Effect of human albumin administration on clinical outcome and hospital cost in patients with subarachnoid hemorrhage

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Object. Human albumin is used to induce hypervolemia (central venous pressure [CVP] > 8 mm Hg) after subarachnoid hemorrhage (SAH). Unfortunately, human albumin may increase the mortality rate in critically ill patients; because of this, its use became restricted in the authors’ hospital in May 1999. The goal of this study was to determine the effect of human albumin on outcome and cost in patients with SAH before and after this restriction was put into place.

Methods. All patients with aneurysmal SAH who were admitted to the authors’ institution between May 1998 and May 2000 were studied. Basic demographic information, dosage of human albumin given, length of stay, and the incidence of in-hospital deaths and complications were collected. The authors obtained Glasgow Outcome Scale (GOS) scores at 3 months after SAH (good outcome, GOS ≥ 4). Data were analyzed using t-test and chi-square analysis. Logistic regression was used to identify independent associations between use of human albumin and outcome.

The authors studied 140 patients: 63 who were admitted between May 1998 and May 1999 (Group 1) and 77 treated between June 1999 and May 2000 (Group 2). Two subgroups of patients were further analyzed. Group 1 patients who received human albumin (albumin subgroup, 37 patients) and Group 2 patients who would have received albumin under the old protocol (that is, those who failed to achieve CVP > 8 mm Hg after normal saline administration; nonalbumin subgroup, 47 patients). Patients in the nonalbumin subgroup were more likely to be male (38% compared with 16%), to experience hypertension (55% compared with 30%), to suffer from hypomagnesemia (49% compared with 5.4%), and to have hydrocephalus (47% compared with 27%). There was a trend for these patients to have more vasospasm (28% compared with 19%, p = 0.2). Patients in the albumin subgroup were more likely to have a good outcome at 3 months.

Conclusions. Administration of human albumin after SAH may improve clinical outcome and reduce hospital cost.

KEY WORDS • albumin • subarachnoid hemorrhage • outcome

SUBARACHNOID hemorrhage following aneurysm rupture is a common clinical entity that carries high morbidity and mortality rates. Clinical outcome in this patient population has improved over the past few years, mostly because of advances in neurosurgical and neurocritical care (that is, early aneurysm clipping, calcium channel blocker administration, and neuromonitoring). Nevertheless, cerebral ischemia secondary to vasospasm remains an important cause of morbidity and death. Cerebral symptomatic vasospasm is most likely to occur between 4 and 14 days after SAH and if left untreated can lead to permanent neurological deficits or death. Patients with SAH frequently become hypovolemic and hemodynamically impaired a few days after symptom onset. This finding has been implicated as a risk factor for development of symptomatic vasospasm and poor clinical outcome. Because of this, postoperative hypervolemic therapy is widely practiced in the US. Fluid infusions in patients with SAH have consisted of isotonic crystalloids (0.9% saline), 5 or 25% human albumin solutions, and more recently, hypertonic crystalloids (3% saline).

Normal saline and human albumin, administered either concomitantly or in alternating fashion, are the solutions most frequently used to maintain normovolemia or hypervolemia in patients after SAH. In all studies reported in the literature in which investigators have commented on the treatment of symptomatic vasospasm after SAH, human albumin has been used as a way of achieving hypervolemia. Therefore, we cannot conclude at this point whether albumin administration exerts any beneficial or deleterious effect in this patient population. Nevertheless, analysis of recent data obtained in animals has shown that human albumin is neuroprotective in acute ischemic stroke models improving neurological function and reducing infarct volume and brain edema. Because cerebral vasospasm leads to cerebral ischemia and infarction, we speculate that human albumin may also exert some neuroprotective effects in patients with SAH.
Clinical Material and Methods

Patient Selection

All medical records of adult patients admitted to our NSU with a diagnosis of SAH between May 1998 and May 2000 were retrospectively screened. Only patients with confirmed aneurysmal rupture and subsequent clip occlusion or endovascular treatment were considered for the study because they were the patients treated with hypervolemia (defined as CVP 8–12 mm Hg). We extracted patients’ demographic data, medical comorbidities, baseline laboratory values, Hunt and Hess grade, Fisher scale score (on head computerized tomography scans), and GCS7 score on admission. We also collected baseline CVP values and the total dose of human albumin administered, along with the duration of stay in the hospital and NSU, in-hospital deaths, and total hospital and radiological costs. Medical complications studied included symptomatic vasospasm, communicating hydrocephalus (as determined by the treating physicians and confirmed by the neuroradiology report), incidence of seizures, congestive heart failure or pneumonia (confirmed on chest x-ray films), electrolyte imbalances, and prolonged respiratory failure (> 96 hours of mechanical ventilation).

