Neurologia medico-chirurgica (2010.10) 50巻10号:879～883.

Effectiveness of Brain Hypothermia Treatment in Patients With Severe Subarachnoid Hemorrhage: Comparisons at a Single Facility
(重症くも膜下出血患者における脳低温療法の効果 1施設での比較)

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Neurol Med Chir (Tokyo) 50, 879～883, 2010

Effectiveness of Brain Hypothermia Treatment in Patients With Severe Subarachnoid Hemorrhage — Comparisons at a Single Facility

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Abstract

The effectiveness of hypothermia treatment for severe subarachnoid hemorrhage (SAH) was evaluated at the same facility under the same director. A total of 187 patients with SAH, 67 admitted before the introduction of hypothermia treatment in May 1999 (early cases) and 120 treated thereafter (late cases), were transported to the National Cardiovascular Center and treated in the acute phase between November 1997 and September 2001. Brain hypothermia treatment was performed in 19 patients of the 120 late cases, 10 males and 9 females aged 33–72 years (mean 57. 6 years), treated by direct surgery in 15 and endovascular surgery in 4. The indications for hypothermia treatment were age of 75 years or younger, SAH due to rupture of a cerebral aneurysm, Japan Coma Scale score of 100 or higher, and initiation of treatment within 24 hours after the onset. The body core temperature was sustained at 34°C for 48 hours, rewarming was performed over 48 hours, and normothermia was maintained thereafter. The outcome, evaluated according to the modified Rankin scale (m-RS) on transfer to another hospital or after 3 months, was m-RS 3 in 1 patient, m-RS 4 in 4, m-RS 5 in 3, and death in 11. Before the introduction of hypothermia treatment (early period), 16 patients showed the indications for the treatment, and their outcomes were m-RS 3 in 2, m-RS 4 in 3, m-RS 5 in 2, and death in 9. Cerebral vasospasm was important as a prognostic factor, markedly deteriorating the outcome. Hyperthermia after therapeutic hypothermia induced brain swelling and markedly affecting the outcome. Brain hypothermia treatment did not improve the outcome of severe SAH compared with the period before its introduction. The emphasis in treating severe SAH should be placed on the maintenance of normothermia to prevent brain swelling and elimination of factors that may induce cerebral vasospasm, rather than interventional hypothermia for aggressive brain protection.

Key words: hypothermia, subarachnoid hemorrhage, cerebral vasospasm, normothermia, rewarming

Introduction

Hypothermia has a neuroprotective effect,[2] with known effects in head trauma[13,14,20] and cerebral ischemia,[3,4,7,15] but the clinical effectiveness for subarachnoid hemorrhage (SAH) remains unclear, probably because many factors including fever during the course,[9] vasospasm,[18] and excess decompression by skull bone removal are involved in the prognosis of SAH. The effectiveness of brain hypothermia treatment has been difficult to demonstrate in the large-scale studies conducted,[10,19,23] because of slight differences in the grading of SAH,[22] selection of treatment, and perioperative management.[1,11,16] In particular, the indications and selection of treatment may vary between facilities, and, in longitudinal studies at a single facility, the judgment of whether the results are specific to that facility or can be ascribed to hypothermia treatment is difficult.

The present study compares the outcomes in patients who underwent hypothermia treatment and those who did not at the same facility under the same director, and evaluates the effectiveness of

Received January 5, 2010; Accepted April 28, 2010

treatment and the significance of maintaining the optimal body temperature.

Methods

A total of 187 patients with SAH were transported to the National Cardiovascular Center and treated in the acute phase between November 1997 and September 2001. Of these patients, 67 were treated before the introduction of hypothermia treatment in May 1999 (early period), and 120 thereafter (late period). Brain hypothermia treatment was performed in 19 patients with severe SAH, 10 males and 9 females aged 33–72 years (mean 57. 6 years), treated by direct surgery in 15 and endovascular surgery in 4 among the 120 late cases (Table 1).

Indications for brain hypothermia treatment were age of 75 years or younger, SAH due to rupture of a cerebral aneurysm, Japan Coma Scale (JCS) score of 100 or higher, and initiation of treatment within 24 hours after onset. Since the main objective of hypothermia treatment is the prevention of secondary following primary damage, initiation of treatment within 24 hours after onset was included in the indications to promote the early initiation of treatment. Patients judged incapable of tolerating general anesthesia or hypothermia treatment and those with completely absent brainstem response were excluded.

