Hypervolemic Versus Normovolemic Therapy in Patients with Ruptured Cerebral Aneurysm

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Background: Postoperative triple H therapy is regarded as a mainstay for prophylaxis and treatment of delayed ischemic neurologic deficit (DIND) after subarachnoid hemorrhage (SAH). However, there are doubts about its effectiveness. This study was performed to assess hypervolemic dynamic fluid therapy in patients with ruptured cerebral aneurysms.

Methods: The authors retrospectively studied a total of 393 patients with ruptured cerebral aneurysms, consisting of early surgery with or without intraoperative ventriculostomy during a recent 5 year period (July 1998–June 2003). Hypervolemic dynamic fluid therapy was initiated postoperatively in patients with DIND. Since January 2001, however, patients were maintained in normovolemia and normotension, and when DIND had manifested, low molecular weight dextran was only added. The incidence of DIND and outcome according to Glasgow Outcome Scale at 6 months of the normovolemic group were compared with the hypervolemic group. All patients were followed for at least 14 days after the admission including clinical assessment, TCD recording, CT scanning, CVP measurements, and nimodipine infusion.

Results: Subjects in the two treatment groups were similar with regard to age, sex, Fisher grade, Hunt-Hess grade, aneurysm location, and aneurysm size. No differences were found between the two groups regarding the incidence of DIND (29/182: 15.9% vs 29/211: 13.7%). Surgical outcome in the normovolemic group (good, 171/211: 81.0%) was comparable to the hypervolemic group (good, 154/182: 84.6%).

Conclusions: Although careful fluid management to avoid hypovolemia may reduce the risk of DIND after SAH, prophylactic hypervolemic dynamic fluid therapy is unlikely to confer an additional benefit.


Key Words: Normovolemic therapy, Delayed ischemic neurologic deficit, Aneurysm

INTRODUCTION

Some discrepancies may exist between clinical experience and animal models for vasospasm because the latter are artificially made by injection of blood and have inter-species differences, compared with the clinical state which has pressure-dependent subarachnoid hemorrhage (SAH). Therefore, most of the treatment effects have been shown to be less compelling when trials have been conducted in clinical settings.

Previously published series1-4 have reported that postoperative hypervolemic dynamic fluid therapy can reverse ischemic deficits in symptomatic patients. Accordingly, this intervention is now routinely performed at most medical centers for the prevention of delayed ischemia and improvement of clinical outcomes. However,
the results have been inconsistent and there are doubts about its effectiveness.\textsuperscript{5–7} This study was performed to assess hypervolemic dynamic fluid therapy in patients with ruptured cerebral aneurysm.

**MATERIALS AND METHODS**

The authors studied a total of 393 patients with ruptured cerebral aneurysms, consisting of early surgery with/without intraoperative ventriculostomy during the most recent 5 years (July 1998–June 2003) in a retrospective study. Patients were excluded for the following conditions: 1) patients exceeding 70 years of age; 2) patients with an associated intracerebral hematoma; 3) patients with Hunt–Hess grade of 5 (no brain stem reflex, poor angiographic filling); 4) patients with past history of major heart, lung, or renal disease; 5) patients with hypotension on admission. Delayed ischemic neurologic deficit (DIND) was defined as the delayed onset of consciousness decrement or focal neurological deficits not attributable to metabolic disturbances, hydrocephalus, or cerebral edema. To identify DIND, all patients had complete neurological examinations and were also monitored with transcranial Doppler (TCD) daily for at least 14 days after their admission. TCD measurements were conducted through the temporal window with the use of a 2 MHz transducer (EME TC 2020). Brain CT scanning was done on all patients when it was required. All patients had central venous pressure (CVP) measurements and nimodipine infusions. When a new neurological deterioration developed, we did TCD examinations or an angiography to confirm vasospasm. Angiographic confirmation of vasospasm was available in 15 patients but was not an absolute requirement. TCD criteria for vasospasm were defined as an increase in mean flow velocity of 120 cm/sec or more in the MCA\textsuperscript{8} and also with a high Lindegaard ratio of more than 6.\textsuperscript{9} All patients were managed according to a uniform perioperative policy that included intensive care, invasive hemodynamic monitoring, and the same anesthetic technique.