Diagnosis of Symptomatic Vasospasm

All records were carefully reviewed to identify episodes of neurological deterioration as documented by physicians in the NSU. A diagnosis of symptomatic vasospasm was based on the following previously published criteria:10,20 1) clinical deterioration in the patient’s neurological condition between 3 and 14 days after SAH (including insidious onset of confusion, disorientation, or decline in the level of consciousness) or focal deficits that may fluctuate in severity; 2) exclusion of structural causes of neurological worsening by appropriate investigations, including computerized tomography scanning of the head; and 3) absence of other identifiable causes of neurological worsening such as serum electrolyte or glucose alterations, hypoxia, hypercapnia, or seizures confirmed by clinical or electroencephalographic examination.

Clinical features in 140 patients with SAH*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>age (yrs)</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>male sex (%)</td>
<td>49 (35)</td>
</tr>
<tr>
<td>caucasian (%)</td>
<td>88 (63)</td>
</tr>
<tr>
<td>medical history (%)</td>
<td>53 (38)</td>
</tr>
<tr>
<td>hypertension</td>
<td>34 (24)</td>
</tr>
<tr>
<td>former smoker</td>
<td>7 (5)</td>
</tr>
<tr>
<td>alcohol use</td>
<td>10 (7)</td>
</tr>
<tr>
<td>CAD</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>DM</td>
<td>6 (4)</td>
</tr>
<tr>
<td>examination</td>
<td>98 (70)</td>
</tr>
<tr>
<td>Hunt &amp; Hess grade = III (%)</td>
<td>43 (31)</td>
</tr>
<tr>
<td>Fisher Grade 1–2 (%)</td>
<td>38 (27.1)</td>
</tr>
<tr>
<td>baseline CVP (mm Hg)</td>
<td>5.1 ± 2</td>
</tr>
<tr>
<td>Hct</td>
<td>34.0 ± 4.3</td>
</tr>
</tbody>
</table>

* CAD = coronary artery disease; DM = diabetes mellitus; Hct = hematocrit.
† Age, baseline CVP, and hematocrit are given as the mean ± SD.

Management Protocol for Patients With SAH

All patients underwent early (≤ 48 hours of admission) aneurysm clip placement or coil occlusion, and received nimodipine for prophylaxis of symptomatic vasospasm and phenytoin for prophylaxis of seizures. All patients were treated with hypervolemia (CVP > 8 mm Hg) immediately after ruptured aneurysms were secured. Initial fluid management consisted of intravenous bolus administration of normal saline (500 ml) to achieve hypervolemia. If patients failed to achieve hypervolemia after the initial treatment, they then received human albumin (12.5 g) followed by alternating boluses of normal saline and human albumin. After May 1999, patients were treated only with normal saline to achieve hypervolemia. Elevation of blood pressure (mean arterial pressure 110–130 mm Hg) was instituted in patients with symptomatic vasospasm. In patients with a history of heart disease or pulmonary edema, catheters were inserted to maintain pulmonary artery occlusion pressures of 12 to 18 mm Hg. Endovascular procedures (angioplasty and/or intraarterial papaverine injections) were performed at the discretion of the treating physicians if patients failed to improve clinically.
Human albumin in patients with subarachnoid hemorrhage

findings. Clinical diagnosis of symptomatic vasospasm was confirmed using transcranial Doppler ultrasonography and cerebral angiography in all patients.

Outcome Measures

We obtained the GOS[17] score from outpatient records or via telephone interview to correspond to 3 months after diagnosis of SAH. The GOS has been validated in numerous clinical trials in patients with various neurological and neurosurgical conditions and assessments are easily obtainable via telephone or personal interview. The GOS scores range from 1 to 5 and include the following categories: GOS 5, no or minimal disability; GOS 4, moderate disability; GOS 3, severe disability; GOS 2, vegetative state; and GOS 1, death. For purposes of statistical analysis the GOS was dichotomized as good outcome (Scores 4–5) or poor outcome (Scores 1–3).

This study was reviewed and approved by the Institutional Review Board at our institution, and all procedures described in this study were in accordance with Board guidelines. All patients or their legal representatives gave their consent before we obtained GOS scores. Also, patients' primary care physicians or physicians of record at the time of admission were contacted before we reviewed the medical records.

