Prophylactic Management of Excessive Natriuresis With Hydrocortisone for Efficient Hypervolemic Therapy After Subarachnoid Hemorrhage

Nobuhiro Moro, MD; Yoichi Katayama, MD, PhD; Jun Kojima, PhD; Tatsuro Mori, MD, PhD; Tatsuro Kawamata, MD, PhD

Background and Purpose—Hyponatremia caused by excessive natriuresis is common in patients with aneurysmal subarachnoid hemorrhage (SAH). Natriuresis decreases the total blood volume through osmotic diuresis and increases the risk of symptomatic cerebral vasospasm. In such patients, hypervolemic therapy is difficult to achieve without causing hyponatremia because sodium replacement provokes further natriuresis and osmotic diuresis. We examined the effects of hydrocortisone, which promotes sodium retention, in patients with SAH.

Methods—Twenty-eight SAH patients were randomized into 2 groups after direct surgery: group 1 patients without hydrocortisone treatment (n=14) and group 2 patients with hydrocortisone treatment (1200 mg/d for 10 days; n=14). Both groups underwent hypervolemic therapy by aggressive sodium and water replacement. The goal of the hypervolemic therapy was to maintain the serum sodium level >140 mEq/L and the central venous pressure (CVP) within 8 to 12 cm H₂O.

Results—Group 2 demonstrated a lower sodium excretion (P<0.05) and higher serum sodium level (P<0.05) compared with group 1. Hyponatremia developed in 6 patients (43%) in group 1 and 0 patients in group 2 (P<0.05). Group 2 also demonstrated a lower urine volume, lower infusion volume (P<0.05) required for hypervolemic therapy, and higher CVP (P<0.05). Failure to maintain CVP was observed in 12 patients (86%) in group 1 and 3 patients (21%) in group 2 (P<0.05). Hydrocortisone caused no serious side effects.

Conclusions—Hydrocortisone clearly attenuates excessive natriuresis. Prophylactic hydrocortisone administration appears to have a therapeutic value in inducing hypervolemia efficiently after SAH. (Stroke. 2003;34:2807-2811.)

Key Words: hydrocortisone ■ hyponatremia ■ natriuresis ■ subarachnoid hemorrhage

Hyponatremia occurs in 10% to 34% of patients after aneurysmal subarachnoid hemorrhage (SAH). Such patients demonstrate excessive natriuresis and resultant osmotic diuresis, which decreases blood volume. This decrease in blood volume increases the risk of symptomatic cerebral vasospasm (SCV), which is a major cause of morbidity and mortality after SAH.

Excessive natriuresis and diuresis cannot be managed appropriately by sodium and water replacement because sodium replacement provokes further natriuresis and diuresis and water replacement causes hyponatremia. Hypervolemic therapy is a treatment frequently used to prevent SCV. For the same reason, however, hypervolemic therapy is difficult to achieve efficiently by sodium and water replacement alone in SAH patients.

We reported previously that fludrocortisone, which promotes sodium resorption in the kidney through its mineralocorticoid effects, is useful for attenuating excessive natriuresis and for inducing hypervolemic therapy efficiently. However, strong sodium retention induced by fludrocortisone is not easily controllable because of its long elimination half-life. This carries the risk of heart failure. In contrast, hydrocortisone, which is being used widely because of its glucocorticoid effects, has a short elimination half-life. It is possible that excessive natriuresis can be managed more safely. In the present study, we examined the effects of hydrocortisone for preventing excessive natriuresis and its impact on the induction of efficient hypervolemic therapy.

Subjects and Methods

Patient Population and Background

Twenty-eight SAH patients admitted to our hospital between October 1999 and July 2001 were analyzed. These patients underwent direct surgery within 48 hours after onset. Patients who received endovascular surgery and patients with intracerebral hematoma were excluded. Before the direct surgery, careful research was undertaken to rule out patients with significant systemic diseases such as cardiac disease, renal disease, endocrinological disorders, and past neuro-

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logical disease. The present study was approved by the Committee for Clinical Trials and Research on Humans at Nihon University School of Medicine. All patients gave written informed consent.

**Study Design**

After the direct surgery, the patients were stratified by age and Hunt and Kosnik grades and were randomly assigned to 2 groups by an independent controller available by telephone 24 hours a day: group 1 patients (control; n = 14) treated without hydrocortisone and group 2 patients (test; n = 14) treated with hydrocortisone (Saxizon, Nikken Chemicals Co) at 1200 mg/d (300 mg/6 h) from the day after direct surgery until day 10. After day 10, the dose was gradually reduced, and the administration was ended on day 14.

