Hyperdynamic Therapy for Cerebral Vasospasm

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Abstract

The effects of hyperdynamic therapy on patients with cerebral vasospasm following subarachnoid hemorrhage (SAH), under normal blood pressure (BP) and normal blood volume conditions, are reported. Forty-four patients, who underwent surgery for aneurysms in acute stage, received hydroxyethyl starch (500 ml/day) postoperatively to prevent dehydration. Twenty-four of the 44 patients with prominent SAH on the computed tomographic (CT) scan, anticipating to develop cerebral ischemia due to vasospasm, were given dobutamine (DOB). The BP was maintained within the normal range, and the heart rate was kept below 130/min. In the 24 patients treated with DOB, cerebral blood flow (CBF) was measured repeatedly by the 133Xe intravenous injection method. In 8 of these 24 patients, the cardiovascular function was monitored with Swan-Ganz (S-G) catheters. Twelve of the 44 patients (27%) developed delayed neurological deficits associated with cerebral vasospasm. The neurological deficits were reversed by the administration of DOB, at a dose of 8-25 (average 12.4) µg/kg/min. In 43 patients, the ischemic lesions associated with vasospasm did not appear on CT scan and the patients were of normal condition at discharge. However, one patient showed multiple low-density lesions on CT scan. This was because of the failure of hyperdynamic therapy due to pulmonary complications. No case of pulmonary edema or heart failure due to volume overload was noted. In the 24 patients with prominent SAH, CBF increased significantly by up to 20% following DOB administration, although the BP stayed in the normal range. In the 8 patients monitored with S-G catheter, the cardiac index increased markedly after treatment with DOB, but the pulmonary wedge pressure was remained below 10 mmHg. There were no significant changes in either the stroke volume index (SI) or the stroke-CBF (CBF/heart rate).

Hyperdynamic therapy with DOB is effective for the postoperative management of cerebral vasospasm, and neither induced hypertension nor hypervolemia was necessary. DOB had positive inotropic effects, but did not decrease the SI or stroke-CBF, so that hyperdynamic therapy with DOB increased the CBF in patients with vasospasm, and caused no side effects.

Key words: vasospasm, hyperdynamic therapy, cerebral blood flow, dobutamine

Introduction

Cerebral vasospasm following subarachnoid hemorrhage (SAH) is well known and has been discussed considerably. However, no safe and reliable therapy has yet been developed, and the disorder still remains a serious problem greatly affecting the prognosis for the patient. Many reports have suggested that the so-called hypervolemic-hypertensive therapy is effective for preventing and treating cerebral vasospasm, but such therapy often causes complications such as heart failure, pulmonary edema, and cerebral edema because it is a non-homeostatic therapy, and physicians often experience considerable difficulties in managing patients with the therapy. We believe that this therapy acts essentially by improving cerebral circulation associated with damaged autoregulation by increasing the cardiac output and thereby maintaining systemic circulation at a hyperdynamic condition characterized by an accelerated cardiac function. In this study we succeeded in preventing any complications while achieving good therapeutic results in patients with cerebral vasospasm by hyperdynamic systemic circulation management while maintaining blood pressure (BP) and systemic blood volume within the normal range.

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Materials and Methods

The study involved 44 patients who were admitted to our institute from January 1987 through September 1988, and underwent surgery for aneurysms within 3 days after the onset of SAH. There were 15 male and 29 female patients with ages ranging from 34 to 77 years (mean, 55 years).

Table 1 shows the locations of aneurysms, neurological condition on admission according to Hunt & Kosnik's classification, and the computed tomographic (CT) grade of SAH according to Fisher's classification. Postoperatively, patients received the usual fluid transfusions and meals together with 500 ml of hydroxyethyl starch (Hespander) every day to prevent dehydration. If ischemic symptoms due to cerebral vasospasm occurred, the patient received dobutamine (DOB) at an initial dosage of 3 µg/kg/min, which was gradually increased until the symptoms disappeared. In addition, if the development of cerebral vasospasm was predictable from severe SAH on admission, the patient similarly received DOB. Hypertensive patients began to receive various antihypertensive agents from the first day of admission so that their systolic BP could be controlled below 160 mmHg.

The cerebral blood flow (CBF) in the patients with DOB administration was measured repeatedly by the 10 mCi $^{133}$Xe intravenous injection method in order to calculate the whole-brain average of the initial slope index (ISI). In 8 of such patients, Swan-Ganz (S-G) catheters were emplaced in order to calculate the cardiac index (CI), systemic vascular resistance index (SVRI), stroke volume index (SI), and pulmonary wedge pressure (PWP) in an attempt to determine the changes in the cardiovascular function before and after the DOB administration. Furthermore, the changes in the CBF value divided by the heart rate were also investigated in terms of the stroke-CBF, which is the CBF for every pulse beat.

