Effect on Middle Cerebral Artery Blood Flow of Nicardipine Hydrochloride of Acute Intracerebral Hemorrhage: Transcranial Doppler Sonography Study

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Objective: The authors conducted a prospective comparative study to evaluate the effect of intravenous Nicardipine hydrochloride (HCl) on middle cerebral blood flow (CBF) in patients with acute intracerebral hemorrhage (ICH). **Methdos:** This study included 46 patients with acute ICH in a single center between May 2013 and December 2014, who were treated using intravenous Nicardipine HCl. The middle cerebral artery flow velocity (MFV) represented by a regional CBF and pulsatility index (PI) were measured using transcranial doppler sonography at admission (baseline), 24 hr and 7 days. The MFV and PI on the affected side were compared with those of the healthy side. **Results:** Administration of intravenous Nicardipine HCl resulted in a decrease of mean systolic blood pressure (BP) and diastolic BP. The results demonstrated that lower MFV and higher PI were observed on the affected side than on the healthy side throughout the transcranial doppler ultrasonography study. However, MFV and PI on the affected side were not significantly changed compared with those of the healthy side after intravenous Nicardipine HCl infusion at 24 hr and 7 days (p>0.05). **Conclusion:** This study supports the use of intravenous Nicardipine HCl based on the absence of statistically significant CBF changes associated with a reduction of BP after ICH. Further studies are needed in order to investigate whether reduction in BP has an influence on ICH expansion, and CBF dynamics on a larger, controlled, randomized basis to confirm an effect on CBF after antihypertensive drug.

Key Words: Cerebral hemorrhage; Cerebrovascular circulation; Nicardipine; Ultrasonography, doppler, transcranial

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is a severe type of stroke and one of the most severe complications of chronic hypertension. Elevated blood pressure (BP) is common immediately after ICH. Persistent marked elevation of BP can predispose patients to hematoma enlargement. Lowering BP is commonly practiced for prevention of hematoma enlargement in patients with ICH[10,11,14,15,18,20,22,23,28]. However, the association between change of BP and cerebral blood flow (CBF) remains unclear. Therefore there has been considerable controversy regarding the initial control of BP after the onset of ICH. Cerebral autoregulation is the inherent ability of blood vessels to keep CBF relatively constant over a wide range of systemic BP levels by means of complex myogenic, neurogenic, and metabolic mechanisms. The CBF depends on vascular conductance and arterial BP. Excess lowering of BP may cause hypoperfusion in areas adjacent to the hematoma and thus worsen the clinical outcome[5,6,9,16,24,25,27,28].

Transcranial doppler ultrasonography (TCD) is a noninvasive, readily available diagnostic method for offering information on the pressure and blood flow relationship of the cerebral autoregulation. This method may assess the rapid changes in BP as an autoregulatory stimulus and the functional regulation of microcirculation. And, TCD may also assist in predicting hematoma growth, change of intracranial pressure (ICP), and clinical prognosis[8,10,12,17,26]. The aim of this study is to evaluate the effect of antihypertension drug, Nicardipine hydrochloride (HCl) for acute ICH on CBF by means of TCD.

MATERIALS AND METHODS

The study was conducted in 46 patients in our center with dedicated stroke services. The protocol was introduced as standard practice after review by the Institutional Review Board.

1. Patient Selection

The 46 patients in this study represent a prospective method employed in patients who were treated within 6 hr of symptom onset. This study was conducted between May 2013 and December 2014. In patients for whom time of onset could not be determined, the time when patients were last seen intact was regarded as the time of onset. Patients were included as follows: (1) surgical hematoma evacuation was not performed; (2) supratentorial ICH defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, the subarachnoid space, confirmed by clinical history and computed tomography (CT) scan; (3) neurological state was more than 5 points by Glasgow Coma Scale (GCS); and (4) volume of hematoma was calculated by length×width×height/2 (volume of hematoma in ventricle was excluded) in CT scan. Patients were excluded as follows: (1) time of symptom onset could not be reliably assessed; (2) progressive onset or fluctuating characteristics were observed; (3) previously known neoplasms, arteriovenous malformation, intracranial aneurysms, trauma were documented; or (4) location of ICH was infratentorial, such as cerebellum, brain stem, or ventricle only; (5) any history of bleeding diathesis or coagulopathy or medication that promotes coagulopathy; and (6) any history of congestive heart failure, renal failure, myocardial infarction, or blood glucose level less than 50 mg/dL or more than 300 mg/dL.