Statistical Analysis

A Kolmogorov–Smirnov test for normality and an equal variances test were completed before further statistical analysis of these data were performed. Continuous variables were compared using two-tailed t-tests, and proportions were compared using the chi-square or Fisher exact test between groups. Independent risk factors for good outcome at 3 months based on the GOS were determined using logistic regression analysis. We considered a probability value of less than 0.05 significant. All data are expressed as the mean ± SD or as the median.

Results

We identified 164 consecutive patients with SAH who were treated during the study period. Of these, 24 were excluded for the following reasons: in 19 there was no evidence of cerebral aneurysm on cerebral angiography studies, one had an arteriovenous fistula, and four others had arteriovenous malformations. Patients were divided into two groups: those treated between May 1998 and May 1999 (Group 1, 63 patients), and those treated between June 1999 and May 2000 (Group 2, 77 patients). A total of 11 patients were lost to follow up, and they were assigned the worst possible score for the outcome measure studied (five patients in Group 1 and six in Group 2).

Patient Characteristics

Most of the patients studied were female and caucasian, and hypertension was the most common medical comorbidity (Table 1). Physical examination revealed that the majority of patients presented with low Hunt and Hess grades but with a significant amount of intracranial blood as determined by Fisher grades. Patients stayed in the hospital a mean of 12 days and 22% of them died during their admis-

<table>
<thead>
<tr>
<th>Features</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>63</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>age (yrs)</td>
<td>55 ± 14</td>
<td>58 ± 16</td>
<td>0.3</td>
</tr>
<tr>
<td>male sex (%)</td>
<td>16 (25)</td>
<td>33 (43)</td>
<td>0.03</td>
</tr>
<tr>
<td>caucasian (%)</td>
<td>34 (54)</td>
<td>54 (70)</td>
<td>0.16</td>
</tr>
<tr>
<td>GCS score &lt;8 (%)</td>
<td>14 (22)</td>
<td>24 (31)</td>
<td>0.2</td>
</tr>
<tr>
<td>baseline CVP (mm Hg)</td>
<td>5.2 ± 2</td>
<td>4.8 ± 2</td>
<td>0.6</td>
</tr>
<tr>
<td>symp vaso (%)</td>
<td>8 (13)</td>
<td>14 (18)</td>
<td>0.3</td>
</tr>
<tr>
<td>days in hospital</td>
<td>12.4 ± 10.6</td>
<td>13.0 ± 7.1</td>
<td>0.7</td>
</tr>
<tr>
<td>days in NSU</td>
<td>9.6 ± 7.5</td>
<td>10.4 ± 7.1</td>
<td>0.5</td>
</tr>
<tr>
<td>cost data (US$ × 1000)</td>
<td>62.0 ± 39.0</td>
<td>81.0 ± 49.0</td>
<td>0.02</td>
</tr>
<tr>
<td>total hospital</td>
<td>3.7 ± 2.9</td>
<td>4.4 ± 3.5</td>
<td>0.3</td>
</tr>
<tr>
<td>laboratory</td>
<td>15.0 ± 12.0</td>
<td>23.0 ± 16.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

† According to the t-test or chi-square test, as appropriate.

Subgroup Analysis

Because not all patients in Group 1 received human albumin and not all those in Group 2 received extra boluses of normal saline, we further analyzed each group of patients and classified them as albumin and nonalbumin subgroups. The albumin subgroup was made up of 37 patients (58.7%) in Group 1 who received human albumin. The nonalbumin subgroup consisted of 47 patients (61%) in Group 2 who received extra boluses of normal saline to achieve hypervolemia. The latter subgroup of patients would have received human albumin if the policy for administering this agent had not changed. The total dosage of human albumin ranged from 1.5 to 6 g/kg.

In the univariate analysis patients in the nonalbumin subgroup were more likely to be male, to experience hypertension, and to suffer from hypomagnesemia and hydrocephalus (Table 4). There was a trend for this group to experience more symptomatic vasospasm and to have a higher in-hospital mortality rate. There was no difference, however, in the incidence of cardiorespiratory complications between the subgroups. The timing of presentation
of symptomatic vasospasm was similar between the subgroups (albumin subgroup, 5.8 ± 3 days; nonalbumin subgroup, 6.1 ± 3 days). The proportion of patients with good outcome at 3 months was significantly higher in the albumin compared with the nonalbumin subgroup (Table 5). After adjusting for age, sex, race, and GCS score less than 8, a logistic regression showed that human albumin administration was an independent predictor of better outcome 3 months after SAH. Nevertheless, such an effect was not evident at 6 and 12 months post-SAH. Administration of human albumin was not an independent predictor of in-hospital death.

