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Evaluation function of transcranial two-dimensional and color Doppler ultrasonography (TCCS) for patients with different degrees of cerebral vasospasm before and after the nimodipine treatment

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Abstract. – OBJECTIVE: To evaluate the changes in cerebral hemodynamics of patients with different degrees of cerebral vasospasm before and after the nimodipine treatment using transcranial two-dimensional and color Doppler ultrasonography (TCCS).

PATIENTS AND METHODS: A total of 77 patients with subarachnoid hemorrhage was collected; and the maximum peak systolic velocity (Vs), end diastolic velocity (Vd), time averaged maximum velocity (Vm), pulsatility index (PI) and resistance index (RI) of middle cerebral artery (MCA) were measured by spectral Doppler technique. The standard-dose nimodipine was given for clinical treatment, and changes in blood flow velocity of MCA were monitored by TCCS, and the therapeutic effect was observed.

RESULTS: 68 out of 77 patients (88.3%) with subarachnoid hemorrhage were diagnosed as cerebral vasospasm (CVS), including 53 cases (77.9%) of mild spasm, 11 cases (16.2%) of moderate spasm and 4 cases (5.9%) of severe spasm. The sensibility of CVS detected by TCCS after operation was 88.3%. Color Doppler flow imaging (CDFI) showed that the blood flow was multicolored. After the nimodipine treatment, the measured values of MCA-Vs and RI were decreased in different degrees compared with those before treatment.

CONCLUSIONS: Nimodipine has improving effects on CVS in different degrees, and TCCS can be used to evaluate the therapeutic effects on CVS.

Key Words:
TCCS, CVS, Nimodipine, Evaluation.

Introduction

Cerebral vasospasm (CVS) is a kind of persistent vasoconstriction state that has no response to vasodilators. Dizziness and headache are its significant clinical features, and headache is the initial symptom of CVS[1]. Histological examination proves that 90% of patients who die from closed craniocerebral injury suffer from the severe ischemic brain damage. Cerebral circulation disorder and subarachnoid hemorrhage after brain damage can cause CVS and aggravate brain damage[2,3]. Early-stage CVS is often ignored because of non-obvious symptoms, and the severe CVS can cause cerebral ischemia, cerebral infarction and neurological dysfunction, and even death. CVS has a poor response to vasodilators and it is difficult to be reversed, which is the most common cause of delayed cerebral ischemia[4,5]. Therefore, the early, accurate and effective diagnosis of CVS and effective treatment after craniocerebral injury are very important for the prognosis of patients.

CT angiography and transcranial Doppler (TCD) are the main methods of clinical examination of CVS, and the accuracy of CT angiography in finding CVS reaches more than 99%[6,7]. TCD is also a better method of monitoring CVS, whose fundamental principle is to estimate the luminal stenosis degree through the changes in intracranial blood flow velocity[8,9]; TCD has an important value in the diagnosis and prognosis of CVS because of its repeatability and dynamic observation of changes in cerebral hemodynamics[10]; but it is influenced by the incident angle of beam and

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limited by the operator's skills, so its accuracy needs to be further improved. In recent years, transcranial two-dimensional and color Doppler ultrasonography (TCCS) has been widely used in the detection of craniocerebral diseases. Compared with TCD, TCCS has the advantage that the main intracranial vessels can be displayed intuitively and visually, thus conducting the targeted hemodynamic monitoring.

The pathogenesis of CVS is complex and the calcium overload after SAH, shrinking factor imbalance and inflammatory response play important roles in the pathogenesis of DCVS[11-13]. Nimodipine is the second generation of dihydropyridine calcium ion antagonist, and its high lipophilicity determines that it can easily go through the blood-brain barrier, and the dihydropyridine ring in drug molecules makes it have a high degree of selectivity for cerebrovascular smooth muscle[14,15]. Nimodipine can inhibit the extracellular flow of Ca^{2+} through blocking the L-type voltage-gated Ca^{2+} channel on vascular smooth muscle cell membrane. Additionally, Nimodipine can promote the Ca^{2+}-ATP enzymatic activity, eliminates the calcium ion in cytoplasm and enhances the calcium intake of mitochondria and endoplasmic reticulum, which leads to regulating the Ca^{2+} concentration in the cytoplasm and prevents the excessive contraction of blood vessels. At present, the prevention and treatment of CVS after SAH using nimodipine in China and other countries has been recommended by the prevention and treatment guidance of CVS[16,17].