The patients were divided into two groups; a hypervolemic group and a normovolemic group. Briefly, hypervolemic dynamic fluid therapy was done at our institution with a slight modification of the University of Virginia regimen.\textsuperscript{10} Asymptomatic patients were treated with mild volume expansion by means of an intravenous intake of approximately 3,000 ml of saline per day, of which one third was colloid (5% albumin solution) and two third was crystalloid. Induced hypertension was avoided at this stage. In asymptomatic patients with TCD or angiographic vasospasm, the ratio of colloid was only increased to two third of the same total volume without induced hypertension, maintaining the hematocrit at 35 to 40%. In patients with clinically symptomatic vasospasm, hypervolemia with 5% albumin as a volume expander was induced to maintain a central venous pressure between 10–12 mm Hg. Hypertension was induced with a vasopressor (dopamine) to achieve a systolic arterial pressure of 150 to 170 mm Hg. Although mannitol was used in most patients with SAH pre- and postoperatively from January 1998 to June 2001, we did not administrate any osmotic diuretics since July 2001 in almost all good grade patients. The mannitol was administered in those patients who showed intracerebral hematoma, small ventricle, and intraventricular hemorrhage on initial CT or swollen brain intraoperatively. In the postoperative period since 2001, patients were maintained in normovolemia and normotension, and when DIND had manifested, 50 g (500 ml) daily of low molecular weight dextran was only added for 5 days. The two groups were checked for comparability of demographic and clinical variables including age, sex, Fisher grade,\textsuperscript{11} Hunt–Hess grade,\textsuperscript{12} aneurysm location, and aneurysm size. In addition, the incidence of DIND and outcome were compared between both groups. Outcome was assessed at 6 month follow-up intervals according to the Glasgow Outcome Scale (GOS) with "good" or "moderate disability" classified as a good outcome (GOS 1–2) and "severe disability", "vegetative" or "death" classified as a poor outcome (GOS 3–5).

The statistical significance of observed differences between the variables were assessed by a t-test for age and size of aneurysm, Fisher’s exact test for DIND as a cause of mortality and morbidity, and $\chi^2$ test for other variables. A $p$ value <0.05 was considered significant.
Table 1. Patient’s demographic data and clinical characteristics (number)*

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic group</th>
<th>Normovolemic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>182</td>
<td>211</td>
</tr>
<tr>
<td>Age (mean years)b</td>
<td>55±5.4</td>
<td>59±6.2</td>
</tr>
<tr>
<td>Sex (male / female)</td>
<td>71 / 111</td>
<td>84 / 127</td>
</tr>
<tr>
<td>Fisher Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td>11</td>
<td>18</td>
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<td>grade 2</td>
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<td>66</td>
</tr>
<tr>
<td>grade 3</td>
<td>73</td>
<td>55</td>
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<tr>
<td>Hunt/Hess Grade</td>
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<tr>
<td>grade 1</td>
<td>33</td>
<td>27</td>
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<tr>
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<td>grade 4</td>
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<tr>
<td>Aneurysm Location</td>
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<tr>
<td>ACA</td>
<td>62</td>
<td>70</td>
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<tr>
<td>ICA-P com</td>
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<tr>
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<tr>
<td>Post Circulation</td>
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<td>6</td>
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<tr>
<td>Multiple</td>
<td>16</td>
<td>21</td>
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<tr>
<td>Size of Aneurysm (mm)b</td>
<td>7.1±0.4±3.5±0.2</td>
<td>6.9±0.3±3.2±0.2</td>
</tr>
</tbody>
</table>

ACA; anterior cerebral artery, ICA; intracranial internal carotid artery, P com; posterior communicating artery, MCA; middle cerebral artery.
*All clinical variables are not significantly different between two groups (t-test for age and size of aneurysm, χ² test for other variables). bdata are expressed as the mean±the standard error.

RESULTS

One hundred and eighty–two patients were included in the hypervolemic group and 211 in the normovolemic group. Subjects in the two treatment groups were similar with regard to age, sex, Fisher grade, Hunt–Hess grade, aneurysm location, and aneurysm size (Table 1). No differences were found between the two groups regarding the incidence of DIND (29/182: 15.9% vs 29/211: 13.7%, χ² test, p value=0.70), DIND as a cause of mortality and morbidity also did not demonstrate any significant differences between the two groups (5/182: 2.7% vs 3/211: 1.4%, Fisher’s exact test, p value=0.48) (Fig. 1). The complications of prophylactic hypervolemia developed before any evidence of DIND became manifest. There were two cases of pulmonary edema, two of pneumonia, and one dilutional hyponatremia, which were managed effec-

DISCUSSION

Although this therapy has no chemical neuronal protective effect, it can be expected to augment intra-

Figure 1. The incidence of delayed ischemic neurologic deficit (DIND) and DIND as a cause of mortality and morbidity do not show any significant difference between hypervolemic group and normovolemic group.

