Reduction of Nicardipine-Related Phlebitis in Patients with Acute Stroke by Diluting Its Concentration

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Background: Nicardipine is frequently used in the treatment of hypertension for patients with acute stroke; however, its dosing is complicated by a high risk of phlebitis. In the present study, we examined whether restricting nicardipine concentration under a specific value could reduce the incidence of nicardipine-related phlebitis in patients with acute stroke. *Methods:* Intravenous nicardipine-related phlebitis was retrospectively analyzed. From July 2015, a simple proposition was made to dilute maximum intravenous nicardipine concentration to lower than 130 μg/mL. The maximum intravenous nicardipine concentration and the incidence of phlebitis were compared between patients treated from July 2014 to June 2015 (preproposition group) and patients treated from July 2015 to June 2016 (postproposition group). *Results:* A total of 300 patients (preproposition group, 138; postproposition group, 162) were included. The postproposition group demonstrated significantly lower maximum intravenous nicardipine concentration (in μg/mL, 76.9, 47.6-104.5 versus 130.4, 69.8-230.8; $P < .001$) and incidence of phlebitis (9.9%, 16/162 vs. 30%, 42/138; $P < .001$) than the preproposition group. Multivariable logistic regression analysis revealed that the maximum intravenous nicardipine concentration lower than 130 μg/mL (odds ratio [OR] .15; 95% confidence interval [CI] .06-.35; $P < .001$) and National Institutes of Health Stroke Scale on admission (OR .95; 95% CI .91-.99; $P = .007$) were the statistically significant independent factors for phlebitis, which indicated the usefulness of the proposition to dilute maximum intravenous nicardipine concentration to lower than 130 μg/mL. *Conclusions:* The simple and appropriate proposition about nicardipine administration lowered maximum nicardipine concentration and reduced the incidence of nicardipine-related phlebitis in patients with acute stroke. **Key Words:** Nicardipine—phlebitis—acute stroke—hypertension.

Introduction

Nicardipine is recommended as the first-line antihypertensive drug for the treatment of hypertensive emergency in patients with acute stroke by various international guidelines,[1-4] but its dosing is complicated by a high risk of phlebitis.[5-7] Phlebitis is characterized by peripheral vein inflammation due to irritation by intravenous (IV) drug infusions and is frequently observed after nicardipine injections, which can be severe.[8,9] Various risk factors for phlebitis have been proposed, including female sex,[10] advanced age,[11] and high body mass index.[12] Because these risks are likely to be inevitable depending on patient characteristics, methods for the prevention of phlebitis associated with the use of nicardipine in clinical settings remain unclear. A previous report has suggested that nicardipine-related phlebitis is significantly associated with higher administered IV nicardipine concentrations.[5] The

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aim of the present study was to show whether the incidence of nicardipine-related phlebitis could be reduced in patients with acute stroke by a simple and appropriate proposition about nicardipine administration.

Materials and Methods

Study Design and Patient Selection

This was a retrospective, nonblinded cohort study of patients treated for acute stroke and administered IV nicardipine between July 2014 and June 2016 at our hospital. During the study period, 774 patients were treated for acute stroke. Fourteen patients who died within 3 days of admission were excluded. A total of 300 patients who were administered IV nicardipine were included. Our institutional ethics review board approved this study. Because of the anonymous nature of the data, the requirement for an informed consent was waived. Nicardipine (Sawai Pharmaceutical Co., Ltd., Osaka, Japan)[13,14] was used as the first-line IV drug for treating hypertension in patients with acute stroke when oral antihypertensive drugs were ineffective or unavailable because of the disturbance of consciousness or dysphagia.[15-18] The maximum IV nicardipine concentration was calculated as the maximum nicardipine flow rate divided by the minimum flow rate of the administration vehicle solution. Patients were evaluated for the presence of phlebitis daily. Grade 2 or higher phlebitis was considered clinically significant, according to the Infusion Nurses Society Scale.[8] Hypodermic leakage was excluded by ascertaining patency of the venous route with inversion of blood.

Proposition about Nicardipine Administration

Based on a previous study, a maximum IV nicardipine concentration of 130 μg/mL was the threshold for significantly higher nicardipine-related phlebitis occurrence.[5] From July 2015, a proposition was made for IV nicardipine concentration, whereby its maximum IV concentration was restricted to lower than 130 μg/mL.

Outcomes and Measurements

Patients were divided into those treated for acute stroke from July 2014 to June 2015 (the preproposition group) and those treated from July 2015 to June 2016 (the postproposition group) following the recommendation to restrict nicardipine concentration to lower than 130 μg/mL. We compared the following patient characteristics between groups: age, gender, body mass index, type of stroke, and National Institutes of Health Stroke Scale (NIHSS) on admission. The maximum IV nicardipine concentration, proportion of patients who received lower than 130 μg/mL IV nicardipine, and incidence of phlebitis were compared between the 2 groups. The incidence of nicardipine-related phlebitis was compared between patients who were administered lower and higher than 130 μg/mL nicardipine. The maximum IV nicardipine concentrations were compared between patients with each grade.

Risk Factors for Phlebitis

To exclude the effects of temporal bias, we investigated the risk factors for nicardipine-related phlebitis during the entire study period. Patient characteristics, including age,[11] gender,[10] body mass index,[12] type of stroke,[11] nicardipine injection to paralyzed limbs,[19] nicardipine diluted by normal saline,[5] and maximum IV nicardipine concentration lower than 130 μg/mL, were analyzed to evaluate their associations with the occurrence of phlebitis between July 2014 and June 2016.[5]

Treatment Details

In patients with cerebral infarction who had markedly elevated blood pressure and did not undergo fibrinolysis, blood pressure was lowered by 15% during the first 24 hours after the onset of stroke.[2] Systolic and diastolic blood pressure were maintained under 185 and 110 mm Hg, respectively, in patients who were eligible for treatment with alteplase.[2] Acute lowering of systolic blood pressure to 140 mm Hg was considered in patients with nontraumatic intracerebral hemorrhage, who presented with a systolic blood pressure higher than 150 mm Hg (particularly >220 mm Hg) and who had no contraindications to acute blood pressure treatment.[3] Nicardipine was injected continuously via a peripheral venous route, using a syringe pump at a rate of .5-20 mg/h after dilution with various solutions such as normal saline or lactated Ringer's solution. Nicardipine was not administered at the paralyzed side in principle. The injection site of nicardipine was changed every 12 hours.

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[20] Fisher's exact test was used to compare categorical variables and the Mann–Whitney *U* test to compare continuous variables. All variables were first evaluated using univariate analysis. Variables with *P* values less than .10 on univariate analysis were included in the multivariable logistic regression models to exclude confounding factors. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for each variable included in the multivariable model. A *P* value less than .05 was considered statistically significant for all tests. All values are presented to 2 decimal places. Continuous variables are presented as median (25%-75% interquartile range).