In this study, TCCS technique was used to evaluate the patients with different degrees of CVS before and after nimodipine treatment.

Patients and Methods

Patients

This study was approved by the Ethics Committee of People's Hospital of Dezhou. Signed written informed consents were obtained from all participants before the study.

A total of 77 patients with subarachnoid hemorrhage admitted in neurosurgical care unit of People's Hospital of Dezhou from April 2015 to December 2015 was collected, including 56 males and 21 females aged 29-71 years with an average age of (37.2±7.8) years, among which there were 74 patients with severe craniocerebral injury and 3 patients receiving intracranial space-occupying surgery. After admission, all objects of the study received the emergency treatment of removing hematoma or contusion tissues, as well as the temporo parietal bone-flap decompressive craniectomy; there were no patients complicated with other major organ injuries or severe cardiovascular diseases. During operation, the micro-probe of intracranial pressure monitor was placed in brain parenchyma near the operative site, and the intracranial pressure monitor was connected after operation for continuous intracranial pressure monitoring.

Instrument and Methods

HIVISIONAVIUS color Doppler ultrasound diagnostic apparatus (Hitachi, Tokyo, Japan) was used (probe model: 5-1; frequency: 1.8-2.0 MHz); the detection depth of MCA was 12-16 cm. The examination conditions of TCCS were selected.

Methods: The patients were treated with the routine disinfection in temporal window bone flap, and the probe was gently placed over the zygomatic arch and between the outer edge of orbit and ear wing. Two-dimensional ultrasound was used to show the "heart-shaped" low-echo structure of midbrain, which corresponded to the cerebral peduncle, as the positioning mark. After obtaining the optimal two-dimensional image, Color Doppler flow imaging (CDFI) or energy Doppler imaging function was turned on to clearly show the Willis ring structure at the bottom of the brain, and the major intracranial blood vessels were determined through blood flow direction and vascular anatomical location in CDFI. The color scale and gain were adjusted to get the best results, and the red blood flow shadow in ipsilateral middle cerebral artery (MCA) was observed. Then, the spectral Doppler technique was used to adjust the sampling line and color blood stream angle < 60^{o}, and the sampling was conducted every 0.3-0.5 cm, and the changes in blood flow spectrum pattern and audio signal were observed. Then the maximum peak systolic velocity (Vs), end diastolic velocity (Vd), time averaged maximum velocity (Vm), pulsatility index (Vm) and resistance index (RI) of MCA were measured.

Diagnostic Criteria of CVS

Classification of severity: It was divided into three grades: Grade I: local vasospasm with the range of less than 50%; Grade II: local vascular spasm with the range of more than 50%; Grade III: diffuse and massive spasm.

Staging: CVS was divided into two stages, acute stage [1-3 days after subarachnoid hemorrhage (SAH)] and chronic spasm stage that disappeared gradually after about 10 to 14 days. The acute stage of CVS had a high mortality, characterized by the increased intracranial pressure and decreased cerebral blood flow and cerebral perfusion pressure.

Ultrasound diagnostic criteria of CVS and classification of severity: According to Aaslid standard, the average blood flow velocity of MCA more than 120 cm/s suggested the vasospasm. According to the average blood flow velocity of MCA, CVS was divided into mild, moderate and severe. The blood flow velocity of MCA between 120 cm/s and 140 cm/s was defined as mild, the velocity between 141 cm/s and 200 cm/s was defined as moderate, and the velocity of more than 200 cm/s was defined as severe.

Identification of CVS and stenosis via TCCS: CVS is the simultaneous pathological physiological change in multiple blood vessels, and drug treatment can relieve the symptoms and reduce the blood flow velocity. Cerebrovascular stenosis refers to the high-speed blood flow in one site of one blood vessel; spectral Doppler can measure the blood flow velocity through sampling every 5 mm to identify the relationship between CVS and stenosis; at the same time, drug treatment does not change the vascular stenosis significantly.

