Continuous nicardipine infusion to control blood pressure after evacuation of acute cerebral hemorrhage

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Purpose: To explore the long-term effects of the calcium antagonist, nicardipine, on cerebral hemodynamics in patients with acute cerebral hemorrhage, we investigated the effects of nicardipine infusion on intracranial pressure (ICP), middle cerebral arterial blood flow velocity (Vmca), and computed tomographical (CT) findings of bleeding and edema.

Methods: Twenty-two patients with acute cerebral hemorrhage were infused with nicardipine for > 72 hr to decrease blood pressure. Blood pressure, heart rate, conscious level, Vmca, pulsatility index (PI, using transcranial Doppler), ICP, cerebral perfusion pressure (CPP) and platelet counts were monitored. CT examination was also performed to detect the changes of bleeding (hematoma) and/or brain edema.

Results: Blood pressure decreased (20 to 30% from control, $P < 0.05$) without any changes in heart rate. Platelet count did not change neither did Vmca and PI change on either the intact or injured side. The ICP decreased 24 hr after the end of infusion from 30 ± 12 mmHg to 20 ± 9 mmHg ($P = 0.036$) but was still higher than normal. The CPP decreased at 24 hr (75 ± 14 mmHg, $P = 0.026$) and 72 hr (73 ± 15 mmHg, $P = 0.024$) from the baseline (99 ± 17 mmHg). Conscious level improved but not significantly and CT findings did not show any exacerbation in bleeding or edema.

Conclusion: In patients with acute cerebral hemorrhage, nicardipine infusion to decrease blood pressure by 20 to 30% had no effect on Vmca, ICP, cerebral bleeding and edema, but decreased CPP.

Objectif : C'est afin d'explorer les effets à long terme de l'inhibiteur calcique, nicardipine, sur l'hémodynamie cérébrale de patients victimes d'hémorragie cérébrale aiguë, que nous avons examiné les effets d'une perfusion de nicardipine sur la pression intracrânienne (PIC), la vitesse circulatoire de l'artère cérébrale moyenne (Vacm) et la scanographie du saignement et de l'œdème.

Méthode : Vingt-deux patients souffrant d'hémorragie cérébrale aiguë, ont reçu une perfusion de nicardipine pendant > 72 h, pour diminuer la tension artérielle. La tension artérielle, la fréquence cardiaque, le niveau de conscience, la Vacm, l'indice de pulsatilité (IP, au moyen du Doppler transcrânien), la PIC, la pression de perfusion cérébrale (PPC) et la numération plaquettaire ont été surveillés. La scanographie a été aussi réalisée dans le but de détecter des modifications du saignement (hématome) et/ou de l'œdème cérébral.

Résultats : La tension artérielle a baissé (de 20 à 30 % des mesures témoins, $P < 0,05$), mais la fréquence cardiaque, la numération plaquettaire et la Vacm n'ont pas été modifiées. La PI a changé du côté intact et du côté lésé. La PIC a diminué 24 h après la fin de la perfusion, passant de 30 ± 12 mmHg à 20 ± 9 mmHg ($P = 0,036$), mais est demeurée plus élevée que la normale. La PPC a baissé à 24 h (75 ± 14 mmHg, $P = 0,026$) et à 72 h (73 ± 15 mmHg, $P = 0,024$), comparée à la PPC de base (99 ± 17 mmHg). Le niveau de conscience s'est amélioré, mais non de façon significative et la scanographie n'a pas montré d'exacerbation du saignement ou de l'œdème.

Conclusion : Chez les patients victimes d'hémorragie cérébrale aiguë, une perfusion de nicardipine, utilisée pour diminuer la tension artérielle de 20 à 30 %, n'a pas d'effet sur la Vacm, la PIC, le saignement ou l'œdème cérébral, mais diminue la PPC.

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FOR patients with acute cerebral hemorrhage, immediate hypotensive therapy is often necessary and calcium antagonists have been used for this purpose. However, there is controversy whether calcium antagonists can be used safely in patients with acute cerebral hemorrhage because of the risk of increased bleeding¹ and intracranial pressure.² In this study, we explored the safety of hypotensive therapy with the calcium antagonist, nicardipine, in patients with acute cerebral hemorrhage in terms of intracranial pressure (ICP), cerebral blood flow velocity, and computed tomographical (CT) findings of bleeding and edema.

Methods

After the approval of our institutional research committee and informed consent from the patient's family, 22 patients with acute cerebral (putaminal) hemorrhage secondary to hypertension who underwent surgical drainage of the hematoma were studied. Those with liver or renal damage were excluded. The patients, 14 male and 8 female, were 64 ± 15 (range: 47–79) yr old. After surgery under general anesthesia the tracheas were extubated within 24 hr. The PaCO₂ was controlled between 30 and 35 mmHg during ventilation.

