A Randomized Controlled Trial of Hydrocortisone Against Hyponatremia in Patients With Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Hyponatremia is common after aneurysmal subarachnoid hemorrhage (SAH). It is caused by natriuresis, which induces osmotic diuresis and decreases blood volume, contributing to symptomatic cerebral vasospasm (SCV). Hypervolemic therapy to prevent SCV will not be efficient under this condition. We conducted a randomized controlled trial to assess the efficacy of hydrocortisone, which promotes sodium retention in the kidneys.

Methods—Seventy-one SAH patients were randomly assigned after surgery to treatment with either a placebo (n = 36) or 1200 mg/d of hydrocortisone (n = 35) for 10 days and tapered thereafter. Both groups underwent hypervolemic therapy. The primary end point was the prevention of hyponatremia.

Results—Hydrocortisone prevented excess sodium excretion (P = 0.04) and urine volume (P = 0.04). Hydrocortisone maintained the targeted serum sodium level throughout the 14 days (P < 0.001), and achieved the management protocol with lower sodium and fluid (P = 0.007) supplementation. Hydrocortisone kept the normal plasma osmolarity (P < 0.001). SCV occurred in 9 patients (25%) in the placebo group and in 5 (14%) in the hydrocortisone group. No significant difference in the overall outcome was observed between the 2 groups.

Conclusions—Hydrocortisone overcame excess natriuresis and prevented hyponatremia. Although there was no difference in outcome, hydrocortisone supported efficient hypervolemic therapy. (Stroke. 2007;38:2373-2375.)

Key Words: hydrocortisone • hyponatremia • multicenter studies • randomized controlled trials • subarachnoid hemorrhage

This trial was a randomized controlled trial. The purpose of this study is to assess whether hydrocortisone prevents hyponatremia and reduces the incidence of SCV to improve outcome.

Materials and Methods

Patients were collected from 16 Japanese neurosurgical centers between January 2002 and June 2003. Actual number of patients of SAH in this period is unknown. Patients were excluded if they were Hunt and Kosnik Grade V or were both Hunt and Kosnik Grade I and Fisher’s Class 1. Patients with cardiac disease, renal failure, hepatic failure, endocrine or mental disease, or intracranial hematomas other...
The patients admitted to hospitals within 48 hours and were available to receive the test drug within 72 hours were selected. The protocol and consent form used were approved by the Committee for Clinical Trials and Research at each clinical institute. All patients or their relatives gave written informed consent.

Eligible patients were randomly assigned to receive the placebo or hydrocortisone (Saxizon; Nikken Chemicals) by an independent control system. The placebo or hydrocortisone was administrated intravenously at 1200 mg/d (300 mg every 6 hours) from day 0 to 10, 600 mg/d (300 mg every 12 hours) on days 11 and 12, and 300 mg/d on days 13 and 14.

The management protocol was set to maintain serum sodium at >140 mmol/L, central venous pressure (CVP) within 8 to 12 cmH2O, and a positive water balance. Other steroids, drugs affecting angiotensin converting enzyme and nimodipine were not used. Angiography was done for suspected SCV, with angioplasty if vasospasm was seen.

For patients who discontinued the study, data and incidence of SCV from the period while test drug was administered were included for analysis. Outcome was analyzed from all the patients randomly assigned at 30 days after SAH using the Modified Rankin Scale (MRS). The primary end point was the prevention of hyponatremia as in the previous study. Secondary end points included the incidence of SCV and the value of the MRS.

**Statistical Analysis**

Values are expressed as the mean±SE. Differences between groups were assessed using Fisher exact test. Other data were analyzed by general mixed-model analysis of variance, with a post hoc test (Student unpaired t test) when the F value was significant. Statistical significance was concluded with a 2-tailed P<0.05. For analysis, MRS 0 to 2 and 3 to 6 were judged as good and bad outcome, respectively.

**Results**

Seventy-one patients (placebo group: n=36, hydrocortisone group: n=35) entered the study. The 2 groups had no significant differences in background factors (Table), however, there were more patients with Fisher class 3 in the placebo group. Ten patients discontinued in the period (placebo group: delirium, improper administration, and cerebral infarct; hydrocortisone group: refusal by family, congestive heart failure, improper administration, gastrointestinal hemorrhage [2 patients], rupture, and hypokalemia). Four patients had complications, 3 with motor palsy before drug administration started (placebo group: n=1, hydrocortisone group: n=2), and surgery for rupture in 1 patient in the hydrocortisone group.

Sodium excretion (P=0.04) and urine volume (P=0.04) were significantly decreased in the hydrocortisone group.

**Figure 1.** Daily sodium (A) and water (B) in-out of the 2 groups. *P<0.05, **P<0.01, ***P<0.001.
occurred because of its glucocorticoid action. These adverse events did not result in any lasting sequelae, but strict control is necessary. In fact, more patients in the hydrocortisone group were withdrawn from medication for safety reasons. Effectiveness with fewer side effects may be possible with a reduced dose of hydrocortisone. Very rare adverse effects may not be clear in a study of this size.

Larger groups would be required to determine whether adverse events can be reduced by lower dosage and whether this treatment improves outcome.

**Appendix**

Safety Management Members: Nobuo Hashimoto MD, PhD, Department of Neurosurgery, Kyoto University Graduate School of Medicine; Takaaki Kirino MD, PhD, Department of Neurosurgery, Faculty of Medicine, University of Tokyo; Akhiro Ohnishi MD, PhD, Department of Laboratory Medicine, Daisan Hospital, Jikei University School of Medicine; Isamu Saito MD, PhD, Fuji Brain Institute and Hospital; Takashi Yoshimoto MD, PhD, Tohoku University.

**Disclosures**

The authors designed the protocol for the clinical study in collaboration with the study sponsor, Nikken Chemicals. The clinical investigators enrolled the patients, did the clinical trial, and recorded the data independently of any involvement of the sponsor. The sponsor provided monitors to ensure quality of the conduct of the study and the data collected by the investigators on case report forms were consistent with the records in the hospital files. Data entry and analysis was done by the sponsor under the supervision of the authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**References**

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