After emergency admission, the diagnosis of SAH was established, and the level of consciousness was evaluated using the JCS and Glasgow Coma Scale. Then, SAH was graded according to the Hunt and Kosnik and World Federation of Neurosurgical Societies grading scales, the patients were sedated with flunitrazepam, tracheal intubation was carried out using a muscle relaxant, a central venous line was secured in the subclavian region, an arterial line was secured, and controlled respiration was initiated. Cooling was then started using a cooling blanket, which was placed under the patient. The ruptured aneurysm was identified by cerebral angiography, and clipping or coil embolization was performed. The core temperature was measured using a thermistor in the jugular vein. The core temperature was maintained at 34°C for 48 hours, rewarming was performed at 1°C per day, and, after rewarming, normothermia (36°C–<37°C) was maintained until Day 14. The blood flow of the horizontal part (M_1) of the middle cerebral artery was monitored daily by transcranial Doppler (TCD) ultrasonography. Neurological symptoms were difficult to assess during the course due to general anesthesia, so symptomatic vasospasm was judged to be present if the occurrence of cerebral infarction was confirmed by computed tomography or if the mean blood flow velocity of the M_1 segment of the middle cerebral artery determined by TCD was 120 cm/sec or higher and

Table 1 Summary of the 19 patients who underwent hypothermia treatment

Case No	Age (yrs)	Sex	GCS score	WFNS grade	Fisher CT grade	Procedure	m-RS score	Turning point
1	66	M	3	5	4	clipping	death	initial damage
2	59	F	4	5	4	clipping	death	initial damage
3	71	F	4	5	4	clipping	death	initial damage
4	68	M	4	5	3	coil embolization	death	initial damage
5	72	M	5	5	4	clipping	5	spasm
6	69	M	5	5	3	clipping	3	spasm
7	36	M	5	5	4	coil embolization	4	initial damage
8	54	F	6	5	4	clipping	4	initial damage
9	70	F	4	5	4	coil embolization	death	spasm
10	50	F	4	5	4	clipping	4	initial damage
11	63	M	4	5	4	clipping	4	initial damage
12	49	M	7	4	3	sutured	death	spasm
13	25	F	6	5	4	clipping	death	rebleeding
14	59	F	5	5	4	clipping	death	sepsis
15	72	F	3	5	3	clipping	5	spasm
16	69	M	4	5	4	clipping	death	initial damage
17	42	M	7	4	4	clipping	5	initial damage
18	33	M	5	5	4	clipping	death	spasm
19	68	F	4	5	3	coil embolization	death	spasm

CT: computed tomography, GCS: Glasgow Coma Scale, m-RS: modified Rankin scale, WFNS: World Federation of Neurosurgical Societies.

cerebral vessel stenosis was demonstrated by cerebral angiography. Symptomatic vasospasm was regarded as the prognostic determinant. The initial damage was regarded as the prognostic determinant in patients with no symptomatic vasospasm or complication during hypothermia treatment. The prognosis was made after 3 months or at transfer to another hospital using the modified Rankin scale (m-RS).

Results

The outcomes in the 19 patients who underwent brain hypothermia treatment were m-RS 3 in 1, m-RS 4 in 4, m-RS 5 in 3, and death in 11. Initial damage was the most common prognostic determinant in 10 patients, followed by symptomatic vasospasm in 7, sepsis in 1, and hemorrhage in 1. The outcomes in the 10 patients in whom initial damage was the prognostic determinant were death in 5, m-RS 4 in 4, and m-RS 5 in 1. The outcomes in the 7 patients in whom symptomatic vasospasm was the prognostic determinant were death in 4, m-RS 5 in 2, and m-RS 3 in 1. Death was caused by hemorrhage and sepsis, which are considered to be complications of brain hypothermia treatment, in 1 patient each (Table 1).

Sixteen of the 67 patients treated before the introduction of brain hypothermia treatment were considered to show indications for therapy. The outcomes were m-RS 3 in 2, m-RS 4 in 3, m-RS 5 in 2, and death in 9. Outcomes rated as m-RS 3 and 4 were considered satisfactory and those rated as m-RS 5 and death as unsatisfactory, and the chi-square test for independence (degree of freedom = 1, level of significance = 0.05, chi-square value = 3.841, level of significance = 0.01, chi-square value = 6.635) was performed between the patients treated before and after the introduction of hypothermia treatment. The chi-square value was 1. 1036, indicating no difference between the groups. The outcomes of patients who underwent brain hypothermia treatment were apparently poorer (Table 2).

Table 2 Comparison of outcomes before and after the introduction of hypothermia treatment

	Without hypothermia (n = 16)	With hypothermia (n = 19)
Satisfactory outcome	5	5
m-RS 3	2	1
m-RS 4	3	4
Unsatisfactory outcome	11	14
m-RS 5	2	3
death	9	11

The chi-square test for independence (degree of freedom = 1, level of significance = 0.05, chi-square value = 3.841, level of significance = 0.01, chi-square value = 6.635) for patients treated before and after the introduction of hypothermia treatment gave a chi-square value of 1.1036, indicating no difference between the groups.

