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

Yoichi Katayama, MD, PhD; Jo Haraoka, MD, PhD; Hidehiro Hirabayashi, MD, PhD; Tatsuro Kawamata, MD, PhD; Keiji Kawamoto, MD, PhD; Takao Kitahara, MD, PhD; Jun Kojima, PhD; Toshihiko Kuroiwa, MD, PhD; Tatsuro Mori, MD, PhD; Nobuhiko Moro, MD, PhD; Izumi Nagata, MD, PhD; Akira Ogawa, MD, PhD; Kikuo Ohno, MD, PhD; Yoshikatsu Seiki, MD, PhD; Yoshiaki Shiokawa, MD, PhD; Akira Teramoto, MD, PhD; Teiji Tominaga, MD, PhD; Toshihiko Yoshimine, MD, PhD

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

Hyponatremia after aneurysmal subarachnoid hemorrhage (SAH) increases the risk of symptomatic cerebral vasospasm (SCV).

1 It is caused by excess natriuresis in the cerebral salt wasting syndrome (CSWS) leading to osmotic diuresis. Hypovolemia and decreased blood pressure may follow, with reduced cerebral perfusion and increase the potential for SCV. Hypervolemic therapy is less effective when there is CSWS. Mineralocorticoids are reported to be useful for attenuating natriuresis. We have previously reported this effect with hydrocortisone in a single small center study, results of which indicated the need for 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
than SAH were excluded. 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 administrated 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], re-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 re-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.
or permanent sequelae because of adverse events. Failure in the hydrocortisone group. No patients had surgery for intestinal hemorrhage and one developed congestive heart failure in the placebo group. In both groups, CVP stayed within the targeted range. In the placebo group, plasma osmolarity decreased to <280 mOsm/kg whereas it stayed at around 290 mOsm/kg in the hydrocortisone group ($P<0.001$).

SCV occurred in 9 (25%) patients of the placebo group and in 5 (14%) of the hydrocortisone group. Good and bad outcome were measured in 29 (81%) and 7 patients in the placebo group, respectively, and in 26 (74%) and 9 in the hydrocortisone group, respectively. There were no significant differences in the incidence of SCV and the outcome.

Hyperglycemia, hypokalemia, and hypoproteinemia were noted in the hydrocortisone group ($P<0.001$). Although most of the patients used H2 blocker, 2 patients developed gastrointestinal hemorrhage and one developed congestive heart failure in the hydrocortisone group. No patients had surgery or permanent sequelae because of adverse events.

Discussion

CSWS after SAH causes natriuresis, leading to hyponatremia and osmotic diuresis, shown as increased urine volume. Hypervolemic therapy will not be achieved safely under this condition, because massive sodium and fluid supplementation result in low plasma osmolarity. Hydrocortisone prevented natriuresis and supported efficient hypervolemic therapy under appropriate serum sodium level and plasma osmolarity.

Regardless of difference in hyponatremia between the 2 groups, there were trends only and no significant difference in the incidence of SCV or in overall outcome.

Although the mineralocorticoid effect of hydrocortisone was useful for preventing hyponatremia, adverse events 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, Dusan 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

A Randomized Controlled Trial of Hydrocortisone Against Hyponatremia in Patients With Aneurysmal Subarachnoid Hemorrhage
Yoichi Katayama, Jo Haraoka, Hidehiro Hirabayashi, Tatsuro Kawamata, Keiji Kawamoto, Takao Kitahara, Jun Kojima, Toshihiko Kuroiwa, Tatsuro Mori, Nobuhiro Moro, Izumi Nagata, Akira Ogawa, Kikuo Ohno, Yoshikatsu Seiki, Yoshiaki Shiokawa, Akira Teramoto, Teiji Tominaga and Toshiki Yoshimine

Stroke. 2007;38:2373-2375; originally published online June 21, 2007;
doi: 10.1161/STROKEAHA.106.480038

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/8/2373

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/