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A randomized controlled study of intravenous fluid in acute ischemic stroke

Nijasri C. Suwanwela[a,*], Aurauma Chutinet[b], Seangduan Mayotarn[c], Ratchayut Thanapiyachaikul[b], Napasri Chaisinanunkul[b], Thanin Asawavichienjinda[d], Sombat Muengtaweepongsa[e], Yongchai Nilanont[f], Jitlada Samajarn[b], Kanokwan Watcharasaksilp[g], Somsak Tiamkao[h], Pakkawan Vongvasinkul[b], Supparat Charnwut[b], Jeffrey L. Saver[i], on behalf of the IVIS Study Group

[a] Division of Neurology, Department of Medicine, Chulalongkorn University, Rama IV Road, Bangkok, 10330, Thailand
[b] Chulalongkorn Stroke Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[c] Division of Neurology, Department of Medicine, Bhumibol Adulyadej Hospital, Bangkok, Thailand
[d] Division of Clinical Epidemiology, Department of Medicine, Chulalongkorn University, Bangkok, Thailand
[e] Division of Neurology, Department of Medicine, Thammasat University, Pathumtani, Thailand
[f] Division of Neurology, Department of Medicine, Siriraj Hospital, Thailand
[g] Division of Neurology, Department of Medicine, Chiang mai University, Chiang mai, Thailand
[h] Division of Neurology, Department of Medicine, Khon kaen Univerisity, Khon kaen, Thailand
[i] Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, University of California, Los Angeles, CA, United States

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ABSTRACT

Objective: To compare the outcome of patients with acute ischemic stroke who received or did not receive intravenous fluid.

Patients and methods: This study was a prospective, multicenter, randomized, open-label trial with blinded outcome assessment. We enrolled acute ischemic stroke patients without dehydration aged between 18 and 85 years with NIH Stroke Scale score (NIHSS) score from 1 to 18 who presented within 72 h after onset. Patients were randomly assigned to receive 0.9% NaCl solution 100 ml/h for 3 days or no intravenous fluid.

Results: On the interim unblinded analysis of the safety data, significant excess early neurological deterioration was observed among patients in the non-intravenous fluid group. Therefore, the study was prematurely discontinued after enrollment of 120 patients, mean age 60 years, 56.6% male. Early neurological deterioration (increased NIHSS ≥ 3 over 72 h) not of metabolic or hemorrhagic origin was observed in 15% of the non-IV fluid group and 3.3% of the IV fluid group ($p = 0.02$). Predictors of neurological deterioration were higher NIHSS score, higher plasma glucose, and increased pulse rate. There was no difference in the primary efficacy outcome, NIHSS ≤ 4 at day 7, 83.3% vs 86.7%, $p = 0.61$ or secondary efficacy outcomes.

Conclusion: Administration of 0.9% NaCl 100 ml/h for 72 h in patients with acute ischemic stroke is safe and may be associated with a reduced risk of neurological deterioration. These study findings support the use of intravenous fluid in acute ischemic stroke patients with NIHSS less than 18 who have no contraindications.

1. Introduction

In patients with acute ischemic stroke, prompt treatment of dehydration is generally recommended, based on the concept that hypovolemia may lead to cerebral hypoperfusion, decreased collateral blood flow, and aggravation of ischemic brain injury. Conversely, hypervolemia may lead to cerebral edema and cardiac failure. Many guidelines suggest the assessment of volume status and maintenance of adequate hydration in acute stroke patients. For example, the American Stroke Association Guideline 2013 pstates that "Hypovolemia should be corrected with intravenous normal saline *(Class I; Level of Evidence C)*"[1]. The European Stroke Organization guideline recommends normal saline (0.9%) for fluid replacement during the first 24 h after stroke with a class IV level of evidence [2]. These recommendations are based on an uncontrolled study demonstrating that higher serum osmolarity in acute ischemic stroke patients is associated with poor outcome [3]. However, no randomized controlled studies have compared the outcome of patients receiving and not receiving intravenous fluid.

We performed a randomized controlled study to compare the clinical outcomes of patients who did and did not receive intravenous fluid.

* Corresponding author.
E-mail address: nijasris@yahoo.com (N.C. Suwanwela).

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The primary aim of this study was to evaluate the usefulness and adverse events associated with isotonic solution of 0.9% NaCl administered to acute ischemic stroke patients within 3 days after stroke onset.