**Discussion**

We have presented our experience with the use of human albumin in critically ill patients. Our data indicate that human albumin is not harmful for this patient population. In fact, it may be neuroprotective, as shown by improved clinical outcome after discharge and fewer in-hospital neurological complications.

**Use of Human Albumin in Critically Ill Patients**

Albumin is a 67-kD protein that is responsible for 80% of the colloid osmotic pressure of plasma and supplies most of the acid/base buffering action of the plasma proteins. It is a very important component of the body because it also serves as a vehicle for metabolites, is a factor in lipid metabolism, and performs many other functions that are still being elucidated.

Human albumin has been used in critically ill patients for more than 50 years. Analysis of recent data obtained in animals has shown that human albumin is neuroprotective in models of acute ischemic stroke, improving neurological function and reducing infract volume and brain edema. Possible mechanisms advanced to explain this neuroprotective effect of human albumin in cerebral ischemia include the following: 1) a direct protective effect on both parenchymal and vascular elements of the brain; 2) hemodilutional properties; 3) antioxidant effect; 4) maintenance of normal microvascular permeability and inhibition of endothelial cell apoptosis; 5) cerebral dehydration; and 6) stimulation of glial scar formation and sustaining neuronal metabolism by increasing the export of pyruvate to neurons. Because cerebral vaso-
spasm leads to cerebral ischemia and infarction, human albumin administration may be appropriate to ameliorate the resulting neurological disturbances in patients after SAH.

Despite the fact that symptomatic vasospasm is associated with significant rates of morbidity and mortality after SAH, the mechanisms leading to it remain to be fully unraveled. Blood products, particularly oxyhemoglobin, most likely contribute to cerebral vasospasm by an as yet unknown pathway. Nevertheless, various potential consequences of SAH that may be directly linked to the pathological features of symptomatic vasospasm have been revealed in several studies. These consequences include the following: 1) decreased endothelium-dependent relaxation through nitric oxide scavenging, or inactivation of guanylate cyclase; 2) increased reactive O_2• specie and oxidative stress; 3) enhanced production of endothelin-1 and big endothelin-1, which are potent vasoconstrictors; 4) lipid peroxidation; 5) increased activity of the protein kinase C pathway, leading to augmented intracellular calcium concentration; 6) migration of inflammatory cells across the endothelial surface; 7) increased production of endothelial growth factor; and 8) induction of genes such as heme oxygenase-1 that may help counteract vasospasm.

Human albumin has been shown to interact with the endothelial cell surfaces, which influences its properties. Including the following: 1) modulation of intracellular calcium concentrations; 2) modulation of arachidonic acid release and membrane fluidity; 3) inhibition of apoptosis; 4) modulation of nitric oxide metabolism; 5) modulation of cellular antioxidant redox signal by increasing glutathione concentration and decreasing tumor necrosis factor-α mediated nuclear factor-κ B activation; and 6) inhibition of adhesion molecule expression. The presence of a predominant mechanism is unlikely. In fact, it may be more likely that all or many of the mechanisms mentioned are simultaneously exerting their effect. The end result of human albumin–cerebral endothelium interaction would be an amelioration or prevention of symptomatic vasospasm. Because of the complex processes leading to symptomatic vasospasm, the administration of a multifunctional compound with neuroprotective effects (human albumin) to patients with SAH would be logical.

**Study Limitations**

The main limitation of our study is its design; its retrospective, nonrandomized nature and the small sample size (limited power) may have introduced biases regarding patient and data collection. Nevertheless, the fact that patient care protocols except for human albumin administration were not changed during the study period gives reassurance that the results obtained may represent a possible beneficial effect of human albumin on clinical outcome. The patients included represent the cohort of all individuals who were sequentially admitted to our institution during the study period. Some patients were lost to follow up; they were assigned the worst possible outcome. The proportion of patients with such outcomes was slightly higher for Subgroup 1, giving more weight to the possible neuroprotective effect of human albumin.

**Conclusions**

We have presented a retrospective study of the possible neuroprotective effect of human albumin in patients with SAH. Our preliminary data indicate that human albumin administration may be associated with a decreased incidence of symptomatic vasospasm and an increased proportion of good clinical outcome after SAH. Further validation of our data with appropriate prospective studies is needed before human albumin administration can be recommended as a neuroprotective therapy for patients with SAH.

**References**

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