expressed as mean $\pm$ SD or mean $\pm$ SE. The value of $P \leq 0.05$ was considered to be significant. All analyses were done with SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 46 patients met the inclusion criteria and 30 patients went through all 12 TCD examinations and completed the 90 day follow-up. Baseline characteristics are shown in Table 1. No significant difference in demographics, or medical histories was noted. Clinical and radiological grades among the nonsurgical group, the coiling group, and the clipping group did not prove statistically significant.

In this study, not all DSA confirmed cerebral aneurysm patients were able to receive surgical clipping or coiling. Reasons for ineligibility for surgical intervention included: manipulation of the aneurysm may cause severe neurological compromise because of deep perforating arteries supplying function area grew out of the aneurysm; Hunt-Hess scales exceeded III class; patient refused surgery. Among patients who failed to accept obliteration of aneurysm, two died of rebleeding at follow-up.

Table 1 Baseline characteristics of all 30 patients

	Nonsurgical (n = 9)	Coiling (n = 9)	Clipping (n = 12)	Total (n = 30)	P value
Age, (mean $\pm$ SD; years)	43.8 $\pm$ 8.9	47.3 $\pm$ 8.4	47.3 $\pm$ 7.9	46.3 $\pm$ 8.3	0.573
Female (n)	3	6	4	13	0.240
Medical history (n)					
Hypertension	2	5	6	13	0.301
Diabetes mellitus	0	1	0	1	0.299
Hyper-lipoidemia	0	1	1	2	0.612
Smoking	4	2	2	8	0.340
Alcoholism	4	1	1	6	0.09
SAH	0	0	0	0	-
WFNS IV–V (n)	1	1	0	2	0.612
Fisher grade (n)					
1–2	4	3	1	8	0.156
3–4	5	6	11	22	
Location of aneurysm					
Anterior circulation	7	9	11	27	0.282
Posterior circulation	2	0	1	3	

Comparing of TCD Hemodynamics after Different Treatments

A total of 21 patients underwent coiling or clipping and “Triple H” therapy. Within 14th day, the values of ACA-MCBFV were 74.5 $\pm$ 6.04 cm/s in nonsurgical group, 65.8 $\pm$ 6.04 cm/s in the coiling group, and 70.1 $\pm$ 5.23 cm/s in the clipping group; ACA-LI was 3.86 $\pm$ 0.35 in nonsurgical group, 3.66 $\pm$ 0.35 in the coiling group and 3.83 $\pm$ 0.30. The values of MCA-MCBFV were 100.2 $\pm$ 14.1 cm/s in nonsurgical group, 76.3 $\pm$ 14.1 cm/s in the coiling group, and 86.9 $\pm$ 12.2 cm/s in the clipping group; MCA-LI was 5.47 $\pm$ 0.65 in nonsurgical group, 3.80 $\pm$ 0.65 in the coiling group, and 4.15 $\pm$ 0.56 in the clipping group.

ACA: The reANOVA for the ACA-MCBFV showed a significant difference among three treatment groups ($P = 0.0001$) and *post hoc* analysis revealed a significant difference between three groups (nonsurgical vs. coiling: $P = 0.026$; coiling vs. clipping: $P = 0.044$; nonsurgical vs. clipping: $P = 0.023$; Table 2). The reANOVA for the ACA-LI also showed a difference between three groups ($P = 0.006$), but *post hoc* analysis found the significant difference only existed between nonsurgical group and coiling group ($P = 0.041$; Table 2). Combined coiling and clipping as the surgical group, the ACA-MCBFV and ACA-LI in the nonsurgical group patients were also higher than in the surgical group ($P = 0.001$ and $P = 0.005$).

