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Massive Cerebrospinal Fluid Replacement Reduces Delayed Cerebral Vasospasm After Embolization of Aneurysmal Subarachnoid Hemorrhage

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Background: Delayed cerebral vasospasm (DCVS) following aneurismal subarachnoid hemorrhage (SAH) is a leading cause of poor prognosis and death in SAH patients. Effective management to reduce DCVS is needed. A prospective controlled trial was conducted to determine if massive cerebrospinal fluid (CSF) replacement (CR) could reduce DCVS occurrence and improve the clinical outcome after aneurysmal SAH treated with endovascular coiling.

Material/Methods: Patients treated with endovascular coiling after aneurysmal SAH were randomly divided into a control group receiving regular therapy alone (C group, n=42) and a CSF replacement group receiving an additional massive CSF replacement with saline (CR group, n=45). CSF examination, head CT, DCVS occurrence, cerebral infarction incidence, Glasgow Outcome Scale prognostic score, and 1-month mortality were recorded.

Results: The occurrence of DCVS was 30.9% in the C group and 4.4% in the CR group ($P<0.005$). The cerebral infarction incidences in the C and CR groups were 19.0% and 2.2% ($P<0.05$), respectively, 1 month after the treatments. Mortality was not significantly different between the 2 groups during the follow-up period.

Conclusions: Massive CR after embolization surgery for aneurysmal SAH can significantly reduce DCVS occurrence and effectively improve the outcomes.

MeSH Keywords: Cerebrospinal Fluid • Subarachnoid Hemorrhage • Vasospasm, Intracranial

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Background

The high incidence and mortality of delayed cerebral vasospasm (DCVS) of aneurismal subarachnoid hemorrhage (SAH) is a difficult problem in clinical management [1,2]. DCVS continues to be a leading cause of poor prognosis in SAH patients after regular treatment. SAH-induced inflammation has become a new therapeutic target to alleviate vascular spasm [3]. For example, oxyhemoglobin and thromboxane A(2) have been suggested as synergistic spasmogens, and the phospholipase C inhibitor neomycin attenuates vasospasm in a dose-dependent manner [4]. Because the physiological clearance of inflammatory cells and factors from the cerebrospinal fluid (CSF) is time-consuming, lumbar CSF drainage was used to accelerate the clearance [2]. Lumbar CSF drainage has been conducted to prevent cerebral vasospasm in many institutions after aneurysmal SAH, and can lower the risk of shunt-dependent hydrocephalus and improve the clinical outcome [5]. The amount of CSF drainage is limited due to concerns about cerebral hernia caused by low intracranial pressure. We have developed a massive CSF replacement (CR) protocol to replace an equal amount of CSF (about 150 ml) with saline, which maintains a stable intracranial pressure while accelerating the clearance of inflammatory elements in the CSF of SAH patients. We performed the present controlled single-center trial comparing the effect of CR on the early and late outcome in patients with aneurysmal SAH.

Material and Methods

General information of patients

Qualified patients in this study were aneurismal SAH patients who had accepted endovascular intervention in our hospital from September 2005 to July 2011. After admission, all patients underwent transcranial Doppler (TCD) and computed tomography (CT) examination. All the SAH patients were diagnosed by brain CT, and aneurysmal rupture was identified by digital subtraction angiography (DSA). Hospitalized patients were randomly assigned to either the control group (C group, regular treatment only) or the CR group according to admission on an odd- or even-numbered day of the month. Informed consent forms approved by the Institutional Review Board were signed by patients, or their relatives if the patient was unconscious. For conscious patients, surgical consent forms were signed by the patients themselves and their families together.