Evaluation of Curative Effect of Nimodipine on CVS Using TCCS

The standard-dose nimodipine was given for clinical treatment, and changes in blood flow velocity of MCA were monitored by TCCS, and the therapeutic effect was observed.

Statistical Analysis

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Percentage (%) was used to express the enumeration data and chi-square test was used for data analysis. p values < 0.05 were considered statistically significant.

Results

The Sensibility of CVS Detected by TCCS After Operation

There were a total of 77 patients with subarachnoid hemorrhage. According to Aaslid standard, 68 patients were diagnosed as CVS, including 53 cases (77.9%) of mild spasm, 11 cases (16.2%) of moderate spasm and 4 cases (5.9%) of severe spasm. The sensibility of CVS detected by TCCS after operation was 88.3%.

Blood Flow Characteristics of CVS Patients Showed by CDFI

CDFI showed that the blood flow was multicolored; the spectral Doppler showed that MCA had the high peak pattern and the spectral window disappeared, showing the filling spectrum. The blood flow velocity in mild CVS was increased, and its hemodynamic characteristics were as followed: the blood flow velocity increased gradually, and the spectral pattern changed with the blood flow velocity (Figure 1). Early blood flow spectrum pattern can be manifested in the symmetrical increase of flow velocity in systole and diastole phases, high-edge systolic peak, and some patients had the "notch sign" in the early diastole phase (Figure 2). At this point, if patients suffered from severe vasospasm, resulting in cerebral anoxia, cerebral edema, increased in-

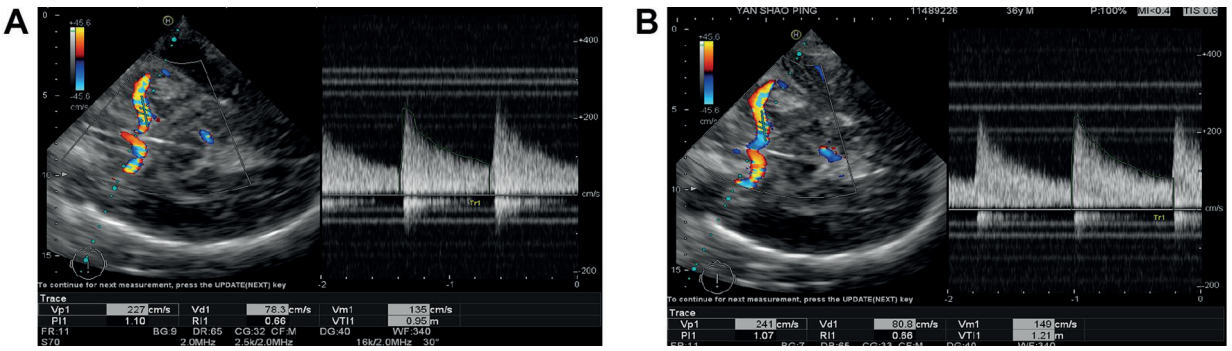

Figure 1. ***A,*** In patients with open craniocerebral injury, MCA showed mild spasticity, with an average flow velocity of 135 cm/s. ***B,*** In the same patient, MCA spasm developed to moderate, with an average flow velocity of 149 cm/s.