MCA: The MCA-MCBFV and MCA-LI from high to low was the nonsurgical group, the clipping group, and the coiling group. But there is no significant difference ($P = 0.243$ and 0.317 ; Table 3). Combined coiling and clipping as the surgical group, the MCA-MCBFV and MCA-LI in the nonsurgical group patients were

Table 2 Hemodynamic variables in different treatments of anterior cerebral artery

	Mean blood flow of anterior cerebral artery (cm/s, mean $\pm$ SD)			Lindegard index of anterior cerebral artery (mean $\pm$ SD)		
	Nonsurgical (n = 9)	Coiling (n = 9)	Clipping (n = 12)	Nonsurgical (n = 9)	Coiling (n = 9)	Clipping (n = 12)
Baseline	57.7 $\pm$ 17.1	60.3 $\pm$ 12.7	54.0 $\pm$ 19.3	2.87 $\pm$ 0.73	3.39 $\pm$ 0.99	2.93 $\pm$ 1.13
Day 4	65.7 $\pm$ 26.4	68.8 $\pm$ 23.8	64.3 $\pm$ 19.7	3.08 $\pm$ 1.48	4.22 $\pm$ 2.02	3.70 $\pm$ 1.46
Day 5	65.3 $\pm$ 26.8	66.3 $\pm$ 23.9	64.8 $\pm$ 19.1	3.74 $\pm$ 1.62	3.33 $\pm$ 1.50	3.81 $\pm$ 1.37
Day 6	62.7 $\pm$ 26.7	60.0 $\pm$ 27.9	62.6 $\pm$ 28.8	3.06 $\pm$ 1.32	2.88 $\pm$ 1.50	3.49 $\pm$ 1.62
Day 7	72.7 $\pm$ 36.1	67.9 $\pm$ 28.5	69.9 $\pm$ 24.3	3.78 $\pm$ 1.39	3.50 $\pm$ 1.31	3.60 $\pm$ 1.36
Day 8	86.7 $\pm$ 23.1	78.4 $\pm$ 32.6	83.2 $\pm$ 27.0	4.21 $\pm$ 1.14	4.16 $\pm$ 2.64	4.42 $\pm$ 1.64
Day 9	79.2 $\pm$ 26.1	63.0 $\pm$ 22.3	82.3 $\pm$ 27.8	3.88 $\pm$ 1.41	3.36 $\pm$ 1.77	4.29 $\pm$ 1.45
Day 10	86.4 $\pm$ 31.8	68.1 $\pm$ 25.0	72.1 $\pm$ 29.5	4.50 $\pm$ 1.47	4.00 $\pm$ 1.73	4.19 $\pm$ 1.63
Day 11	92.1 $\pm$ 31.9	70.4 $\pm$ 20.4	72.2 $\pm$ 33.4	5.26 $\pm$ 2.17	4.16 $\pm$ 0.90	3.92 $\pm$ 1.58
Day 12	79.6 $\pm$ 31.4	56.7 $\pm$ 16.0	73.5 $\pm$ 29.4	4.01 $\pm$ 1.66	3.34 $\pm$ 0.78	3.92 $\pm$ 1.53
Day 13	79.3 $\pm$ 28.4	64.2 $\pm$ 18.4	71.3 $\pm$ 26.0	4.32 $\pm$ 1.21	3.85 $\pm$ 1.05	3.79 $\pm$ 1.37
Day 14	67.0 $\pm$ 30.6	65.8 $\pm$ 14.4	71.1 $\pm$ 21.3	3.64 $\pm$ 1.65	3.67 $\pm$ 0.95	3.87 $\pm$ 1.21
Mean (mean $\pm$ SE)	74.5 $\pm$ 6.04	65.8 $\pm$ 6.04	70.1 $\pm$ 5.23	3.86 $\pm$ 0.35	3.66 $\pm$ 0.35	3.83 $\pm$ 0.30
P value	0.0001 ^a	0.006 ^b				
P value	0.026	0.044	0.023	0.041	0.089	0.566

^aThe mean blood flow velocity of anterior cerebral artery (ACA) from high to low is nonsurgical group, clipping, and coiling. And there is significant difference ($P = 0.0001$). Nonsurgical versus coiling: $P = 0.026$; Coiling versus clipping: $P = 0.044$; nonsurgical versus clipping: $P = 0.023$.

^bThe Lindegard index of ACA from high to low is nonsurgical group, clipping, and coiling. Although there is difference between three groups ($P = 0.006$), *post hoc* analysis found the significant difference only existed between nonsurgical group and coiling group ($P = 0.041$). Coiling versus clipping: $P = 0.089$; nonsurgical versus clipping: $P = 0.566$.