Treatments

All SAH patients received endovascular aneurysm coil embolization within 24–72 h after the onset. Regular treatments were given to all patients, including colloid fluid infusion to keep central venous pressure (CVP) at 8–12 cm H_2O and intravenous nimodipine administration for 7–10 days after the embolization. "Regular treatments" means the triple-H treatment (raising blood pressure, and increasing blood volume and hemodilution), and the use of calcium antagonists. For patients with disturbance of consciousness and Hunt-Hens classification class 4 or above, 20% mannitol 125 ml was used 2 times daily. Intravenous injection of 20 mg nimodipine within 8 h was performed once a day with a micro-pump. Gabapentin or ibuprofen for headache was included. Patients in the CR group additionally accepted CSF replacement (CR) beginning 2–3 days after the embolization. Briefly, CSF pressure was measured after conventional lumber puncture. If the pressure was >30 cm H_2O, 20% mannitol 250 ml plus 40 mg furosemide was rapidly infused to obtain a safe CSF pressure before subsequent procedures. Then, 10 ml CSF was drained followed by injection of 10 ml medical saline (0.9% sodium chloride). The procedure was done slowly and carefully to avoid the induction of cerebral hernia. We repeated these 2 steps every 3 min until approximately 150 ml of fluid was replaced. This CSF replacement procedure was performed every other day until the CSF became clear, and headache symptoms disappeared or were obviously improved. CSF replacement was usually performed a total of 4–7 times. At the end of the operation, patients had a CSF examination and head CT, and their DCVS occurrence, cerebral infarction incidence, and mortality within the first month of SHA onset were recorded. The CR protocol was reviewed and approved by the hospital Ethics Committee before the study began.

Lateral ventricle drainage was applied to patients who had sudden disturbance of consciousness with level 4 or above of Hunt-Hens classification. These patients were not included in this study.

Diagnosis of DCVS

Patient condition was closely observed and their neurological status evaluated based on clinical manifestations. For patients suffering aggravating headache, new or worsening focal neurological dysfunction, or decreasing consciousness level within 2 weeks after the SAH attack, an emergency head CT scan was done to exclude aneurysm re-bleeding, hydrocephalus, and new intracranial hematoma. If no epileptic seizure, hypoxemia, or electrolyte disorder was identified, a diagnosis of DCVS was considered. The average blood flow velocity of the middle cerebral artery (MCA) >120 cm/s at any time with TCD examination was also used as an indicator of DCVS [1–4], regardless of whether the patients had clinical signs. The TCD and CT examinations were done immediately after the operation and 1 week later. Because CT-based diagnosis of aneurysm and cerebral vascular malformation is insufficient, it was used in combination with DSA and TCD. In this study, DCVS and

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Table 1. Patient characteristics.

Characteristic	C group	CR group
Cohort size	42	45
Mean age (95% CIs), y	47.5 (35.2–59.8)	46.2 (33.7–58.7)
Sex, male: female	22: 20	23: 22
Hunt-Hess grade		
I	5	7
II	16	15
III	17	18
IV	4	5
Aneurysm type		
Anterior communicating artery	14	15
Middle cerebral artery	10	11
Posterior communicating artery	13	14
Other cerebral arteries	5	5
Hypertension	29	30
Diabetes	13	15
Smoking	21	23
Fisher grade		
I	10	10
II	27	26
III	5	6
IV	0	3

DCVS-induced cerebral infarction were defined at 1–3 weeks after the operation.

The occurrence of DCVS, the incidence of cerebral infarction, and the mortality rate were compared between the 2 groups. All patients were followed up for 1–3 years, with the Glasgow Outcome Scale (GOS) as an index of prognosis [5]. The prognosis was classified as good (GOS ≥4) or poor (GOS<3).

Statistical analysis

Data were analyzed with the chi square test. Differences between experimental groups were considered to be significant at a P value <0.05.

Results

Comparing clinical efficacy of RC protocol

Table 1 shows patient characteristics, indicating that the disease severity and the general situation of the 2 groups were comparable. The effect of CSF replacement was evaluated in terms of DCVS occurrence, cerebral infarction incidence, and mortality within 1 month after the embolization surgery (Table 2). The occurrences of DCVS (4.4% *vs.* 30.9%, P<0.05) and cerebral infarction (2.2% *vs.* 19.0%, P<0.05) were significantly lower in the CR group. Although 2 patients died in the C group, the mortality was not significantly different between the 2 groups (Table 2).

GOS prognostic evaluation

After discharge, the patients were followed up for 1–3 years and no patient was lost in this period. Table 3 shows the GOS prognostic score grades of the patients. A good prognosis existed in 85.71% (36/42) of patients in the C group and in 100% (45/45) in the CR group (P<0.05).

Discussion

Surgical treatment has greatly reduced cerebral re-hemorrhage and infarction in SAH patients. DCVS is still a major problem even though advanced microneurosurgery technology, triple-H treatment, and calcium antagonists have become routine therapies [1,2]. DCVS is a pathological process with cerebral

Table 2. Therapeutic effect of CSF replacement.