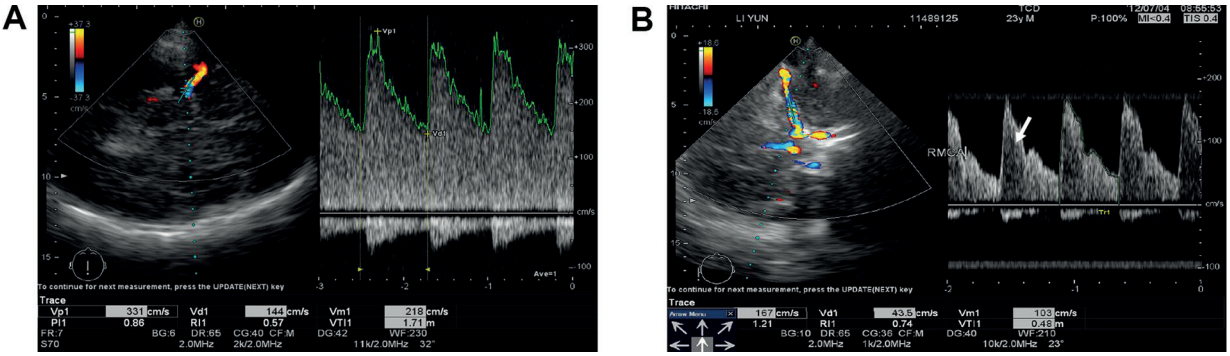

Figure 2. ***A,*** In patients with open craniocerebral injury, MCA showed severe spasticity, with an average flow velocity of 218 cm/s. ***B,*** In patients with acute craniocerebral injury, MCA showed the blood flow velocity decreased and the blood flow spectrum "Diastolic notch sign" (*arrow*) after treatment.

tracranial pressure, and they were not treated in time, the cerebral blood flow velocity would be decreased gradually, especially the end diastolic velocity, showing high-resistance hemodynamic characteristics.

Changes in Blood Flow Parameters of MCA Before and After the Nimodipine Treatment

After treatment, measured values of MCA-Vs and RI (Table I) were decreased compared with those before treatment (Figure 3).

Discussion

Cerebral vasospasm (CVS) is a kind of common phenomenon in neurosurgical diseases and a common complication of subarachnoid hemorrhage (SAH), as well as a kind of vasoconstriction state without response to the vasodilators[18,19]. After SAH occurs, cerebral vascular contraction is significant, but the increased intracranial pressure leads to decreased cerebral blood flow, decreasing cerebral perfusion pressure and seriously affecting intracranial circulation. The effect of drug treatment is more sensitive at this point. However, the increased intracranial pressure and decreased cerebral blood flow and cerebral perfusion pressure suggest that the microcirculation has been affected. Some researchers believe that drug treatment is more sensitive in this stage. Therefore, the early accurate diagnosis of CVS is very important for obtaining better therapeutic effect and prognosis, so as to prevent further development into the severe cerebral ischemia[20,21]. Chronic CVS is not sensitive to drug treatment, and cranial nerves will be damaged if it is not improved timely. Pathological studies[22,23] have shown that endothelial cell changes, death, detachment and necrosis after vasospasm are the main features of chronic CVS. CVS is not sensitive to vasodilators, and it is difficult to change the symptoms, which is also the most common cause of cerebral ischemia, and this factor is often overlooked in early diagnosis and treatment. Severe CVS can cause cerebral ischemia, cerebral infarction and neurological dysfunction, even death.

Nimodipine can prevent Ca^{2+} into the cells and inhibit smooth muscle contraction, relieving the vasospasm. Cerebral vessel expansion and increased cerebral blood flow increase the cerebral circulation gradually, which can be clinically used to prevent the vasospasm after subarachnoid hemorrhage, expand the cerebral blood vessels, increase cerebral blood flow and significantly reduce ischemic brain damage caused by vasospasm.

Table I. Comparison of MCA blood flow parameters before and after treatment with CVS.

Severity of CVS	Case	Vs (cm/s) before	Vs (cm/s) after	RI before	RI after
Mild	53	127 ± 6.9	101 ± 5.7	0.73 ± 0.06	0.67 ± 0.04
Moderate	11	164 ± 8.7	119 ± 5.9	0.76 ± 0.07	0.69 ± 0.06
Severe	4	258 ± 12.1	161 ± 10.5	0.81 ± 0.09	0.70 ± 0.08