2. Treatment of Acute Hypertension Protocol

The goal in the treatment group was to maintain systolic BP <140 mmHg and diastolic BP <100 mmHg within 24 hr from onset of symptoms. Initial treatment was started using intravenous nicardipine (10 mg/hr) if required as follows: if target BP was not achieved, the dose was increased by 2.5 mg/hr every 15 min up to the maximum tolerable dose (15 mg/hr), or until side effects of nicardipine limited the use of the regimen prior to reaching maximum dose. We did not use oral nicardipine during maintaining the BP.

The protocol was made available as preprinted order sheets and incorporated as routine orders in the chart after initial evaluation. BP was monitored using an intra-arterial catheter or automated cuff inflation device at the discretion of the physician through 7 days. The lower end of systolic BP and diastolic BP was 110 mmHg and 70 mmHg, respectively. If the BP fell below the specified levels and symptoms related to or possibly exacerbated by hypoperfusion developed, nicardipine medications were discontinued and further management was performed according to the direction of the treating physician.

3. Clinical Data

From a standard questionnaire, data were recorded on all patients treated using the current protocol for antihypertensive medication. We collected information from each eligible patient's medical record, that is, age, sex, and the presence of any of the following risk factors before onset of hemorrhage: hypertension, diabetes mellitus, previous cerebral stroke, and heart disease. Neurological status at presentation was determined using the initial GCS score and National Institutes of Health Strokes Scale (NIHSS) score as documented by initial examination.

4. TCD Monitoring

The patients were placed in a 30 degree recumbent position on a standard hospital bed. TCD monitoring was performed using Power M-Mode™ technology Digital equipment (Spencer Technologies, Seattle, USA). The middle cerebral artery (MCA) proximal segments were insonated across a 66 mm depth range using a 2-MHz probe. For long term monitoring, the system is used in conjunction with the Spencer Technologies Marc series head-frame. After stabilization of hemodynamic parameters, spontaneous fluctuations were recorded during a period of 10 min.

The following parameters were recorded continuously: (1) mean MCA flow velocity (MFV); which was directly calculated by the equipment; (2) pulsatility index (PI) according to Gosling's formula ([peak systolic CBF velocity − end-diastolic CBF velocity]/mean CBF velocity), which was also directly calculated by the equipment. Mean MFV and PI of the ipsilaterally affected and contralaterally healthy sides were recorded. In all patients with an asymmetrical distribution of the ICH as determined from the CT scans, the doppler probe was placed on the side with more blood, and the parameters of the ipsilateral MCA were evaluated.

5. Statistical Analysis

Continuous and categorical variables were expressed as mean and frequency, respectively. Statistical analysis was performed by t-test (linear mixed model), Wilcox rank sum test, and Fisher exact test. A p-value of less than 0.05 was considered significant. Statistical software SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

RESULTS

A total of 46 patients were included in this registry. They included 21 men (45.7%) and 25 women (54.3%) with a mean age of 64±12.5 years. There were preexisting known risk factors, including hypertension in 42 patients who required antihypertensive medication; other risk factors included diabetes mellitus (5 patients), previous cerebral stroke (9 patients), coronary heart disease (5 patients), and end-stage renal disease

(2 patients). Mean hematoma volume was 17.6±18.5 cc (mostly small and medium sized hematoma). On admission, the mean GCS score was 13.1±2.1 and NIHSS score was 7.2±2.9. ICH was mainly observed in typical locations (putamen 19, thalamus 18, lobar 9) and, in most cases, small-to-medium in volume (mean hemorrhage volume 17.6±18.5) (Table 1). Hourly BP recordings for the treatment are presented for all of the treated patients. The mean initial systolic and diastolic BPs at baseline (admission) were 160.8±30.5 mmHg and 98.5±20.4 mmHg, respectively. Administration of Nicardipine HCl by protocol resulted in a decrease in the mean systolic and diastolic BP (124.6±15.8 mmHg, 72.6±11.5 mmHg [24 hr] and 120.4±13.4 mmHg, 74±10.8 mmHg [7 days]) (Table 2). TCD monitoring was performed at baseline (admission), 24 hr, and 7 days after ICH onset. CBF represented by mean MCA velocity was recorded for all patients. Mean MCA velocity in Nicardipine HCl treated patients was not significantly reduced on the affected ipsilateral side (50±7.8 cm/sec) compared with CBF of the healthy contralateral side (44±13.3 cm/sec; p=0.51) at baseline (at admission). And, mean MCA velocity at 24 hr and 7 days was also not significantly reduced compared with CBF between affected ipsilateral side and healthy contralateral side