Discussion

The present study compared the outcomes of treatment in the acute phase of SAH, at the same facility under the same director, in 67 and 120 patients before and after the introduction of brain hypothermia treatment, respectively, of whom 19 of the latter group underwent brain hypothermia treatment. Sixteen patients treated before the introduction of brain hypothermia treatment showed the indications for the hypothermia therapy, but their outcomes were more favorable than those for patients who underwent the therapy, so effectiveness could not be established.

Initial damage was the prognostic determinant in 10 patients, and half of them died, but the 4 patients with no complication or symptomatic vasospasm during the course had outcomes of m-RS 4. Cerebral vasospasm was the prognostic determinant in 7 patients, who had outcomes of death in 4 and m-RS 5 in 2, suggesting that cerebral vasospasm markedly exacerbates the outcome. Fever after rewarming causes marked brain swelling due to a rebound phenomenon,[12] and Case 9 developed brain swelling and cerebral vasospasm and died. In Case 11, hyperthermia after rewarming occurred on Day 8, and from the bitter experience in Case 9, the temperature of the blanket was reduced, and ice bags were applied to the axillary area and neck. In addition, the depth of sedation was increased to further reduce metabolic activity. These actions prevented brain swelling and cerebral vasospasm, and an outcome of m-RS 4 was obtained (Fig. 1). Therefore, careful monitoring of the patients is essential to maintain normothermia rewarming.

Body temperature rises within 10 days after SAH in 70% of patients and intraventricular hematoma is important role in this temperature increase.[6] Fever is also regarded as an independent factor of a poor prognosis.[9] Particularly, there have been reports that fever was related to cerebral vasospasm,[8,17,21,24] and that cerebral vasospasm could be controlled by brain hypothermia treatment.[19]

This study failed to confirm the effectiveness of brain hypothermia for the treatment of severe SAH, but emphasized the necessity for appropriate control of the body temperature rather than the evalua-

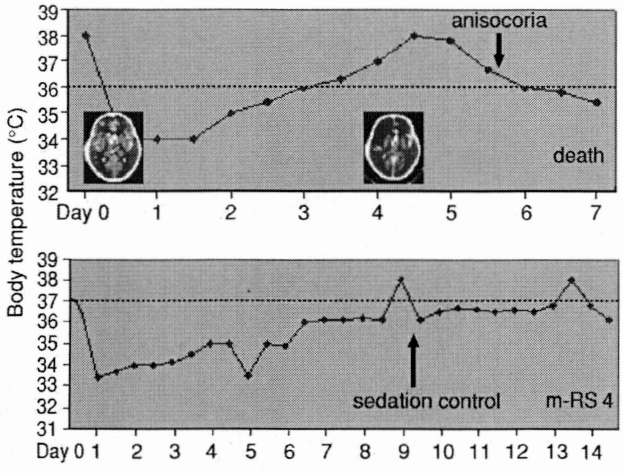

Fig. 1 Body temperature profiles in two patients who developed hyperthermia following rewarming. *Upper*: Case 9 became hyperthermic on Day 4, developed brain swelling, and died. *Lower*: Case 11 developed hyperthermia on Day 8, but controlling sedation and maintaining normothermia resulted in an outcome of modified Rankin scale (m-RS) 4.

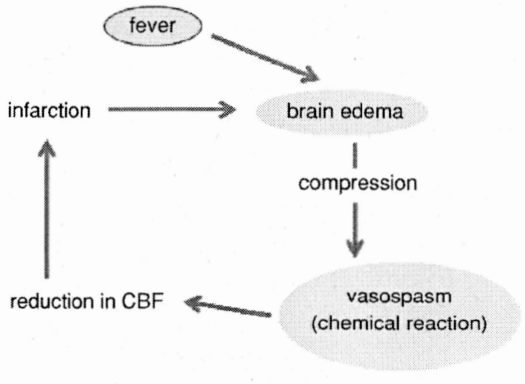

Fig. 2 Fever and vasospasm cycle. Fever promotes brain swelling and induces both cerebral vasospasm as a chemical reaction and reduction in cerebral perfusion due to compression caused by increased intracranial pressure. Cerebral infarction exacerbates such brain swelling and initiates a vicious cycle. CBF: cerebral blood flow.

tion of individual cases. Although this study was conducted at the same facility under the same director to eliminate variations in the therapeutic approach and perioperative management, possibly the number of patients was insufficient to definitively assess the effectiveness of hypothermia treatment. SAH is associated with a special condition called delayed cerebral vasospasm, and the present series also suggests that cerebral vasospasm markedly exacerbates the outcome. Multiple factors are involved in cerebral vasospasm,[5] but cerebral vasospasm as a chemical reaction coupled with a decrease in the perfusion pressure due to brain swelling caused by hyperthermia induces a further decrease in the cerebral blood flow, aggravating the swelling of the ischemic brain in a vicious cycle (Fig. 2). Although the appropriateness of introducing hypothermia treatment is unclear, optimal control of the body temperature is considered necessary to break this vicious cycle.

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