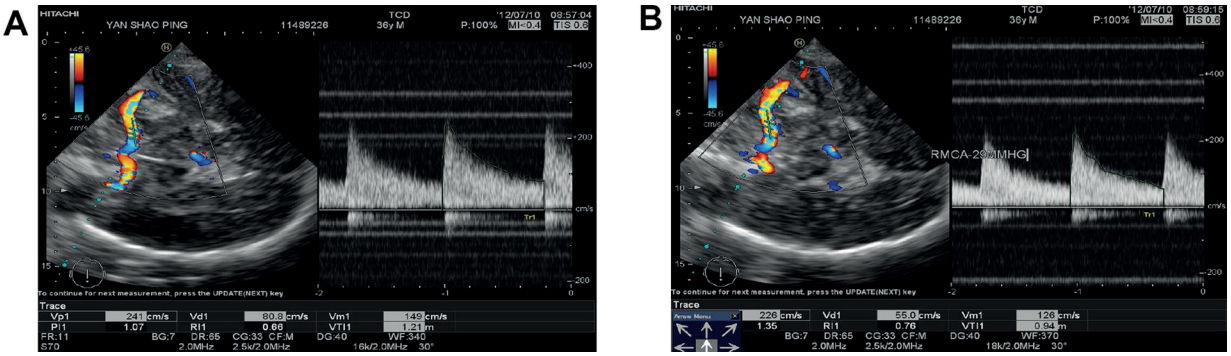

Figure 3. ***A,*** In patients with open craniocerebral injury, MCA showed moderate spasticity, with an average flow velocity of 149 cm/s. ***B,*** In the same patients, the blood flow spectrum, MCA blood flow velocity decreased, and the average blood flow velocity was 126 cm/s.

Angiography is the golden standard for the diagnosis of CVS, including DSA, CTA and magnetic resonance angiography (MRA). The greatest advantage of DSA is the ability to identify vasospasm, and the angioplasty or intra-arterial injection of vasodilators can be directly provided. But there are also deficiencies: an invasive examination, risks of moving patients and DSA-induced CVS and other limitations, which limit its clinical applications. Patients cannot receive MRA after incarceration of aneurysm, and conventional CT scan cannot directly find CVS. TCD is currently a commonly-used noninvasive cerebral hemodynamics technique to detect and monitor changes in cerebral blood flow, but there are some problems with method and accuracy. TCCS is more advanced technically. It can visually display the situations of intracranial parenchyma and it can display accurately the position of the high-speed blood flow, so it can locate and detect the hemodynamics parameters of main basicranial arteries, such as the blood flow velocity, flow direction, PI, RI, spectral pattern and audio changes; also, it can determine the arterial diameter and flow changes, so as to diagnose CVS. In this study, CDFI suggested that the blood flow velocity in mild CVS was accelerated, and its hemodynamic characteristic was that the blood flow velocity was gradually increased, and the spectral Doppler suggested that the spectrum pattern changed with the blood flow velocity. Early blood flow spectrum pattern can be manifested in the symmetrical increase of flow velocity in systole and diastole phases, high-edge systolic peak, and "notch sign" in the early diastole phase. At this point, if patients suffered from severe vasospasm, resulting in cerebral anoxia, cerebral edema, increased intracranial pressure, and they were not treated effectively in time, the cerebral blood flow velocity would be decreased gradually, especially the end diastolic velocity, further aggravating the brain tissue ischemia and anoxia, namely the high-resistance hemodynamic characteristics. In this study, the changes in blood flow parameters of MCA after nimodipine treatment were also observed. The results showed that the blood flow velocity and vascular resistance of MCA were decreased significantly after drug treatment, and vasospasm was relieved. Nimodipine treatment has a certain effect on mild spasm and severe spasm, and it can also alleviate the severe stenosis well. TCCS can also effectively differentiate CVS and cerebrovascular stenosis. CVS is the simultaneous pathological physiological change in multiple blood vessels, and drug treatment can relieve the symptoms and reduce the blood flow velocity. Cerebrovascular stenosis refers to the high-speed blood flow in one site of one blood vessel; at the same time, drug treatment does not change the vascular stenosis significantly; spectral Doppler can measure the blood flow velocity through sampling every 5 mm to differentiate CVS and stenosis. In this study, there are some deficiencies: CVS patients did not receive the timely DSA due to severe conditions, so the determination of TCCS for CVS degree was mainly according to Aaslid et al[24] standard.

Conclusions

In short, TCCS can accurately display the position of the intracranial vessel to be inspected, can accurately display the anatomical location and shape of blood vessels, and distinguish vas-

cular stenosis from vascular spasm via changes in blood flow velocity. Additionally, TCCS can also be used to eliminate other vascular abnormalities, providing important informations for clinical differential diagnosis.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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