**Clinical Evaluations**

Serum sodium and potassium levels, plasma osmotic pressure, serum protein levels, and serum glucose level were measured at 24-hour intervals. The daily urine volume, sodium and potassium excretions, and osmotic pressure were also determined for urine samples stored every 24 hours. Outcome was evaluated with the Glasgow outcome scale at 6 months after onset.

**Management Protocol**

All patients were encouraged to ingest fluid and foods orally. Water balance was calculated every 8 hours from the difference between the total amount of water intake (sum of transvenously infused water, orally ingested water, and metabolized water) and water losses (sum of urine, transpirated water, water included in stool, and various drainage fluids), and water replacement was performed according to the balance. Hypervolemia was induced immediately after surgery, and administration of plasma expander at 1 L/d was begun 3 days after onset until day 14. The goal of the hypervolemia was to maintain the central venous pressure (CVP) between 8 and 12 cm H$_2$O by additional water supplementation.

Sodium balance was calculated every 24 hours from the difference between the total amount of sodium intake (sum of sodium given transvenously and orally) and sodium excretion. The goal of the sodium replacement was to maintain the serum sodium level $>140$ mEq/L. The amount of sodium replacement for the next 24 hours was determined by the following equation: body weight (kg) $\times$ $0.6 \times [140 -$ present serum sodium concentration (mEq/L)]. The potassium balance was also calculated every 24 hours, and potassium replacement was performed according to the balance.

Systolic arterial blood pressure was maintained at a level $\approx 15\%$ higher than the original level. Hyperosmolar fluids (mannitol and glycerol) and blood products were not used. When the serum glucose level increased to $>250$ mg/dL, insulin therapy was initiated with repeated measurement of the blood glucose level. When SCV developed, percutaneous angioplasty and transarterial local injection of papaverine hydrochloride were performed.

**Statistical Analysis**

Values are expressed as mean±SE. Differences between the 2 groups were assessed with Fisher’s exact test. Other data were analyzed by general mixed-model analysis of variance (ANOVA). A posthoc test (Student’s unpaired t test) was carried out when the F value for the group factors of ANOVA was significant ($P<0.05$). In the posthoc test, values of $P<0.05$ were considered significant. All probability values were 2 tailed. Statistical analysis was performed with the SAS system (version 8.2; SAS Institute, Inc).

**Results**

Regarding sex, age, Hunt and Kosnik grades, Fisher classification on initial CT, and location of the aneurysms, there were no significant differences in distribution between the 2 groups (Table 1).

**TABLE 1. Clinical Characteristics of Patients**

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
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<td>Female</td>
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<td>Hunt and Kosnik grade</td>
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<td>Location of ruptured aneurysm</td>
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<td>Anterior cerebral artery</td>
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<td>7</td>
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<td>Middle cerebral artery</td>
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<td>Internal carotid artery</td>
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**Serum Sodium Level**

In group 1, the serum sodium level gradually decreased after SAH, fell below 140 mEq/L on day 4, and never returned to $>140$ mEq/L (Figure 1). In group 2, the serum sodium level was maintained between 140 and 143 mEq/L for 14 days. The difference was significant in terms of the time course ($P<0.05$) and the values during the period after day 3 until day 14 ($P<0.05$). When hyponatremia was defined as a serum sodium level of $<135$ mEq/L for at least 2 consecutive days, hyponatremia was found to develop in 6 patients (43%) of group 1. This occurred between days 6 and 13. In contrast, hyponatremia did not develop in any patients of group 2. The difference in prevalence of hyponatremia was significant between the 2 groups ($P<0.05$). In both groups, no patients exceeded 150 mEq/L in their serum sodium level.

In group 1, the plasma osmotic pressure decreased gradually, reached 280 mOsm/kg on day 6, and stayed at this level.

![Figure 1. Daily serum sodium levels in groups 1 (○) and 2 (●).](image)
In group 2, the plasma osmotic pressure was maintained at 288 to 295 mOsm/kg. This difference was significant in terms of the time course \((P<0.05)\) and the values during the period after day 4 \((P<0.05)\).

**Sodium Excretion and Intake**

In both groups, the sodium excretion increased gradually after SAH (Figure 2). In group 1, its value reached 800 mEq/d on day 6, increased continuously, and finally exceeded 1200 mEq/d. In group 2, the sodium excretion slowly increased and stayed at \(\approx 600\) mEq/d after day 5. The difference was significant in terms of the time course \((P<0.05)\) and the values during the period after day 6 until day 14 \((P<0.05)\).

