Risk Factors of Nicardipine-Related Phlebitis in Acute Stroke Patients

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Background and Purpose: Intravenous nicardipine is generally used to treat hypertension in acute stroke patients but is associated with frequent phlebitis. We aimed to identify the incidence and risk factors of phlebitis in such patients. *Methods:* The incidence and risk factors of phlebitis were investigated in 358 acute stroke patients from July 2014 to June 2015. *Results:* In total, 138 patients received intravenous nicardipine. Of 45 (12.6%) phlebitis patients in 358 acute stroke patients, 42 (93.3%) were administered nicardipine, which was significantly associated with phlebitis occurrence ($P < .01$). Other candidate risk factors of phlebitis of acute stroke patients in univariate analysis were intracerebral hemorrhage ($P < .01$), nicardipine injection to paralyzed limbs ($P = .023$), dilution of nicardipine with normal saline ($P < .01$), higher maximum flow rate of nicardipine (7.2 ± 4.1 mg/h versus 1.6 ± 3.1 mg/h; $P < .01$), and higher maximum concentration of nicardipine (271.5 ± 145.0 μg/mL versus 37.6 ± 75.0 μg/mL; $P < .01$). The only statistically significant independent factor following multivariate logistic regression analysis, according to the optimal cutoff values defined from receiver operating characteristic curve analyses, was the maximum concentration of nicardipine greater than 130 μg/mL (OR 57.9; 95% CI 21.5-156; $P < .01$). A gradual decline of pH below 4.3 was observed when the concentration of nicardipine solution increased to greater than or equal to 130 μg/mL in vitro. *Conclusions:* Nicardipine-related phlebitis is frequently observed in acute stroke patients and is significantly associated with administration of a maximum concentration of nicardipine greater than 130 μg/mL.
Key Words: Phlebitis—nicardipine—acute stroke—risk factor.

Introduction

Nicardipine (NIC) is one of the most potent calcium-channel blocking agents used in the treatment of hypertension, particularly for acute stroke patients, due to its rapid action.[1] Despite its attractive pharmacological profile, phlebitis is frequently observed following NIC injections which can be extremely severe and may necessitate invasive interventions such as debridement or skin grafting.[2] In other words, phlebitis is characterized by peripheral vein inflammation due to irritation by intravenous drug infusions. Identification of the incidence and risk factors of NIC-related phlebitis in acute stroke patients may contribute to reducing its occurrence and facilitating treatment.

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Materials and Methods

Patient Selection

All patients treated for acute stroke between July 2014 and June 2015 at our hospital were included in the study

analysis. The presence of phlebitis was evaluated every day during hospitalization. Patients diagnosed as having phlebitis of grade 2 or higher according to the Infusion Nurses Society Scale at any time were defined as having clinically significant phlebitis.[3] Hypodermic leakage was excluded by ascertaining a patency of venous route with inversion of blood.

NIC (Sawai Pharmaceutical Co., Ltd., Osaka, Japan)[4,5] was used as the first-line intravenous drug to control hypertension in acute stroke patients when oral antihypertensive drugs were ineffective or unavailable due to disturbance of consciousness or dysphagia.[6-9] Acute lowering of systolic blood pressure to 140 mm Hg was considered in nontraumatic intracerebral hemorrhage (ICH) patients presenting with a systolic blood pressure greater than 150 mm Hg, particularly greater than 220 mm Hg, and without contraindications to acute blood pressure treatment.[10] In cerebral infarction patients with markedly elevated blood pressure and who did not undergo fibrinolysis, blood pressure was lowered by 15% during the first 24 hours after onset of stroke.[11] Systolic and diastolic blood pressures were lowered and maintained under 185 and 110 mm Hg, respectively, in patients eligible for treatment with alteplase.[12] NIC was injected continuously via a peripheral venous route using a syringe pump at a rate between .5 mg/h and 20 mg/h and diluted with various solutions, such as normal saline or lactated Ringer solution.

Patient characteristics including age, sex, body mass index, serum albumin, type of stroke, NIC injection to paralyzed limbs, flow rate of intravenous NIC, and types and flow rate of diluting solutions were analyzed to evaluate associations with the occurrence of phlebitis. The maximum concentration of NIC was calculated as the maximum NIC flow rate divided by the minimum flow rate of the diluting solution.

Measurements of the Osmolality and pH of NIC Solutions

Osmolality and pH values at each concentration of NIC diluted with normal saline (Otsuka Normal Saline; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan)[13] were measured using an automatic osmometer (Osmostation om-6060; Arkray, Kyoto, Japan)[14] and a pH meter (pH/Ion Meter F-53; Horiba, Kyoto, Japan)[15] 5 times, with mean values calculated and used for further analyses.[16]

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17] Fisher's exact test was used to compare categorical variables. Student's or Welch's *t*-tests were used to compare continuous variables according to the variance in the normal distribution of each population, evaluated using the F test. Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal cutoff values. All variables were first evaluated using univariate analysis. Variables with *P* values of <.15 on univariate analysis were included in the multivariate logistic regression models with backward stepwise selection depending on the *P* value to exclude confounding factors and test for an independent association with the occurrence of clinically significant phlebitis. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each variable included in the multivariate model. *P* values of <.05 were considered statistically significant. All values are presented to 2 decimal places; *P* values of <.01 were expressed as $P < .01$.

Results

Number of Cases

From July 2014 to June 2015, there were 358 cases of 352 patients who were admitted for the treatment of stroke within 72 hours of onset. Of these patients, 138 received intravenous NIC injections.

Patient Characteristics With or Without Intravenous NIC Injections

Of the 138 patients who received NIC injections (NIC group), 42 (30.4%) developed phlebitis at a significantly higher frequency than patients who did not receive NIC injections (non-NIC group, 3 out of 220 cases; $P < .01$). Overall, the NIC group was younger (69.8 ± 15.3 years versus 74.7 ± 13.0 years, $P = .03$), and had a higher incidence of ICH (59.4% versus 16.4%, $P < .01$) and subarachnoid hemorrhage (18.1% versus 6.4%, $P < .01$), a lower incidence of cerebral infarction (22.5% versus 77.3%, $P < .01$), and longer hospital stays (28.1 ± 17.5 days versus 23.3 ± 15.2 days, $P < .01$), with no significant difference in body mass index observed (23.3 ± 4.5 kg/m^2 versus 23.0 ± 4.2 kg/m^2, $P = .55$).

Risk Factors of Phlebitis in Acute Stroke Patients

As shown in Table 1, the presumed risk factors for phlebitis were as follows: ICH ($P < .01$), noncerebral infarction ($P < .01$), NIC injection ($P < .01$), NIC administration to paralyzed limbs ($P = .023$), dilution of NIC with normal saline ($P < .01$), higher maximum flow rate of NIC (7.2 ± 4.1 mg/h versus 1.6 ± 3.1 mg/h; $P < .01$), and higher maximum concentration of NIC (271.5 ± 145.0 µg/mL versus 37.6 ± 75.0 µg/mL; $P < .01$). Optimal cutoff values were defined according to ROC curve analyses as the maximum flow rate of NIC of 3 mg/h and the maximum concentration of NIC of 130 µg/mL. Multivariate logistic regression analyses were performed for factors including ICH, NIC administration to paralyzed limbs, NIC, maximum flow rate of NIC greater than 3 mg/h, maximum concentration of NIC greater than 130 µg/mL, and dilution of NIC with normal saline. A maximum concentration of NIC