(Table 2). PI recorded for patients, representing a reliable predictor of functional clinical outcome, on the affected ipsilateral side (11.1±0.25 cm/sec) was not significantly changed compared with CBF of the healthy contralateral side (10.1±0.4 cm/sec; p=0.22) at baseline (at admission). The results of PI at 24 hr and 7 days also did not show meaningful differences between affected ipsilateral side and healthy contralateral side (Fig. 1). When results were grouped according to affected and healthy sides, lower MFV and higher PI were observed on the affected side than on the healthy side throughout the TCD study. However, the difference between the affected side

Table 1. Characteristics of patients

Characteristics	Value (n=46)
Sex	
Male	21
Female	25
Age	64.0±12.5
GCS score	13.1±2.1
NIHSS score	7.2±2.9
Location	
Putamen	19
Thalamus	18
Lobar	9
Intraventricular hemorrhage	15
Hematoma size	
Overall volume (cc)	17.6±18.5
Small (<30 cc)	40
Medium (30-60 cc)	4
Large (>60 cc)	2
Risk factors	
Hypertension	42
Diabetes mellitus	5
Coronary disease	5
CVA	9
End-stage renal disease	2

The data is presented as number or mean±range.
GCS: Glasgow Coma Scale; NIHSS: National Institutes of Health Strokes Scale; CVA: cerebrovascular accident.
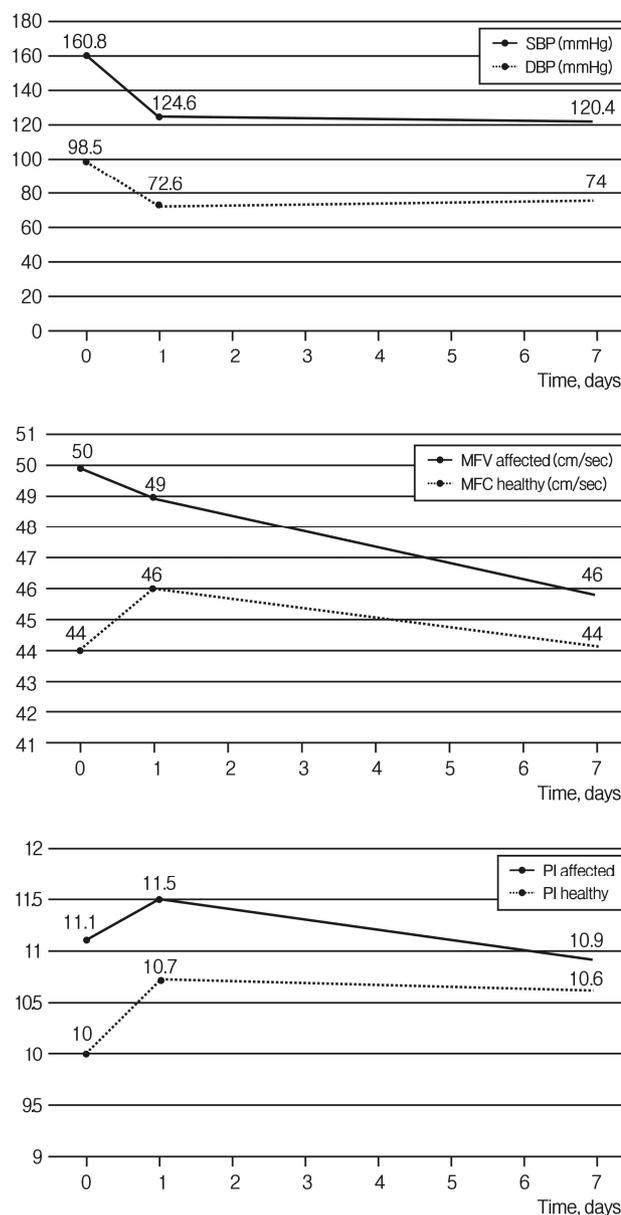

Fig. 1. Summary of results. SBP: systolic blood pressure; DBP: diastolic blood pressure; MFV: middle cerebral artery flow velocity; PI: pulsatility index.

Table 2. Blood pressure, middle cerebral artery flow velocity, and pulsatility index

Parameter	Mean SBP (mmHg)	Mean DBP (mmHg)	MFV healthy (cm/sec)	MFV affected (cm/sec)	p-value	PI healthy	PI affected	p-value
Baseline	160.8±30.5	98.5±20.4	44.0±13.3	50.0±7.8	0.51	10.1±0.4	11.1±0.25	0.22
24 hr	124.6±15.8	72.6±11.5	46.0±15.0	49.0±8.81	0.39	10.7±0.3	11.5±0.29	0.11
7 days	120.4±13.4	74.0±10.8	44.0±10.5	46.0±7.2	0.72	10.6±0.26	10.9±0.3	0.25