Table 3 Hemodynamic variables in different treatments of middle cerebral artery

	Mean blood flow of middle cerebral artery (cm/s, mean $\pm$ SD)			Lindegard Index of middle cerebral artery (mean $\pm$ SD)		
	Nonsurgical (n = 9)	Coiling (n = 9)	Clipping (n = 12)	Nonsurgical (n = 9)	Coiling (n = 9)	Clipping (n = 12)
Baseline	62.3 $\pm$ 20.4	70.9 $\pm$ 19.7	63.0 $\pm$ 18.6	3.12 $\pm$ 0.83	3.75 $\pm$ 1.10	3.33 $\pm$ 1.34
Day 4	69.0 $\pm$ 30.0	71.6 $\pm$ 25.3	78.8 $\pm$ 25.2	3.52 $\pm$ 1.95	3.54 $\pm$ 1.44	4.43 $\pm$ 1.69
Day 5	91.1 $\pm$ 66.0	78.0 $\pm$ 28.3	77.2 $\pm$ 24.2	5.23 $\pm$ 4.27	3.20 $\pm$ 1.02	4.52 $\pm$ 2.19
Day 6	103.2 $\pm$ 66.2	76.6 $\pm$ 29.8	76.0 $\pm$ 31.9	5.41 $\pm$ 3.69	3.58 $\pm$ 1.15	4.31 $\pm$ 2.10
Day 7	102.7 $\pm$ 65.6	88.7 $\pm$ 33.3	87.3 $\pm$ 49.6	5.04 $\pm$ 3.11	3.99 $\pm$ 1.81	4.39 $\pm$ 2.69
Day 8	119.8 $\pm$ 68.8	83.8 $\pm$ 28.5	92.3 $\pm$ 54.8	6.08 $\pm$ 4.01	4.20 $\pm$ 3.10	5.03 $\pm$ 3.64
Day 9	116.1 $\pm$ 66.4	73.2 $\pm$ 31.1	97.2 $\pm$ 50.4	5.98 $\pm$ 3.82	3.47 $\pm$ 2.20	5.18 $\pm$ 2.90
Day 10	115.6 $\pm$ 69.8	78.8 $\pm$ 26.4	90.8 $\pm$ 52.9	6.16 $\pm$ 3.79	3.85 $\pm$ 1.78	5.02 $\pm$ 2.90
Day 11	114.9 $\pm$ 68.6	73.3 $\pm$ 26.5	93.2 $\pm$ 61.0	6.41 $\pm$ 3.83	3.86 $\pm$ 1.71	4.83 $\pm$ 2.97
Day 12	104.3 $\pm$ 72.1	72.9 $\pm$ 30.4	98.5 $\pm$ 59.7	5.83 $\pm$ 3.55	3.74 $\pm$ 1.53	5.06 $\pm$ 2.73
Day 13	102.6 $\pm$ 67.7	75.1 $\pm$ 27.7	98.1 $\pm$ 57.2	6.07 $\pm$ 4.38	3.87 $\pm$ 1.39	5.01 $\pm$ 2.74
Day 14	101.2 $\pm$ 64.4	73.2 $\pm$ 24.5	90.0 $\pm$ 49.8	6.10 $\pm$ 3.60	3.70 $\pm$ 1.48	4.81 $\pm$ 2.47
Mean(mean $\pm$ SE)	100.2 $\pm$ 14.1	76.3 $\pm$ 14.1	86.9 $\pm$ 12.2	5.47 $\pm$ 0.65	3.80 $\pm$ 0.65	4.15 $\pm$ 0.56
P value	0.243 ^a	0.317 ^b				

^aThe mean blood flow velocity of middle cerebral artery (MCA) from high to low is nonsurgical group, clipping, and coiling. But there is no significant difference ($P = 0.243$).

^bThe Lindegard index of MCA from high to low is nonsurgical group, clipping, and coiling. But there is no significant difference ($P = 0.317$).

also higher than those in the surgical group ($P = 0.261$ and $P = 0.022$).