Group	Case numbers	DCVS occurrence*	Rate of cerebral infarction	Mortality rate
CR group	45	4.4% (2/45)	2.2% (1/45)	0% (0/45)
C group	42	30.9% (13/42)	19.0% (8/42)	4.76% (2/42)
P-value		<0.005	<0.05	>0.05

* If the VMCA of the middle cerebral artery was larger than 120 cm/s at any time with Transcranial Doppler (TCD) examination, cerebral vasospasm was defined.

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Table 3. The GOS prognostic score grades ($P<0.05$).

GOS prognostic score (grade)	C group (n=42)	CR group (n=45)
Good prognosis	36	45
5	29	41
4	7	4
Bad prognosis	6	0
3	3	0
2	1	0
1	2	0
Died 12 months later	1	0
Died 23 months later	1	0

Grade 5 – good recovery, back to normal life despite the mild defects; Grade 4 – mild disability but can live independently and be able to work with accommodation; Grade 3 – severe disabilities and daily care needed; Grade 2 – vegetative with minimal reaction; Grade 1 – death.

blood vessel constriction, decreased or absent blood supply of the involved tissue cells, and possible neural dysfunction. It may be related with the dysfunction of vascular endothelial cells and smooth muscle cells induced by blood cell debris [6], inflammatory factors [3,7], and metabolites [4]. CSF replacement could be a good choice to restore brain homeostasis before the causative agents of vasospasm are identified.

In this study, DCVS and DCVS-induced cerebral infarction were defined 1–3 weeks or even longer after the operation. Theoretically, it is not difficult to discern whether cerebral infarction is caused by DCVS or the operation. Aneurismal embolization has the potential to mechanically cause cerebral infarction, in which case the infarction usually occurs during or early after the operation. In contrast, DCVS-induced cerebral infarction is a process of ischemic damage of the involved tissue, which is usually a gradual and late process.

In Fisher classification, the severity of cerebral vasospasm was assessed by the amount of bleeding and by CT imaging. According to the standard, level 3 is wide SAH with intracerebral hematoma, and level 4 is the substrate pool and the surrounding brain cistern sylvian cistern bleeding with more than 50% probability of vasospasm [8]. Many clinical studies and animal experiments have confirmed that the extent and the severity of vasospasm are closely related with the volume of bleeding and the size of the blood-dispersed area. Therefore, the modified Fisher grade, which is closely related with the bleeding level, can be used as an early warning criterion for the occurrence of DCVS [9]. Our CSF replacement protocol significantly reduced the occurrences of DCVS to only 4.4%, which was one-seventh that of the control group.

In human adults, the volume of circulating CSF is approximately 150 ml due to the continuous production-absorption cycle. In the present study, up to 150 ml of CSF was replaced in a single operation to more rapidly remove harmful components, including impacted tissue-released substances, inflammatory cells, and blood cells, which may reduce the morbidity of DCVS. It should be mentioned that the total 150 ml fluid was not pure CSF. Because only 10 ml of CSF was replaced by saline in each injection, there was an increased proportion of saline in the sequentially drained fluid. The equal-volume exchange of CSF avoided a sudden decrease of intracranial pressure and the induction of cerebral hernia.

Repeated TCD can be used to assess cerebral hemodynamics, and for diagnosis and prognosis of cerebral vasospasm. The most important part of the TCD examination is estimation of lumen stenosis according to changes in blood flow velocity, and bilateral MCA usually should be measured and compared. The blood flow in the extracranial internal carotid artery can also be monitored. Normal blood flow velocity of the MCA is 30~80 cm/s. The diagnostic criteria of blood flow velocity for mild, moderate, and severe cerebral vasospasm is more than 120, 140, and 200 cm/s, respectively [10,11]. The indirect diagnosis of cerebral vascular spasm by the TCD-based blood flow velocity has high specificity and low sensitivity. In the case of suspected vasospasm, dynamic TCD examination should be carried out during the entire treatment period.

Conclusions

Our massive CSF replacement protocol not only significantly reduced the occurrence of DCVS and infarction, but also effectively improved patient outcome, indicating great potential in resolving the problematic DCVS in SAH and other cerebral diseases.

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