Intravenous Nicardipine Dosing for Blood Pressure Lowering in Acute Intracerebral Hemorrhage: The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-Intracerebral Hemorrhage Study

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Background: Intravenous nicardipine is commonly used to reduce elevated blood pressure in acute intracerebral hemorrhage (ICH). We determined factors associated with nicardipine dosing and the association of dose with clinical outcomes in hyperacute ICH. *Methods:* Hyperacute (<3 hours from onset) ICH patients with initial systolic blood pressure (SBP) greater than 180 mm Hg were included. All patients initially received 5 mg/hour of intravenous nicardipine. The dose was adjusted to maintain SBP between 120 and 160 mm Hg. Associations of maximum hourly and total doses with early neurologic deterioration (END), hematoma expansion (>33%), and modified Rankin Scale score 4-6 at 3 months were assessed. *Results:* Two hundred six patients (81 women, 65.8 ± 11.8 years) were studied. Initial SBP was 201.9 ± 15.9 mm Hg. Maximum and total nicardipine doses were 9.1 ± 4.2 mg/hour and 123.7 ± 100.2 mg/day, respectively. Multivariate analyses revealed that men (standardized regression coefficient [β] = .20, P = .0030 for maximum dose; β = .25, P = .0002 for total dose), age (β = −.28, P = .0002; β = −.25, P = .0005), and initial SBP (β = .19, P = .0018; β = .18, P = .0021) were independently associated with both maximum and total doses. Body weight (β = .20, P = .0084) was independently associated with total dose. After multivariate

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Received June 20, 2014; accepted June 30, 2014.

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.06.029

adjustment, maximum dose (per 1 mg/hour; odds ratio [OR], 1.25; 95% confidence interval [CI], 1.09-1.45) was independently, and total dose (per 10 mg/day; OR, 1.06; 95% CI, .998-1.132) tended to be independently, associated with END. Nicardipine dose was not associated with hematoma expansion or 3-month outcome. *Conclusions:* Nicardipine dose is roughly predictable with sex, age, body weight, and initial SBP in acute ICH. The maximum dose was associated with neurologic deterioration. **Key Words:** Acute stroke—blood pressure—calcium-channel blocker—intracerebral hemorrhage—nicardipine.

Introduction

High blood pressure (BP) is commonly observed in patients with acute intracerebral hemorrhage (ICH) on admission,[1] and lowering BP is an acute management tactic.[2-4] The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 showed that systolic blood pressure (SBP) lowered to less than 140 mm Hg tended to improve functional outcome at 90 days.[5] However setting of target BP and antihypertensive drug selection are based on attending physicians' decisions, which generally varied based on different guidelines. An American guideline suggests intravenous administration of labetalol, nicardipine, or other agents to control elevated BP in acute ICH.[6] The European Stroke Initiative also recommends intravenous antihypertensive drugs including intravenous nicardipine in acute ICH.[3] The recommended continuous infusion rate of nicardipine is 5-15 mg/hour in both guidelines[3,6] and on the drug label in the United States. There is no recommended dosing of intravenous nicardipine for acute ICH in Japan because nicardipine was contraindicated for patients with hyperacute ICH for years, until the ministry ordered pharmaceutical manufacturers of nicardipine to revise the label in 2011 based on results of a nationwide survey on antihypertensive use.[7]

Nicardipine (hydrochloride) was originally made in Japan in 1972, and its intravenous formulation was approved for short-term treatment of hypertension in the United States in 1988. Nicardipine is a dihydropyridine calcium-channel blocking agent that works as a vasodilator; thus, it reduces BP without an intrinsic decrease in myocardial contractility. Several studies reported that decreases in both SBP and diastolic blood pressure (DBP) correlated well with plasma nicardipine levels, and that time to achieve therapeutic response was shorter with higher drug doses.[8,9] Cook et al[9] reported that at least 4 mg/hour of intravenous nicardipine was needed to produce significant BP reductions in severely hypertensive patients who had a pretreatment DBP greater than 115 mm Hg. Because nicardipine hydrochloride has acidic properties (pH ≈ 4.0) and sometimes causes phlebitis, we often dilute nicardipine hydrochloride with the same or larger amount of saline.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) study showed the safety and feasibility of acute SBP lowering between 140 and 170 mm Hg or between 110 and 140 mm Hg using intravenous nicardipine.[10] In that study, nicardipine was initiated at 5 mg/hour, and then increased by 2.5 mg/hour every 15 minutes as needed. The maximum dose was 15 mg/hour. In our multicenter Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-Intracerebral Hemorrhage (SAMURAI-ICH) study,[11] we followed the initial nicardipine dosage and the adjustment strategy of the ATACH study.

Because there are scarce data of nicardipine dosing for BP control in cases of acute ICH, this study aimed to determine factors associated with nicardipine dosing and association with clinical outcomes, including early neurologic deterioration (END), for acute ICH patients using the SAMURAI-ICH study data set.

Methods

The SAMURAI-ICH study is a prospective, multicenter, observational study designed to determine the safety and feasibility of early SBP reduction less than or equal to 160 mm Hg with intravenous nicardipine in patients with spontaneous ICH. The details of the study have been described previously.[11-13] Briefly, acute spontaneous supratentorial ICH patients with hypertension (initial SBP >180 mm Hg) who began treatment within 3 hours of symptom onset were registered. Other inclusion criteria were age greater than or equal to 20 years; total Glasgow Coma Scale (GCS) score greater than or equal to 5; computed tomography (CT) less than 2.5 hours from onset, demonstrating a hematoma volume less than 60 mL; and absence of extensive intraventricular hemorrhage. Each local ethics committee approved this study. Written informed consent was obtained from all patients or their next of kin.

Blood Pressure Management and Monitoring

BP and pulse rate were taken using manual or automated cuff measurements under established guidelines. Levels of BP and pulse rate were measured every