Figure 2. Overall outcome. Outcome, which is assessed at 6 months follow-up intervals according to the Glasgow Outcome Scale (GOS) with a good outcome (GOS 1-2) and a poor outcome (GOS 3-5), between hypervolemic group and normovolemic group does not show significant difference.
vascular volume, increase cardiac output, and improve the rheology of blood flow in the microcirculation. Particularly, the rationale for providing volume expansion with colloid is based on observations of cardiac output and local CBF in regions of ischemic brain. To further support the need for volume expansion, Mori et al. observed that SAH patients were hypovolemic before starting hypervolemic therapy. Therefore, the hemodynamic goals should be to improve cerebral perfusion by initially restoring and then expanding intravascular volume.

DIND is a diagnosis that should be reserved for patients with delayed-onset focal and/or global neurological deterioration, where other causes of worsening are ruled out. An angiogram or TCD appears to be a viable diagnostic alternative for checking arterial narrowing. We did not use angiography as the gold standard to confirm vasospasm as it is impractical and perhaps even hazardous to perform repeated angiograms after subarachnoid hemorrhage. The relationship between angiographic spasm and clinical ischemia is by no means clear.

Initiation of triple-H therapy as a prophylactic regimen should take into account potential complications, such as pulmonary edema, myocardial ischemia, hyponatremia, renal medullary washout, indwelling catheter-related complications, bleeding from other aneurysms if present, and cerebral edema. The use of a 5% albumin solution as a volume expander lowers the glomerular filtration rate and prompts renal sodium retention after SAH when compared to crystalloid solutions. These properties may limit the amount of total fluid required to maintain a given central venous pressure value.

Despite widespread use of triple-H therapy for almost 20 years, the endpoints for maintenance of this therapy remain arbitrary, variably practiced, and vaguely reported. The only prospective, randomized study is a preliminary report by Rosenwasser et al., who experienced a decreased incidence of clinical vasospasm and improved outcome with volume expansion compared to a control group (15 cases for each group) that received vasodilators, centrally acting agents, and only small doses of diuretics. However, their cases were too small in number to determine the true efficacy of this mode of therapy. Several investigators have reported that prophylactic volume expansion can effectively minimize DIND and increase CBF in patients with SAH. In the absence of a control group, however, it is difficult to estimate the beneficial effects of this approach regarding the prevention of neurological symptoms. Subsequently, Medlock et al. did not demonstrate any additional benefit to the patient as measured by a clear reduction in the risk of DIND or improved outcome when compared with historical controls, and they also showed a high rate of pulmonary edema. Oda et al. thought that early aneurysm surgery and postoperative dehydration therapy in acute stages of brain edema resulting from primary brain damage were effective in the treatment of patients with severe SAH but reversible brain damage. Recently, Lennihan et al. concluded that hypervolemic therapy resulted in increased cardiac filling pressures and fluid intake but did not increase CBF or blood volume compared to normovolemic therapy in 82 randomly assigned patients receiving hypervolemic or normovolemic fluid management.

The incidence of DIND did not change significantly between the two groups in this study. Surgical outcomes in the normovolemic group were also comparable to the hypervolemic group. Outcomes were influenced by several variables, including referral and admission policies, patient selection, and therapy. Previously, the author suggested that surgical technique predominantly affects the change of surgical outcome, and consequently, considering usual level of surgical technique, a more careful approach with the assistance of an experienced vascular neurosurgeon rather than surgery by oneself will be necessary for the first 4 to 5 years of aneurysm surgery. The report by Medlock et al. showed a similarity to our results with respect to the incidence of DIND and outcome. Whereas historical cohorts from other series, particularly those derived from retrospective analysis, are less relevant than prospective studies, we would discount a significant role of bias for the following reasons: 1) this is a single-institution study; 2) a stan-
dardized management policy was used to treat all patients for the treatment periods; 3) all aneurysms were operated by the same experienced surgeon since March, 1990, which means operation by homogenous surgical techniques between the two groups; 4) there was no significant difference of patient distribution and characteristics between the two groups.

It is difficult to determine whether beneficial effects attributed to hypervolemic dynamic fluid therapy resulted in good outcomes, because of unclear pathogenesis of vasospasm, no adequately controlled studies, and different approaches in overall patient management. Thus, based on the available studies and our results, although our study had several limitations being a retrospective and a historical control study, these results first suggest in our country that postoperative hypervolemic dynamic fluid therapy probably has no advantage over normovolemic management policy. Thus, based on the available studies and our results, although our study had several limitations being a retrospective and a historical control study, these results first suggest in our country that postoperative hypervolemic dynamic fluid therapy probably has no advantage over normovolemic therapy for the prevention of delayed ischemia after SAH. However, common clinical practice consists of avoiding negative fluid balance after SAH and more careful fluid therapy for poor grade patients.

REFERENCES