The results demonstrated that middle cerebral artery flow velocity (MFV) and pulsatility index (PI) were higher on the affected side than on the healthy side throughout the transcranial doppler study. MFV and PI on the affected side were not significantly changed compared with those of the healthy side after Nicardipine hydrochloride (HCl) infusion at 24 hr and 7 days (p>0.05). With those results, the use of Nicardipine HCl based on the absence of significant regional cerebral artery blood flow changes associated with a reduction of blood pressure in intracerebral hemorrhage.
SBP: systolic blood pressure; DBP: diastolic blood pressure; MFV: middle cerebral artery flow velocity; PI: pulsatility index.

and healthy side was not significant, and as time changes after development of ICH, the variables of MFV and PI of the affected side were going to original value (Table 2). From the above results, we found that there was no significant change in regional CBF after BP reduction by antihypertensive drug, Nicardipine HCl. By calculation of the difference in CBF by time change, no correlations were found between change in BP and change in regional CBF expressed either as mean MFV and PI changes. These results imply that there were no correlations of the autoregulatory function for CBF and time since ICH onset.

DISCUSSION

Arguments against treatment of hypertension in patients with acute ICH are based primarily on the concern that reducing BP means CBF reduction. Several previous studies have suggested the presence of transient reduction in CBF in surrounding and distant regions from the hematoma, presumably induced by compression of adjacent microvasculature. It is further hypothesized that autoregulation is impaired in the perihematoma region due to local ischemia and acidosis. Therefore, reduction in systemic BP may theoretically further impair blood flow with reduced CBF and provoke ischemia. In addition, reducing systemic BP may lead to autoregulatory vasodilatation of cerebral vessels and adversely affect ICP. Elevated BP could also be a protective Cushing-Kocher response to preserve cerebral perfusion. Under normal conditions, changes in BP over a wide range have little or no effect on CBF. This autoregulation of CBF is mediated by changes in the diameter of resistance arterioles in response to changes in cerebral perfusion pressure (CPP). When CPP decreases, arterioles dilate to reduce resistance and maintain CBF. This autoregulatory vasodilation has a limit, and when it is reached, CBF will start to fall[1-7,9,16,21-23,25,27,28].

In general, previous studies have suggested that autoregulation is preserved after ICH and therefore, lack of change in CBF seen after reduction of mean BP is not inconsistent with ICH. They did not observe any clear evidence of an ischemic penumbra in the acute period after ICH. They observed that despite the presence of elevated ICP, BP reduction was not associated with changes in CBF in the regions around and distant to the hematoma. The decrease in cerebrovascular resistance after administration of antihypertensive agents suggests that CBF is maintained by compensatory vasodilation[16,24,25]. In addition, previous studies have demonstrated a phase of initial hypoperfusion presumably by compression of the adjacent microvasculature by hematoma. This early CBF reduction apparently reflects the immediate and maximal hemodynamic adjustment in the brain after ICH. They observed an immediate period of very high ICP that resolved during the next few min[25]. It is possible that there may have been ischemia early in the course of ICH. Nath et al.[16] reported that ischemia after ICH persisted only to a marginal degree beyond 10 min and that CBF had returned to normal by 3 hr. Similarly, Yang et al.[28] observed a 50% reduction in CBF after ICH that had returned to control values by 4 hr. Powers et al.[19] evaluated the effect of BP reduction in 14 patients with supratentorial ICH of 6 to 22 hr after onset. CBF was measured using positron emission tomographic scan. Pharmacologic reduction of mean arterial pressure with nicardipine HCl by up to approximately 17% from baseline (mean arterial pressure 143-119 mmHg) produced no change in global or perihematoma CBF while maintaining the CPP at >65 mmHg. Kuwata et al.[13] reported that autoregulation in both hemispheres was globally impaired mainly with BP reduction of more than 20% 3 days after ICH. Impairment was less pronounced around the clot because of possible false autoregulation. Poor periclot autoregulation with restored autoregulation in the hemisphere was observed. And in some patients, later decline of individual autoregulatory ability can occur, resulting in significantly worse outcome. Poorer or worsening autoregulation on the affected sides was related with lower CPP between days 3 and 5. Delayed impaired autoregulation was a predictor of poor clinical outcome independent from other hemodynamic variables or factors that may be the result of greater brain damage by subsequent episodes of hypo or hyperperfusion. Both impaired autoregulation and bad outcome could be the common result of a more severe mass effect and brain injury affecting CPP, CBF, and autonomic pathway.