The paired Student t-test was employed for statistical analysis, in which the level of 5% or less was accepted as a significant difference.

Results

I. Therapeutic results

Twelve (27%) of the 44 patients developed neurological deficits associated with cerebral vasospasm but the ischemic symptoms were reversed in all of them by the administration of increasing doses of DOB. The total dosage of DOB required for the elimination of clinical symptoms was 8–25 µg/kg/min (mean, 12.4). In 43 patients (98%), no ischemic lesions associated with vasospasm appeared on CT scans and the patients were in normal condition at discharge (Table 2). However, the CT scan of one patient with severe bronchopneumonia showed multiple low-density lesions (Fig. 1). No complications such as pulmonary edema, heart failure, hemorrhagic infarction, and brain swelling occurred, although mild electrolyte imbalances were observed in 5 patients. Polyuria and tachycardia were also absent.

II. Effect of DOB on cerebral circulation and systemic circulation

Measurements of CBF were made before and after the DOB administration in 24 patients, in all of whom the CBF showed a significant increase by more than 20% from a mean of 40.2 to a mean of 60.3.
48.8 ml/100 gm/min. However, no change was observed in the stroke-CBF (Fig. 2). The DOB administration was followed by significant increases in the heart rate, systolic BP, and pulse pressure whereas the mean BP and diastolic BP remained unchanged (Fig. 3). There was no patient in whom BP and heart rate had to be maintained at a high level in order to improve the ischemic symptoms due to vasospasm.

For the 8 patients in whom the cardiovascular function was monitored with S-G catheter, CI showed a significant increase from 3.4 to 4.91/min/m². SVRI significantly decreased from 2465 to 1852 dyne·sec·cm⁻⁵·m² whereas SI was unchanged and PWP was kept below 10 mmHg in all 8 patients (Fig. 4).

**Discussion**

The therapeutic approaches to cerebral vasospasm may be divided into two major categories; one is treatment from the outside of blood vessels and the other is treatment from the inside of blood vessels. Treatment from the outside of blood vessels may be represented by the removal of subarachnoid hematoma in aneurysm surgery. The procedure aims at preventing cerebral vasospasm by removing subarachnoid hematoma¹⁶ but, according to our experience, they are more liable to cause excessive brain retraction and damage to the perforating arteries because they require an adequately large operating field.¹² Furthermore, if the patient requires a bilateral craniotomy, the procedure is associated with severe operative invasion, making it difficult for a
surgeon to remove the hematoma over the brain surface. Thus they may not be regarded as a satisfactory preventive measure against cerebral vasospasm. Kodama et al. obtained good therapeutic results by means of cisternal irrigation therapy with urokinase and ascorbic acid. However, their method does not always succeed in completely preventing symptomatic cerebral vasospasm; in addition, the technique requires bilateral craniotomy to facilitate drainage, and continuous monitoring of the infusion and drainage fluid volumes thus requiring much personnel time for postoperative patient control. In short, treatment from the outside of blood vessels seems to be complicated and limited in application.

Treatment from the inside of blood vessels, in which the vasodilating effects of Ca antagonists is utilized has attracted an increasing amount of attention recently. However, no report has shown that Ca antagonists have successfully been used to increase CBF in the period of cerebral vasospasm. Furthermore, Ca antagonists cannot completely prevent the occurrence of cerebral ischemic symptoms associated with vasospasm. Thus they cannot be accepted as a perfect therapeutic method for symptomatic vasospasm. As there are currently no drugs that fully dilate spastic blood vessels, the crucial point in the treatment is how the blood flow within the spastic blood vessels can be successfully kept above the threshold of cerebral ischemia. In this context, hypervolemic-hypertensive therapy could be expected to be an effective therapeutic method by which emphasis can be placed on hemodynamic circulatory control.

I. Limitations of hypervolemic-hypertensive therapy

Hypervolemic therapy aims at improving cerebral circulation by increasing the systemic blood volume and raising the left ventricular diastolic pressure, thus increasing cardiac output. However, if a hypervolemic condition is to be maintained in a patient having a normal renal function, a large fluid transfusion volume exceeding the urine volume must be given. Such a fluid transfusion often causes complications including pulmonary edema, heart failure, bleeding tendency, and electrolyte imbalances, and hence the patient must be subject to strict monitoring using S-G catheter and other methods. In addition, the use of a plasma expander such as albumin has a social limitation because of the high cost and thus cannot be administered in safety and in large doses as a volume expander. Finn et al. found that the changes in PWP well correlated with alleviation in the aggravation of neurological symptoms, but its critical level was hazardous since it was close to the critical level of heart failure, suggesting limitations for the non-homeostatic management of patients. The problem is that it is an attempt to maintain systemic circulation in a hyperdynamic condition by hypervolemia only. In short, the therapy cannot be recommended for elderly patients and patients with cardiovascular disorders.