2. Patients and methods

This study was a prospective, multicenter, randomized, open-label trial with blinded outcome assessment. The clinical trial was conducted at 8 centers in different parts of Thailand. The protocol was approved by the Institutional Review Board at each participating site, and informed consent was obtained from each subject. Data was analyzed by the Chulalongkorn Research Center, and the safety of the study was monitored closely by an independent monitoring board. The study was registered at http://www.controlled-trials.com (unique identifier: ISRCTN70000879). All patients presenting with acute ischemic stroke who presented to the participating institutions were screened for study eligibility between January 2013 and January 2015. The study enrolled acute ischemic stroke patients aged between 18 and 85 years who presented at the study site within 72 h after stroke onset and had an NIH Stroke Scale (NIHSS) score of at least 1 and not more than 18. The randomization process and treatment were initiated within 24 h after hospital presentation. We excluded patients who received more than 120 ml of intravenous fluid before randomization; patients who were candidates for intravenous thrombolysis or required intravenous fluid for treatment; patients with cardiogenic embolism, history of congestive heart failure or ejection fraction less than 40%; patients with history of atrial fibrillation or dilated cardiomyopathy; and patients with renal impairment (serum creatinine $>$ 2 or GFR $<$ 60). All patients were screened for swallowing dysfunction by a trained nurse using standard protocol. Those who did not pass the swallowing test, had tube feeding or receiving any intravenous medications were also excluded. Evidence of dehydration on clinical examination or urine specific gravity exceeding 1.030 also precluded patients from the study. Patients with large infarction in the middle cerebral artery (more than one-third of its territory) or large cerebellar infarction (more than half of unilateral cerebellar hemisphere) were excluded. The study patient flow diagram is shown in Fig. 1.

2.1. Routine patient management

All patients were admitted to an inpatient stroke unit with board-certified neurologists at each participating centers. They were treated with standard therapies including antiplatelet agents and general medical care. Patients were encouraged to consume the same amount of oral fluid as their previous usual intake.

2.2. Randomization and intervention

Patients were randomly assigned to receive 0.9% NaCl solution (IV fluid group) or no intravenous fluid (non-IV fluid group) at a ratio of 1:1. Randomization was performed by telephone using a 24-h central randomization system. For patients allocated to the IV fluid group, 0.9% NaCl solution was administered intravenously at a rate of 100 ml/h for 72 h. In the non-IV fluid group, no intravenous fluid was given. Fluid intake/output, urine specific gravity, serum electrolytes, and adverse events, especially neurological deterioration, as well as clinical symptoms and signs of heart failure were closely monitored during the treatment period over the first 72 h. Serial NIH Stroke scales were assessed on a daily basis during admission. In case of neurological worsening, a prompt diagnostic evaluation for the cause was undertaken. Extracranial causes were evaluated by physical examination, vital signs including oxygen saturation measurements, and laboratory investigations (complete blood count, serum electrolytes, kidney and liver function tests). Emergent CT scan of the brain was performed to search for the causes of neurological deterioration such as brain edema, recurrent stroke, and hemorrhagic transformation. Diagnosis of the cause of neurological worsening was performed by the treating physician and also was independently adjudicated by a Clinical Events Committee.

2.3. Follow-up and outcomes

The primary outcome of the study was the proportion of patients with good outcome defined by NIHSS score equal or less than 4 at day 7 after randomization or at the day of discharge from the hospital, whichever came first. Secondary outcomes included the proportion of patients with modified Rankin scale less than or equal to 2 at day 7 after randomization or the day of discharge, whichever came first, and proportion of patients with MRS less than or equal to 1 and 2 at 90 days after randomization. The outcomes were assessed by independent neurologists, blinded to study arm assignment.

Safety outcomes were defined as the proportion of patients with heart failure, proportion of patients with neurological deterioration (worsening of NIHSS by $\geq$3 points that cannot be explained by metabolic derangements or hemorrhagic transformation of the infarction), proportion of patients with symptomatic cerebral edema (defined by neurological worsening together with shifting of the midline structures on CT scan), and proportion of patients with alteration of serum electrolytes (sodium, potassium, and chloride). Framingham heart failure risk score was used to screen for congestive heart failure during the treatment period. The initial safety outcomes were assessed and reported by the investigators and adjudicated by the safety monitoring committee.

2.4. Statistical analysis

The sample size was calculated based on a previous pilot study in 24 patients (unpublished data), in which good outcome defined by NIHSS less than 4 at 90 days was found in 75% of the IV fluid group and 60% of the non-IV fluid group. With α error at 0.05 and ß error 0.10, the calculated sample size was 215 patients per group. Therefore, to allow for potential loss to follow-up, we proposed to enroll 500 subjects in this study. Outcomes were analyzed according to the intention-to-treat principle, with all randomized patients included in the analysis. Descriptive statistics were calculated for baseline characteristics for all subjects by treatment group. For continuous variables, independent *t*-tests or Welch *t*-tests were used to compare the difference in average value. For discrete variables, Chi-square tests or Fisher exact tests were used to compare the difference in proportions. The analysis of outcomes were conducted using logistic regression, adjusted for the following prespecified prognostic variables: age, sex, body mass index, initial pulse rate, risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol drinking), initial hematocrit, white blood cell count, and BUN/Cr ratio. The statistical significance level was defined as a *p*-value $<$ 0.05 (two-tailed). Analyses were performed using STATA software version 11.0 (StataCorp. 2009. Stata Statistical Software: release 11, College Station, TX: StataCorp LP.) Interim analysis was planned after enrollment of 100 patients.

Data analysis was performed by Data Management Center of Chula Clinical Research Center Faculty of Medicine, Chulalongkorn University.

3. Results

3.1. Study discontinuation

On the interim unblinded analysis of the safety data, excess early neurological deterioration within 72 h was observed among patients in the non-IV fluid group. Therefore, the safety monitoring committee decided to discontinue the study after enrollment of 120 patients.