Effect on Ischemia of Nicardipine Hydrochloride in Acute Intracerebral Hemorrhage: Perfusion Computed Tomography Study

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Objective: We performed brain perfusion computed tomography (CT) studies to correlate the effect of intravenous nicardipine hydrochloride (HCl) with ischemia around the hematoma in patients with intracerebral hemorrhage (ICH).

Methods: Thirty-two patients (mean age±range, 60±11.5 years) with hypertensive ICH who visited a single center from March 2013 to December 2015 were treated with intravenous injection of nicardipine HCl. Cerebral blood flow (CBF), maximum oxygen extraction fraction (OEFmax) and maximum cerebral metabolic rate of oxygen (CMRO2max) were measured by the brain perfusion CT to determine if there is any ischemia around the hematoma and the contralateral normal site at the time of admission and after 24 hr twice.

Results: Perihematoma data were compared with mirror contralateral normal region. Systolic blood pressure (BP) and diastolic BP were significantly decreased after nicardipine administration, and perihematoma CBF was not significant different from that of the normal contralateral site after 24 hr from admission. Mean OEFmax slightly was higher in the perilesional area than in the contralateral normal area and CMRO2max of perilesional area was slightly lower than that of the contralateral area. But there were no significant changes between the two groups.

Conclusion: This study suggests that lowering BP using nicardipine after ICH does not show significant changes in CBF, OEFmax, and CMRO2max measured by perfusion brain CT. Based on this, it is possible to support the controlled use of intravenous nicardipine HCl at acute phase of hypertensive ICH. Large-scale controlled studies, long-term results are needed to evaluate the actual effect of the ischemic changes around the hematoma when using this drug to lower BP.

Key Words: Cerebral hemorrhage; Cerebrovascular circulation; Nicardipine; Perfusion imaging; Tomography, X-ray computed

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is one of the most serious complications that occur in patients with hypertension and atherosclerotic changes in blood vessels. Patients who diagnosed as ICH have a marked increase in blood pressure (BP) at the time of admission. Sustained increased BP in patients with ICH may lead to enlargement of the hematoma, so lowering BP is generally recommended in patients with acute ICH.2,7,9,15,16)

However, there are studies that refute these treatments because excess lowering BP after onset of ICH can lead to cerebral ischemia as a result of lowering cerebral blood flow (CBF). Other studies have suggested that localized ischemia and acidosis in the ICH and surrounding areas may impair the intrinsic brain protective mechanism due to compression of the microvasculature, resulting in regional reductions in CBF and ischemia at the distant area of ICH. And, elevated BP can be a positive result of Cushing-Kocher reaction to keep cerebral perfusion, and if it is lowered, it could be an adverse role that interferes with the protective mechanisms of blood vessels itself.3,5,6,8,10,17,18,21).

The imaging technique of perfusion computed tomography (CT) is useful to identify tissue hypoperfusion of surrounding the hematoma (penumbra), even though there was conflicting interpretation of ICH patients.1-3,7,11,12,19,22.

Therefore, we investigated the effect of BP on perihematoma ischemia to provide a reasonable basis for nicardipine hydrochloride (HCl) therapy using a standardized BP management protocol in hypertensive ICH patients through this perfusion CT study.
MATERIALS AND METHODS

This study was performed in 32 patients in our single center, and the same protocol was applied as a standard practice in all practices. This protocol was introduced as a standard practice for review by the Institutional Review Board. During the study period, all clinical data were collected for acute ICH patients treated with nicardipine HCl protocol.

1. Patient Selection

The 32 patients included in this study were those who visited our single institution between January 2013 and December 2015 and were treated within 6 hr after the onset of symptoms. When the onset time was not described, the last time that was normal was regarded as the onset time. This study represents a continuous cohort.

Patient inclusion criteria were (1) no surgical hematoma removal was performed; (2) the patient with Glasgow coma scale is above 8; (3) The size of the hematoma measured by the formula of length×width×height/2 on CT is less than 60 mL; (4) Patients with hypertension with systolic BP >140 mmHg at admission. Patients exclusion criteria were: (1) If they can not reliably assess the onset time or have a symptom before 24 hr; (2) fother intracranial lesions such as an aneurysm, arteriovenous malformation, or tumor; (3) hematoma in the cerebellum, brainstem or only in ventricles; (4) when taking medication that promotes a history of coagulopathy or congenital coagulopathy status.

And we collected information about the following risk factors: age, sex, previous diagnosed hypertension, diabetes, previous cerebrovascular attack, chronic kidney disease, any heart disease in each patient. This information was collected based on information from patients or family members or from previous medical records.

2. Treatment of Acute Hypertension Protocol

The treatment group’s BP target was to maintain systolic BP <140 mmHg and diastolic BP <100 mmHg within 24 hr of symptom onset. The initial treatment is as follows: nicardipine HCl was started intravenously at 10 mg/hr and increased to the maximum acceptable dose (15 mg/hr) by increasing 2.5 mg/hr every 15 min if target BP was not achieved, BP was monitored at the physician’s discretion using an intra-arterial catheter or non-invasive BP monitor. If the systolic BP drops under 110 mmHg, or diastolic BP drops under 70 mmHg, or if any symptoms due to hypotension are present, the antihypertensive treatment is discontinued and additional care is performed immediately by the physician.

3. Imaging Protocol

All patients underwent non-contrast CT immediately after visit to the emergency room for diagnosis.