Hypertensive therapy aims at improving the cerebral circulation by increasing the systemic BP and hence increasing the cerebral perfusion pressure. However, an excessive increase in the BP may promote cerebral edema and hemorrhagic infarction. Furthermore, administration of catecholamine in large doses may cause marked tachycardia and arrhythmia. The therapy has thus many problems in the actual management of patients. An attempt to raise the BP by angiotensin may lead to an increase in the peripheral vascular resistance, resulting in an increase in afterload, as a result of which the cardiac output decreases instead of increases, thereby causing hypodynamic conditions. So even if the peripheral vascular resistance other than the cerebral circulation increases, resulting in an increase in the percentage of cerebral circulation blood volume of the total stroke volume, the CBF may eventually decrease, provided that a decrease in the whole cardiac output occurs. Our experience includes a case with hypertension in which we did not provide countermeasures against cerebral vasospasm because the BP was too high and the patient eventually incurred symptomatic vasospasm, which resulted in serious neurological deficits. The limitations to this therapy seen to be because attention is directed to the

Fig. 4 Changes in cardiac index (CI), stroke volume index (SVRI), and pulmonary wedge pressure (PWP) (n = 8). CI increased and SVRI decreased significantly after DOB treatment, although there were no significant changes in SI and PWP. *p < 0.01, **p < 0.001.
perfusion-pressure difference of the cerebral circulation alone on the basis of the assumption that cerebral circulation is just like water flowing through a pipe.

Both hypervolemic therapy and hypertensive therapy are based on the administration of, for example, dopamine, and may be classified as methods aiming at the hyperdynamic control of patients by increasing cardiac output if considered from the aspect of systemic circulation. Tanabe et al. and Finn et al. also pointed out the importance of hyperdynamic control of the systemic circulation, but there is a limit to the increase in cardiac output by volume overload, and if further hyperdynamic control is required, catecholamine must be administered. If used independently, both hypervolemic therapy and hypertensive therapy are inadequate to improve the cerebral circulation, and patient control with them is considered to be very complicated and uncontrollable. Conversely, if the cardiac function has been accelerated sufficiently enough to improve the cerebral circulation in the period of cerebral vasospasm, there is no necessity for the control to promote further over-hydration and a significant increase of BP. The therapy reported here has improved this aspect, and it can be said that DOB administration while preventing dehydration provided safe patient control and a reliable method to improve cerebral circulation.

II. Hyperdynamic therapy

No clear explanation of why the cerebral circulation in the period of cerebral vasospasm can be improved by hyperdynamic control of systemic circulation in the literature. In experiments using normal adult cats, Davis and Sundt found that CBF was decreased by hypovolemia induced by phlebotomy. Their findings are based on physiological control of cerebral circulation but may also be applicable to cerebral circulation in cerebral vasospasm, by suggesting that hypovolemia caused by dehydration may decrease vascular beds and lower CBF. They also reported that even when a hyperdynamic state was produced by an increase in the cardiac output by administration of isoproterenol, the CBF remained unchanged. This statement should be interpreted as indicating that the cerebral circulation remains unchanged even if the cardiac function is accelerated, as long as autoregulation is maintained. However, cerebral blood vessels in vasospasm are spastic vessels lacking elasticity while the cerebral circulation is strongly influenced by the systemic circulation. So it would be reasonable to think that the acceleration of the cardiac function might directly lead to an improvement in cerebral circulation. Dopamine, one of the cardiotonic drugs, is liable to induce dehydration due to its potent diuretic effect by increasing renal blood flow. Dopamine and isoproterenol have positive inotropic effects but produce a decrease in stroke volume because they strongly promote increased heart rate, possibly leading to a

Fig. 5 Schematic drawing of changes in BP, cardiac output (CO), stroke volume (SV), and stroke-CBF. A: Normal state. B: Hyperdynamic state under normal BP and normal blood volume conditions treated with DOB. CO increased and there are no changes in BP, SV, and stroke-CBF. C: Hyperdynamic state under hypertensive and hypovolemic conditions treated with dopamine. BP and CO increased, although SV and stroke-CBF decreased. D: Hypodynamic state under hypertensive and hypovolemic conditions treated with angiotensin. BP increased, although CO, SV, and stroke-CBF decreased.
decrease in the cerebral circulatory blood volume for every pulse beat. This decrease of CBF associated with one pulse beat may contribute to a decrease in the inside pressure of the spastic vessels, thus damaging cerebral circulation, even if there is an apparent increase in BP. In short, it is important to keep the systemic circulation in a hyperdynamic state in such a way that the stroke volume is not lowered but rather increased. In this context, DOB which has a strong positive inotropic effect but low heart rate promotion and diuretic effects is probably the best catecholamine currently available for the treatment of cerebral vasospasm.9)

Essentially DOB is used in the form of continuous microdose administration on the basis of the number of y calculated per body weight and time (min), but it should not be administered on a BP basis. In setting the dose, we referred to the cardiac index and set the target at 4.5-5.5 l/min/m² as proposed by Finn et al.10) In view of the report pointing out the development of tachyphylaxis,10) caution should be exercised in choosing the dosage. Insertion of a S-G catheter is required for the precise evaluation of systemic circulation, but catheter insertion is not always possible in patients. Therefore, less invasive approaches including the dye dilution method must be considered.