After surgery, an infusion of nicardipine was started at $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and the rate was adjusted to keep systolic blood pressure between 120 mmHg and 160 mmHg (20 to 30% reduction compared with the pre-nicardipine value) indicated by neurosurgeons. Nicardipine infusion was continued for more than 72 hr. Concentrated glycerin fructose solution (Glyceol™, osmolarity is seven times of lactated Ringer's solution, Ootsuka, Osaka, Japan), 400–600 mL (divided doses twice to three times a day), 250 mg phenytoin (divided dose twice a day) per day, and antibiotics were administered in all cases. Blood pressure (directly measured through a catheter in the radial artery), heart rate, consciousness level, middle cerebral arterial blood flow velocity (Vmca), pulsatility index (PI), ICP and platelet counts were monitored before, 24 and 72 hr after the start of nicardipine infusion and 24 hr after the end of nicardipine infusion. Computed tomographic (CT) examination was performed before, 24 and 72 hr after the start of nicardipine infusion and 24 hr after the end of nicardipine infusion to detect the changes of bleeding (hematoma) and/or brain edema, which was diagnosed by the neurosurgeons. Consciousness was monitored using Japan Coma Scale (JCS, see Appendix). The Vmca was measured and PI was calculated by Transcranial Doppler ultrasound flowmetry (TC2-64™, EME, Überlingen, Germany). PI was calculated using the following formula: $\text{PI} = (\text{peak systolic}$

$\text{velocity} - \text{end diastolic velocity}) / (\text{mean velocity})$. The ICP was monitored continuously using a sensor inserted upon brain parenchyma at surgery and cerebral perfusion pressure (CPP) was calculated as $\text{mean blood pressure} - \text{ICP}$.

Data are expressed as mean $\pm$ standard deviation. Statistical analysis was performed with one-way repeated measures analysis of variance (ANOVA) followed by paired *t* test for blood pressure, heart rate and ICP. For Vmca and PI, two-way repeated measures ANOVA followed by the contrast was used. The changes of JCS and CT findings were analyzed with Friedman test. A *P* value < 0.05 was considered statistically significant.

Results

The infusion dose of nicardipine was 1.14 ± 0.45 (range: $0.61\text{--}1.69$) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at 24 hr and 0.60 ± 0.45 ($0.24\text{--}1.06$) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at 72 hr after the start of infusion. In total 484 ± 343 (138–826) mg of nicardipine was administered for 213 ± 114 (92–323) hr.

Blood pressure decreased during and 24 hr after the end of the nicardipine infusion but heart rate did not change during the study (Figure 1). The PaCO₂ after extubation was 34 ± 6 mmHg, which was not different from that during ventilation (32 ± 3 mmHg).

Platelet counts were $12.6 \pm 5.2 \cdot \text{mm}^{-3}$, $10.6 \pm 6.9 \cdot \text{mm}^{-3}$, $10.4 \pm 7.2 \cdot \text{mm}^{-3}$, and $11.1 \pm 5.7 \cdot \text{mm}^{-3}$ before and at 24 hr and 72 hr after the start of infusion, and 24 hr after the end of infusion, respectively (*P*: NS). Hematocrit was $29 \pm 4\%$, $28 \pm 5\%$, $31 \pm 4\%$, and $32 \pm 3\%$ before infusion, at 24 hr and 72 hr after the start of infusion, and 24 hr after the end of infusion, respectively (*P*: NS).

The Vmca and PI did not change in either the intact or injured side during the study (Figure 2). There were no differences between the intact and injured sides. Intracranial pressure decreased 24 hr after the end of the infusion but was still higher than normal (Figure 3): CPP decreased at 24 and 72 hr but was > 50 mmHg (Figure 3). Consciousness levels (shown as JCS) did not change (Table I) and CT findings did not show any exacerbation of bleeding and edema (Table II).

Discussion

The present study showed that continuous infusion of nicardipine to decrease blood pressure in patients after evacuation of acute cerebral hemorrhage did not affect Vmca and ICP, but decreased CPP. It did not exacerbate bleeding, edema, or neurological outcome.

Another calcium antagonist, nimodipine, increased surgical bleeding in cardiac surgery.¹ The reason for

FIGURE 1 Blood pressure and heart rate

Blood pressure (upper; closed circle: systolic, open circle: diastolic) and heart rate (lower) are shown. Total number of the patients were 22. Bars indicate standard deviation. *: $P < 0.05$ vs the control value (Before infusion).

this increased bleeding was suggested to be due to vasodilatation and/or due to the antiplatelet action of nimodipine.¹ In contrast, oral nimodipine has minimal antiplatelet activity.³ The calcium antagonist nifedipine reduced platelet aggregation and prolonged bleeding time after a single oral dose of 20 mg.⁴ Nicardipine might also attenuate platelet secretion.⁵ In the present

FIGURE 2 Mean cerebral blood flow velocity of middle cerebral artery (upper) and pulsatility index (lower) are shown. Total number of the patients were 22. Bars indicate standard deviation. Closed circles are intact side and open circles are injured side. No significant differences are seen between intact and injured side.

study, we measured only platelet count and not platelet function. However, CT findings showed no increase in bleeding or hematoma. Therefore, even if nicardipine has antiplatelet function, it did not exacerbate cerebral bleeding in patients after evacuation of acute cerebral hemorrhage.