Outcomes and Follow-Up Results

The occurrence rate of favorable outcomes for surgical group was 81.0% (17/21) and 14.3% for the nonsurgical group 66.7% (6/9; $P = 0.343$). The occurrence rate of poor outcomes in the nonsurgical group, coiling group, and clipping group were 33.3% (3/9), 33.3% (3/9), and 8.3% (1/12; $P = 0.284$), respectively. Eleven patients developed CV and the occurrence rate of CV in the nonsurgical group, coiling group, and clipping group were 44.4% (4/9), 33.3% (3/9), and 33.3% (4/12), respectively, but only one had a poor outcome (1/11). Six out of 19 patients who were not found with vasospasm evidenced by TCD had poor outcomes (6/19; $P = 0.096$). Two patients in nonsurgical group died of rebleeding within the 90-day follow-up period. Two patients who had ruptured anterior communicating aneurysms and received surgical clipping and coiling, respectively, became worse with increased mRS to IV class, meanwhile severe vasospasm in bilateral anterior arteries was found in TCD and infarction lesion in the related area in CT scan. Three older patients whose mRS were class III did not reveal vasospasm by TCD, but have refractory neurological disorders post-intervention.

Discussion

In this study, we measured the TCD hemodynamic parameters and calculated Lindegard index daily from onset to the 14th day post SAH and found that CV postintervention in the nonsurgical group is more significant than that of surgical group (coiling and clipping) in acute aSAH. The mean blood flow and/or LI of nonsur-

gical group were higher than that of surgical group in both ACA (Table 2) and MCA (Table 3), especially in ACA, and LI is much sensitive than MCBFV. Although we found patients in the surgical group had a good trend in outcomes, as compared with the nonsurgical group, the difference was not significance that may be because of small sample size. The degree of variation in MCA was larger than that of ACA, which may explain some results of MCA didn't show significant differences.

Based on our patient population and groupings, CV of the nonsurgical group was more severe and more frequent in comparison with the surgical group. One reason is the "Triple H" therapy can't be administered to untreated aneurysms because of the high risk of rebleeding [12, 13]. Before aneurysm obliteration, gentle volume expansion with slight hemodilution and a slight rise in blood pressure should be used, but extreme hypertension must be avoided to reduce the risk of rebleeding [12]. Investigators haven't reached agreement on blood pressure control before obliterating aneurysms. Early surgical intervention protects patients from subsequent aneurysm bleeding and allows aggressive treatment of CV. Meanwhile, clipping can early remove distal clot, which weakens CV, presumably by reducing the level of presumptive spasmogens [14, 15]. Therefore, our TCD results support that early obliteration of aneurysms indirectly reduces the risk of CV.

In addition, we found that older adults, whose hemodynamic variables did not meet the criteria of CV, suffered from cerebral ischemia. Several previous studies suggested that the incidence of CV in older aSAH patients is lower [16, 17]. The lower incidence may be secondary to the age-related increase in atherosclerosis, which results in impairment of contractility and elasticity of the muscle wall of small arteries and arterioles [18]. In contrast, younger patients, with more compliant and collapsible vessels, might have a greater decrease in CBF as cerebral perfusion pressure reached a critical closing pressure [19]. Hence, aged

patients with more rigid vessels may be able to maintain small-vessel patency at similar pressures [20, 21]. Although cerebral ischemia is usually associated with CV, attention has now turned to other etiologies, such as microthrombosis because of activation of the coagulation cascade [22, 23] and prolonged cortical spreading depression [24, 25]. Thus, even if the hemodynamic variables in older patients are unable to meet the regular criteria of CV, the probability of vasospasm or cerebral ischemia still exists.

Following this pilot study, questions remain that must be addressed. First, our relatively small sample size prohibits confirming results through statistical significance (i.e., some hemodynamic variables and clinical outcomes). Second, our investigation was limited to results obtained from hemodynamics by TCD even though CV and outcomes of aSAH are related to multiple factors. Therefore, multivariate analysis of CV is needed. Third, although the DSA is the gold standard for CVs diagnosis, almost all patients in our study indeed didn't accept DSA; thus, the CVs were confirmed by parameters of TCD instead. Fourth, the patients in our study are relatively young to achieve bilateral favorable temporal acoustic bone windows. Furthermore, it is still not easy for patients in acute SAH to coordinate pillow window examination and there

are more variations in distribution of intracerebral arteries of posterior circulation. Thus, this study was limited by the exclusion of the posterior circulation arteries. Our findings imply that in acute aSAH, clipping or coiling not only decreases the rebleeding risk, but also indirectly relieves the severity of CV.

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Disclosures

None.

Conflict of Interest

The authors declare no conflict of interest.

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