III. Patient control

Prevention of dehydration: As mentioned above, it is highly probable that dehydration may decrease cerebral circulation during the period of cerebral vasospasm. Patients with ruptured aneurysms are liable to become dehydrated due to the decrease in water consumption caused by disturbance of consciousness, fever, vomiting, and use of dehydration agents. The central venous pressure (CVP), which is measured to evaluate the circulatory blood volume, only reflects the pressure of the right heart, and this pressure is not correlated with the PWP once it exceeds 8 mmHg.14) In elderly patients and patients with cardiovascular disorders, furthermore, it is dangerous to accept the value as it is.10) Dehydration may also be caused by fever resulting from catheter bacteremia, and thus caution should be exercised in the patients with CVP catheter. In patients with intracerebral hematoma, dehydration agents such as mannitol must additionally be used but excessive dehydration should be avoided. We make it a rule to minimize the use of dehydration agents, believing that the free use of dehydration agents is contradictory to DOB therapy. If the patient develops tachycardia of over 130/min with the DOB administration, we usually supplement the fluids sufficiently because we believe that the heart is simply working ineffectively if dehydration is present. Earlier we resorted to blood products including albumin as volume expanders, but we are now using hydroxyethyl starch instead because blood products are too expensive to be used freely. Hydroxyethyl starch is an inexpensive and completely effective agent for preventing dehydration and causes no complications, but even hydroxyethyl starch is not required in patients who do not present the state of dehydration on usual fluid transfusion.

Measurement of CBF: We make it a rule to conduct serial measurements of CBF by the 133Xe intravenous injection in patients with cerebral vasospasm. Although the method does not provide a three-dimensional analysis, it is a useful tool to evaluate the cerebral circulation because it is highly reproducible and permits repeated measurements. Immediately after the operation, the brain tissue usually becomes hyperemic and presents high CBF values. Therefore, by using the CBF level at around day 4 after the onset as a reference, we usually administer DOB promptly if CBF falls below that level. Furthermore, this kind of repeated quantitative evaluation of CBF is also useful for evaluation of the therapeutic effect of DOB administration. It is important in the treatment of vasospasm that the physician should not miss the optimum time for initiation of treatment. Once a patient develops decrease in food intake, restlessness or akinesia, talkativeness or silence and an uncooperative attitude aside from the well known neurological symptoms such as paresis and aphasia, the physician should start the treatment at once, assuming that they represent ischemic symptoms due to vasospasm. More recently, the measurement of the flow velocity based on the transcranial Doppler technique has been practiced. This is a very useful method to identify spastic blood vessels before the development of symptomatic vasospasm.

Management of BP and respiration: As reported above, we could obtain satisfactory therapeutic results in patients with cerebral vasospasm without raising the BP. In the treatment of our hypertensive patients, therefore, we make it a rule to reduce the BP soon after the operation, employing the systolic BP of 150 mmHg as a reference. Oral administration of peripheral vasodilators such as Ca⁺ antagonists and angiotensin I converting enzyme inhibitors constitutes our first choice of treatment, but we often find it necessary to administer β-blockers in patients with essential hypertension showing marked left ventricular hypertrophy. Use of DOB in the treatment of cerebral vasospasm during the administration of β-blockers may appear to be contradictory, but the therapeutic effects may be more easily evaluated by.
controlling the systemic circulation hyperdynamically through the graded DOB administration after the BP is reduced to within the normal range before the patient enters the period of cerebral vasospasm.

The series of patients reported here included one patient in whom cerebral infarction occurred due to cerebral vasospasm. This patient has a history of thoracoplasty due to pulmonary tuberculosis and was found to have a complication of severe bronchopneumonia on the remaining lung. The patient required forced and controlled ventilation which resulted in a significant increase of airway pressure, leading to a decrease in venous return and reduction of cardiac output, which was probably responsible for the development of cerebral infarction. Control ventilation causing a significant increase in airway pressure as well as excessive positive end-expiratory pressure may decrease the venous return, leading to reduction of the cardiac function and even damage to the cerebral circulation in the end. In the treatment of patients with bronchopneumonia special attention should be paid to this point. In addition, operations conducted under general anesthesia with forced ventilation, such as shunt operations, should not be carried out in the period of cerebral vasospasm.

References


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