If the patient was to be eligible, additional brain perfusion CT images were added, followed immediately by IV nicardipine, and brain perfusion CT images were taken again after 24 hr to discriminate the change of CBF on perihematoma region. The perfusion CT images were obtained by intravenous iodide contrast agent (40 mL) for more than 10 sec and CT images were collected for 50 sec (80 kVp, 200 mA per image) every 1 sec.

4. Measurement of Variables

Raw contrast-enhanced CT images were transferred to a personal computer workstation and analyzed using a custom designed software package. Manual selection of a contralateral site of hematoma was used for correction of bolus delay and dispersion with a singular value of deconvolution algorithm. Quantitative perfusion maps including CBF were generated on a voxel-wise basis. From voxel-wise tissue impulse response curves, maximum oxygen extraction fraction (OEFmax) maps was designed based on transit time parameters. Arterial concentration of oxygen (CaO2) was estimated from arterial blood gas analysis from individual patients and the maximum cerebral metabolic rate of oxygen (CMRO2max) was derived from CBF × OEFmax × CaO2 on a voxel-wise basis (Fig. 1).

5. Statistical Analysis

Statistical analysis was performed with t-test of linear mixed mode, Wilcox rank sum test and Fisher exact test. A p-value of 0.05 or less was considered to be statistically significant.

Fig. 1. A 36-year-old woman with right putaminal hemorrhage. (A) Region of interests (ROIs) are drown in both hemispheres of cerebral blood flow map (empty circles). In right hemisphere, affected ROI is placed around the hematoma (filled arrow), and contralateral normal ROI is placed in same site of normal hemisphere (empty arrow). (B) Mean transit time is also measured at same ROIs of both hemispheres.
Continuous variables were expressed as mean values and categorical variables were expressed as frequency.

RESULTS

A total of 32 patients were studied, 18 were men (56.3%) and 14 (43.8%) were women and their average age was 60 years (range, 25-84 years). Among the all subjects, 27 patients had a history of hypertension, a risk factor for ICH, was already diagnosed and the patient was taking medication. Other risk factor was diabetes (5), coronary heart disease (2), stroke (5), and end stage renal disease (1). Patients with coagulopathy, including platelet function, were excluded. On admission, the mean Glasgow coma scale was 12.9±1.1. ICH was mainly observed in typical locations (putamen 16, thalamus 13, lobar 3) and, in most cases, small-to-medium in volume (mean hemorrhage volume 19.3±11.6) (Table 1).

During the first 24 hr after admission, the BP of all patients was recorded hourly. Initial mean systolic and diastolic BPs were 176.8±15.6 mmHg and 94±13.9 mmHg, respectively. Administration of nicardipine HCl by protocol reduced mean BP for the first 2 hr immediately after infusion, but did not show any decrease in BP until 24 hr. Mean systolic and diastolic BPs for 24 hr were 136.6±17.8 mmHg and 74.5±12.5 mmHg after injection, respectively (p<0.001, mixed effect linear model).

Initial CBF of affected perihematoma region was (51.2±8.3/ 100 g/min), and ipsilateral normal tissue CBF was slightly increased (43.2±12.8/100 g/min) and p-value was 0.32. After 24 hr continuous intravenous infusion of nicardipine HCl, CBF in normal tissues was slightly increased (46±9.5/100 g/min) compared to the that of admission, whereas affected CBF was slightly decreased (49±10.2/100 g/min), but p value did not show significant statistical difference.

In addition, the affected OEFmax (0.44±0.18) and the normal region (0.45±0.23) were almost the same at first, but after 24 hr, the affected OEFmax (0.43±0.36) showed slightly decreased data compared to the normal region (0.48±0.08) But did not show any statistically significant differences (p=0.71) Although the absolute value of OEFmax was slightly reduced, the oxygen supply to the tissue was within the normal range. The value of CMRO2max around the hematoma was also not different between the initial normal tissue and the affected tissue (3.29±1.55 mL/100 g/min, 3.15±1.27 mL/100 g/min; p=0.76), and there was no significant difference between the two tissues after 24 hr (3.19±1.36 mL/100 g/min vs. 3.28±2.08 mL/100 g/min; p=0.82) (Table 2).

DISCUSSION

Continuous variables were expressed as mean±range or number (%).

The data is presented as mean±range or number (%). CVA: cerebrovascular attack.
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(ICH) leading to cerebral ischemia.

However, on the other hand, a rapid drop in BP that causes loss of autoregulatory mechanisms around the hematoma can reduce CBF in and around the ICH, resulting in ischemia and cerebral perfusion failure. Due to the ability of the autoregulation to maintain CBF as a change in diameter of the arteriole relative to changes in CPP, changes in BP within the normal range have little or no effect on CBF.

Under normal circumstances, the relationship between ICP and CPP can be maintained with autoregulatory mechanism. CBF will return to normal range within a few sec because there is vasodilatation of cerebral resistance vessels, decrease in cerebrovascular resistance and increase in cerebral blood volume as the CPP falls within the autoregulation range. However, if this condition persists, the autoregulation ability will not work and eventually causes a decrease in CBF, resulting in ischemia.

Previous studies have demonstrated an early phase of reduction process of CBF around ICH. The initial decrease in CBF immediately after ICH appears to reflect the immediate and hemodynamic reaction, and a raised ICP was observed. The extent of the perihemorrhagic perfusion zone correlates with hematoma volume in patients with lobar intracerebral hemorrhage. Neuroradiology 56:535-541, 2014

No potential conflict of interest relevant to this article was reported.

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