common pathway.[15–19] In experimental studies of cerebral ischaemia in primate, brain electrical activity diminishes at CBF below approximately 20 ml/100 g/min, whereas membrane failure and cell death occurs in CBF below approximately 10 ml/100 g/min.[20–26]

Intravascular volume expansion with induced arterial hypertension has been employed to ameliorate cerebral ischaemia following vasospasm and has proven to be effective on reversing neurological deterioration over 75% of the patients.[1] Transluminal angioplasty with or without intraarterial administration of papaverine hydrochloride has been employed for cerebral vasospasm that was refractory to conventional medical treatments.[2–7] These results have shown a significant relief of vasospasm and subsequent clinical improvement. In another study, however, the use of intraarterial papaverine hydrochloride showed only transient effects and did not improve final clinical outcomes.[27] Furthermore, angioplasty has been shown to lead favorable outcomes in patients with proximal vasospasm (M_1), but to result in significant rates of morbidity and mortality in patients with distal or diffuse vasospasm.[5]

Recent experimental studies have shown that mild hypothermia (32–34 °C of brain temperature) has been beneficial on cerebral ischaemia. The main mechanism of hypothermic brain protection is the reduction of ischaemia-induced neurotoxic glutamate release and intracellular Ca^{2+} accumulation. Hypothermia has also been shown to prevent the depletion of high-energy phosphate compounds,[11] and reduce free radical production[14] and tissue acidosis[9] caused by ischaemic insults as well as to protect the blood–brain barrier from disruption, thereby preventing postischaemic cerebral oedema[10] and ameliorating postischaemic neuronal injury.[12]

In severe head injury, mild hypothermia has been used to reduce intracranial hypertension[28] and secondary brain injury[29] and improve mortality and morbidity rates. Brain hypothermia demonstrated favorable effects on ICP, outcome and acute derangements of cerebral physiology and metabolism.[28,29] Four patients with cerebral embolism were treated with mild hypothermia for 3–5 days, and the results were more favorable than expected due to suppression of brain oedema and haemorrhagic infarction.[30] Although the beneficial effects of mild hypothermia on long-lasting critical ischaemia due to cerebral vasospasm have not been definitely established, we have employed mild hypothermia in progressive ischaemia for neuronal protection. In the Group 1 patients, mild hypothermia was applied to ameliorate ischaemic neuronal damage by critical ischaemia following vasospasm that could not be controlled with conventional medical and intravascular treatments. In the Group 2 patients, hypothermic treatment was applied to reduce further ischaemic brain injury by preexisting symptomatic vasospasm.

Cerebral blood flow analysis

Because all patients were completely sedated and cooled under controlled ventilation, frequent measurements of CBF using ^{99m}Tc-ECD SPECT were technically difficult. We performed the CBF study in 7 of 8 patients. In patients who developed DINDs, the CBF values were 11–34 (mean 26.7) ml/100 g/min in the region of the affected hemisphere. This finding agrees with the results of Symon,[31] who reported that the CBF values in patients showed an altered level of consciousness and mild to moderate motor and/or sensory deficits were between 18 and 30 ml/100 g/min. Finnerty et al.[32] also demonstrated that the symptoms of global cerebral ischaemia appear when the CBF falls to approximately 30 ml/100 g/min. Mild hypothermia resulted in 6.4 ml/100 g/min decrease in rCBF in our study which was compatible with previous reports[28,29] and rCBF increased by a mean value of 10.8 ml/100 g/min by rewarming.

The patients who showed a good recovery or moderate disability had relatively high rCBF values which were 27 and 34 ml/100 g/min at the onset of DINDs and 19–28 ml/100 g/min during hypothermia. The rCBF values continued to increase by rewarming, and reached to the normal values after the hypothermic treatment. The patient with severe disability showed relatively low rCBF value (11 ml/100 g/min) at the onset of DINDs, and also during and after the hypothermic treatment. Powers et al.[33] reported that in patients with cerebral vasospasm, the hemiparesis eventually recovered when the rCBF values were greater than 15.0 and 16.2 ml/100 g/min and failed to recover when the rCBF values were 12.0 and 11.7 ml/100 g/min using positron emission tomography. In the study of Xenon-enhanced computerised tomography, CBF values fell below 15 ml/100 g/min resulted in an infarction on CT scan and CBF values greater than 18 ml/100 g/min caused neither significant complications nor neurological deterioration.[34] Other previous studies have shown a poor correlation between a focal decrease in CBF and the presence of neurological deficits.[35–38]

While the present findings indicate that measurements of CBF at the onset of DINDs, and during and after mild hypothermia may be useful in differentiating indication and prediction of outcome of hypothermic treatment, we could not draw any definite conclusions regarding this particular treatment in terms of severity, duration or extent of ischaemia, because the fact that cerebral vasospasm is not a static process and we evaluated this dynamic process with only a few measurements during the progress of vasospasm and hypothermic treatment.

Clinical significance of mild hypothermia in vasospasm

Among the 5 patients who proved refractory to medical and intravascular treatments for cerebral vasospasm (Group 1), 4 patients showed favorable outcomes (3 GR, 1 MD) following mild hypothermia. Because the underlying pathology of the cerebral vasospasm is a varying degree of critical ischaemia lasting for more than several days, long-term application of mild hypothermia is a reasonable strategy in reducing neuronal injury. In fact, without hypothermic treatment such patients might exhibit progressive deterioration and poor outcome. However, it must be noted that mild hypothermia does not abrogate or relieve the progression of cerebral vasospasm, as indicated in case 1. When the DINDs are evident in a patient with an untreated aneurysm, surgeons face a dilemma in deciding whether or not to operate; that is, manipulation of spastic arteries inevitably worsens the vasospasm, leading to clinical deterioration, and aggressive hyperdynamic therapy to overcome vasospasm cannot be started without obliterating the aneurysm. In the present study, we applied mild hypothermia to protect the critically ischaemic brain during and after the surgery. Transluminal angioplasty and intraarterial infusion of papaverine hydrochloride were performed postoperatively when angiography and CBF study indicated a progression of the vasospasm. Thus mild hypothermia exerted protective effects on critical ischaemia and provided a significant therapeutic time window to employ an interventional therapy. All 3 patients in Group 2 achieved favorable outcomes. Good outcomes in Groups 1 and 2 with mild hypothermia, indicates the therapeutic benefit of this treatment with respect to neurological improvement.

Complications of prolonged mild hypothermia

It is important to be aware of the harmful effects of mild hypothermia. During the hypothermia therapy, cardiopulmonary

suppression, serum electrolytes abnormalities, abnormal coagulopathy and multiple organ failure were occasionally encountered. Such complications were examined daily and treated according to the laboratory data and close physical monitoring.

Pneumonia was the most common and serious complication, which was treated with antibiotics, frequent intratracheal irrigation and suction and changes in body position. Multiple organ failures, including liver, heart and kidney, were also encountered and were treated with intensive medical care. Of the two fatalities encountered in this study, neither was attributed to any of the above complications.

CONCLUSION

Mild hypothermia led to a significant favorable outcome in patients with severe cerebral vasospasm that was refractory to medical and intravascular treatments. This therapy is recommended in patients with good preoperative neurological grade and in patients who receives a delayed aneurysmal clipping with DINDs due to vasospasm. Although the present cohort was relatively small, the promising results suggest that the application of this treatment is warranted in selective patients with uncontrollable severe cerebral vasospasm following SAH.

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