TCD allows assessment of hemodynamics in the MCA terri-

tory, which predominately reflects cortical arterioles. Regarding the applied TCD, the presence of a mass lesion could have led to physical distortion of the insonated MCA. In this situation, CBF velocity signal in the MCA still reflects downstream arteriolar resistance. Strong distortion should have led to compression or kinking of the MCA, leading to a stenotic signal with clearly elevated, turbulent CBF velocity. PI was calculated according to the formula of Gosling as follows: PI =(systolic blood flow velocity-diastolic blood flow velocity)/ mean blood flow velocity. PI of the intracranial arteries as measured by TCD may serve as a surrogate parameter for ICP. It serves as a reliable predictor of functional outcome in patients with ICH. In the result of our study, conducted in patients with ICH, we observed lower MFV and higher PI in the affected hemisphere throughout the study, even in baseline conditions before Nicardipine HCl administration. Blood flow compensation to restore cerebral perfusion in still viable perihematoma tissue on the affected side might explain the lower MFV observed in our study as described for functional neuroimaging in penumbral areas, but during acute and subacute ischemic stroke. The lower MFV previously observed in the affected hemisphere were identified by means of TCD, however we might hypothesize that there are still suffering cerebral areas surrounding the hematoma requiring intracerebral reperfusion. On the other hand, PI is an indirect measurement of distal microvasculature resistance that may be influenced by the local mass effect exerted by the hematoma on the affected side. In our study, the mass effect exerted by the hematoma and the perihematoma edema may not be a consequence of the higher PI observed on the affected side. Indeed, the higher PI on the affected side may be indicative of preserved cerebral hemodynamics and pulsatility in the affected hemisphere. The results of our study demonstrated that cerebral autoregulation is primarily preserved in acute ICH, and a secondary temporary decline and restoration after administration of Nicardipine HCl, being associated with lower MFV and higher PI. In a previous study, it was stated that the brain is capable of preserving autoregulation during small to middle size hematoma. However, with a greater ICH volume, PIs were consistently elevated and MFV consistently decreased, even though the PI ratio did not correlate with the hematoma volume[8,12,26].

There are some limitations to our study design. The first limitation relates to the selection criteria of patients in this study, which were small or medium-sized ICH volume (less than 60 cc) and relatively good GCS score. These findings may not be an accurate reflection of ICH in exclusion of large-sized ICH. And, those with large ICH may have increased ICP associated with a secondary rise in systemic BP. As cerebral arterial perfusion is a function of the difference between systemic BP and ICP, a decrease in systemic BP may compromise cerebral perfusion. This problem may be exacerbated in patients with chronic hypertension. The large hematomas are associated with higher ICP and lower intracranial compliance compared to smaller hematomas. With lower compliance, the affected area of the brain would be "stiffer" and may impair the fast responding myogenic response. The high ICP group showed greater deterioration of dynamic cerebral autoregulation than the low ICP group. Unfortunately, because we did not have ICP measurements on our patients we could not examine the relationship between ICP and blood flow. Second, our study with a relatively small number of cases (46 cases) is not sufficient to definitively conclude the effect of acute ICH treatment with Nicardipine HCl on regional CBF. We cannot rule out the presence of unknown, confounding variables, not accounted for in the final analysis. We cannot rule out the possibility that dynamic cerebral autoregulation was already impaired in the ICH group prior to hemorrhage due to underlying vascular risk factors such as hypertension. In fact, the static cerebral autoregulation curve is thought to be shifted to the right in people with untreated hypertension. Therefore, it is unlikely that our findings of bilateral impairment of dynamic cerebral autoregulation in ICH patients can be explained by their longstanding history of hypertension. Third, direct comparisons with other diagnostic techniques such as positron emission tomography and magnetic resonance imaging are lacking because of major differences in temporal resolution. Finally, there are several well-known confounders of TCD assessment of cerebral autoregulation regulation, some of which are difficult to control outside the intensive care unit setting. And, severe extracranial or intracranial artery stenosis and clinical conditions (for example; chronic hypertension, diabetes mellitus, and silent infarcts) may confound the assessment of cerebral autoregulation.

CONCLUSION

This study supports the controlled use of antihypertensive medications based on the absence of significant hypoperfusion and CBF changes associated with a reduction of mean BP after ICH. It should be recognized that these results are only applicable within the normal autoregulatory limits of CPP, therefore, careful attention should be directed toward preserving adequate CPP. Further studies on a long-term outcome basis are needed to investigate whether reduction in BP has an influence on ICH expansion, CBF. These data can, however, be used to help design such a trial and, in the meantime, provide helpful guidelines when reduction in arterial pressure is deemed necessary in patients with ICH.

CONFLICTS OF INTEREST

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

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