Concomitantly with the increase in sodium excretion, sodium intake increased after SAH (Figure 2). In group 1, its value increased rapidly, reached 900 mEq/d on day 7, and exceeded 1100 mEq/d. In group 2, sodium intake increased up to 600 mEq/d on day 6 and stayed between 600 and 750 mEq/d. The difference was significant in terms of the time course \((P<0.05)\) and the values on day 9 and from day 11 until day 14 \((P<0.05)\).

**Urine and Infusion Volumes**

Urine volume increased progressively, reached 6 L/d on day 3, and exceeded 8 L/d in group 1 (Figure 3). In group 2, its value increased up to 5 L/d on day 4 and stayed at \(\approx 6\) L/d. A urine volume of \(>10\) L/d was observed in 6 patients (43%) of group 1. In contrast, there was no patient in group 2 who showed a urine volume of \(>10\) L/d. This difference in prevalence of polyuria was significant \((P<0.05)\).

Infusion volume increased progressively in group 1 (Figure 3). Infusion volume exceeded 5 L/d on day 3 and 6 L/d on day 11. In group 2, its value increased up to 4 L/d on day 3 and stayed at 4 to 5 L/d until day 13. The difference was significant in terms of the time course and the values during the period after day 10 until day 14 \((P<0.05)\).

**CVP and Systolic Arterial Blood Pressure**

We failed to maintain CVP values within the range of 8 to 12 cm H\(_2\)O, which was the goal of the hypervolemic therapy, in 12 patients (86%) of group 1 and 3 (21%) of group 2 for \(>2\) consecutive days. This difference in prevalence of failure to induce hypervolemia was significant \((P<0.05)\). The CVP values were within 8.5 to 9.5 cm H\(_2\)O in group 1 and 9 to 11 cm H\(_2\)O in group 2 (Figure 4). The difference was significant in terms of the time course and the values on days 3, 9, and 10 \((P<0.05)\).

There was no significant difference in the systolic arterial blood pressure between the 2 groups.

**Changes in Other Systemic Variables**

Asymptomatic hypokalemia, hyperglycemia, and hypoprotenemia were observed in some patients of both groups. Three patients (21%) of group 1 and 6 (43%) of group 2...
Hyponatremia and Hypovolemia After SAH

Hyponatremia and hypovolemia are common complications of SAH. Wijdicks et al demonstrated that in 21 patients with SAH 9 (43%) demonstrated hyponatremia and 11 (52%) showed a decrease in plasma volume by >10%. In group 1, 6 patients (43%) demonstrated hyponatremia, and 12 (86%) failed to maintain CVP within the targeted range.

In agreement with our previous observations, group 1 exhibited uncontrollable sodium excretion, which could account for the hyponatremia. Although the sodium excretion and intake reached 1100 mEq/d, the serum sodium level fell to <140 mEq/L and never returned until day 14 in group 1. This sodium excretion was associated with a huge increase in urine and infusion volume, which was attributable to osmotic diuresis. In group 1, CVP remained 10 cm H2O even though the infusion volume was >6 L/d.

The combination of hyponatremia and hypovolemia is consistent with the cerebral salt-wasting syndrome. Our results suggested that the cerebral salt-wasting syndrome could account for hyponatremia in almost all patients with SAH. Under such conditions, it is difficult to correct hypotension without causing hypovolemia by sodium replacement alone. It appears that acceleration of sodium resorption represents the only means of correcting hypotension without causing hypovolemia in patients with SAH.

Cerebral Vasospasm and Hypervolemic Therapy

Hyponatremia is intimately related to SCV. Morinaga et al reported that in 121 patients with SAH 19 (16%) demonstrated hyponatremia and 16 (84%) suffered from SCV. In the present study, 6 patients (43%) of group 1 demonstrated hyponatremia and 2 (33%) suffered from SCV. SCV was observed only in patients who demonstrated hypotension. It seems likely that hypovolemia is responsible for SCV. Aggressive prophylactic hypervolemic therapy is therefore commonly used to prevent SCV. In reality, however, it was actually impossible to induce therapeutic hypervolemia without causing hyponatremia, as described above.

Hyponatremia naturally results in a decrease in plasma osmotic pressure. In group 1, the plasma osmotic pressure decreased to 280 mOsm/kg. An increase in systolic blood pressure, together with a decrease in plasma osmotic pressure, induces vasogenic edema in areas where the cerebral vascular permeability is elevated. It appears that acceleration of sodium resorption in the kidney represents the only means of achieving therapeutic hypervolemia without imposing hyponatremia.

The physicians involved in the present study were not blinded to the allocation of patients. Therefore, there is a possibility that unblinded physicians could have selected slightly different therapeutic approaches in each group and the results became biased because of such differences. Results of the present study suggest that blinded allocation could be safely performed. Future clinical studies should attempt to establish the therapeutic value of hydrocortisone with a blinded allocation of patients.

Effects of Hydrocortisone

The present study shows that hydrocortisone can inhibit hyponatremia and hypovolemia efficiently. In group 2, sodium excretion and intake remained at 700 mEq/d, and the serum sodium level and osmotic pressure were maintained at >140 mEq/L and 288 mOsm/kg, respectively. CVP was maintained within the targeted range in most patients of group 2, whereas infusion volume did not exceed 5 L/d.

These effects of hydrocortisone are attributable to an acceleration of sodium resorption through its mineralocorticoid action and resultant inhibition of osmotic diuresis. It has been demonstrated that fludrocortisone, which displays a selective mineralocorticoid action, can attenuate hyponatremia after SAH. The effects of hydrocortisone (1200 mg/d) on sodium excretion are comparable to the effects of fludrocortisone (0.3 mg/d). The effects of fludrocortisone carry a risk of heart failure because of its long elimination half-life. In contrast, the effects of hydrocortisone are easily

| TABLE 2. Changes in Systemic Variables* Other Than Sodium and Water Balances |
|-----------------|-----------------|
| **Group 1**     | **Group 2**     |
| Blood glucose, mg/dL | 122.0±6.0        | 155.8±9.4        |
| Daily potassium excretion, mEq/day | 105.9±12.7      | 160.0±15.3†      |
| Serum potassium, mEq/L | 3.9±0.1         | 3.5±0.1          |
| Total protein, mg/dL | 5.5±0.1         | 5.1±0.1          |

*Average±SE for the period between day 1 and day 14. †P<0.05.
controllable because of its shorter elimination half-life.\textsuperscript{14} It appears that hydrocortisone is more useful practically for the management of excessive natriuresis.

The number of patients in the present study was not sufficiently large to yield firm evidence for the effect of hydrocortisone on the incidence of SCV. It is clear, however, that hydrocortisone reduces the requirement of sodium and water replacement and can secure induction of therapeutic hypervolemia.

It has been reported previously that steroids such as methylprednisolone and hydrocortisone are useful for preventing SCV after SAH.\textsuperscript{19,20} In these studies, glucocorticoid actions were thought to provide the major mechanisms. The present data suggest that the mineralocorticoid action may actually play a more important role in patients with SAH.

**Side Effects of Hydrocortisone**

Group 2 demonstrated greater potassium excretion and required more potassium replacement than group 1. This is consistent with the mineralocorticoid action of hydrocortisone. Hypokalemia, however, was readily prevented by potassium replacement.

Hyperglycemia was sometimes observed in both groups. The glucocorticoid action of hydrocortisone may have played some role in inducing hyperglycemia in group 2. Hyperglycemia, however, was readily controlled by insulin therapy. This finding suggests that hydrocortisone may not exert serious side effects on glucose concentration. This does not necessarily mean that hydrocortisone has no effect on glucose concentration. The sample size may have been too small to detect an effect of hydrocortisone in patients with SAH in whom the glucose concentrations were more or less elevated. In addition, appropriate administration of insulin to both groups may have prevented the detection of an effect of hydrocortisone. Future clinical studies should evaluate the effect of hydrocortisone on glucose concentration with a larger sample size and through changes in the required amount of insulin.

Hypoproteinemia, which is commonly caused by SAH, was also observed in both groups. Hydrocortisone may have contributed to the hypoproteinemia to some extent in group 2 through hypermetabolism.\textsuperscript{21} It is also probable that efficient hypervolemia may have enhanced the hypoproteinemia in group 2. Although an immunocompromised state and gastrointestinal hemorrhage are other known side effects of hydrocortisone, we never encountered these events in the present study. It appears that the benefits of hydrocortisone may far surpass the potential risk of side effects.

**Conclusions**

Hydrocortisone can clearly attenuate excessive natriuresis in patients with SAH. This prevents hyponatremia and reduces osmotic diuresis, resulting in a decrease in the requirement of sodium and water replacement for hypervolemic therapy. The present study indicates that the use of hydrocortisone in SAH patients warrants further clinical studies with a larger sample size involving multiple centers. Future clinical studies should determine the therapeutic value of hydrocortisone on the basis of the effects on clinically relevant outcome such as the incidence of SCV.

**References**

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