In anesthetized dogs, nicardipine increased ICP and cerebral blood flow.² Nicardipine also increased

FIGURE 3 Intracranial pressure (ICP, upper) and cerebral perfusion pressure (CPP, lower) are shown. Total number of the patients were 22. Bars indicate standard deviation. *: $P < 0.05$ vs the control value (Before infusion).

ICP in patients with⁶ or without⁷ intracranial hypertension. This increase was associated with decreases in arterial blood pressure and CPP.⁷ The present results showed no increase in ICP, but CPP decreased. The direct effect of nicardipine on ICP can not be determined from the present study because of the administration of concentrated glycerin fructose solution,

TABLE I Consciousness

Consciousness (JCS)	Before infusion	24 hr	72 hr	24 hr after the end of infusion
300	0	0	0	0
200	1	0	0	0
100	1	0	0	0
30	3	4	2	1
20	6	6	4	3
10	7	7	5	4
3	2	3	4	4
2	1	1	3	3
1	1	1	2	4
0	0	0	2	3

The number of patients is shown.

JCS: Japan Coma Scale (See Appendix)

TABLE II CT findings

		24 hr	72 hr	24 hr after the end of infusion
Hemorrhage (Hematoma)	Increase	0	0	0
	No change	4	3	1
	Decrease	18	19	21
Edema	Increase	0	0	0
	No change	10	8	5
	Decrease	12	14	17

The number of patients is shown.

Increase, No change, and Decrease: compared to the findings before nicardipine infusion judged by neurosurgeons who did not know of this study.

Edema was diagnosed by the changes of sulcus and ventricle.

which could decrease ICP. In addition, ICP was recorded only at three times after nicardipine infusion with the first at 24 hr after the start of the infusion. It is possible that the initial increase in ICP was missed. The third suggested reason of the absence of increased ICP in the present study might be that the ICP would have decreased if nicardipine had not been used because ICP remained higher than normal despite the use of hyperventilation and an osmotic diuretic. In the present study, the reduction in ICP appeared to follow the reduction in blood pressure. This would suggest that cerebral autoregulation was impaired and may explain why an increase in ICP was not observed with nicardipine infusion. However, CPP was > 50 mmHg during nicardipine induced hypotension. Therefore, in patients with cerebral hemorrhage to whom osmotic diuretics such as concentrated glycerin fructose solution may be administered, nicardipine infusion may be used safely without increasing ICP or decreasing CPP to a critical level.

Hyperventilation attenuated the increase of ICP by nicardipine in anesthetized dogs.⁸ In the present study, all patients were slightly hyperventilated and this may explain why ICP did not increase in contrast to other studies.^{2,7}

Nicardipine increased local cerebral blood flow and internal carotid blood flow velocity under isoflurane anesthesia.⁹ Topically administered nicardipine to cerebral vessels dilated small arterial cortical vessels and increased cerebral oxygen tension in patients undergoing surgery for extra-intracranial anastomosis.¹⁰ However, in another study, local cerebral blood flow did not change during nicardipine infusion, but blood flow velocity increased after nicardipine infusion.¹¹ The present results showed no changes of Vmca and PI while systemic blood pressure was decreased by nicardipine infusion. A lack of change in PI indicates that the resistance of the middle cerebral artery did not change.¹² Absence of changes in Vmca and PI and the lack of difference in hematocrit suggest that blood flow did not change. Therefore, it is suggested that in the patients with acute cerebral hemorrhage, nicardipine infusion to decrease blood pressure about 25% does not affect cerebral blood flow.

There are no reports of the pharmacokinetics of continuous infusion of nicardipine. Nicardipine is metabolized in the liver and the metabolite had little vasodilating effect. Liver damage but not renal damage might prolong or enhance the effects of nicardipine. However, no patients in the present study had liver damage. Therefore, the dose used might be decreased for the patients with liver damage.

Sympathetic activity was increased by nicardipine infusion and it gradually decreased after three days of the start of infusion.¹³ The rein-angiotensin-aldosterone system was also activated during nicardipine infusion.¹⁴ These changes might have some roles in vasodilatation, ICP, and/or cerebral blood flow.

Nitroglycerin increased mean cerebral blood flow measured by SPECT on the bleeding side but not on the intact side while systemic blood pressure decreased.¹⁵ We could not find any reports of differences in the effects of nicardipine on cerebral blood flow between the bleeding and intact sides. Our present study suggested that nicardipine did not induce different effects on cerebral blood flow in the injured and intact sides.

In conclusion, for patients with acute cerebral hemorrhage, nicardipine infusion to decrease blood pressure by 20 to 30% has no effects on Vmca, ICP, cerebral bleeding and edema, but decreases CPP.

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Appendix

Japan Coma Scale (3-3-9)

- III. Deep coma, coma, or semi coma with noxious stimuli
 - 300: No response to pain
 - 200: Withdrawal response to pain
 - 100: Localizing to pain
- II. Lethargy, hypersomnia, somnolence, or drowsiness without verbal stimuli
 - 30: Eye-opening by repeated verbal stimuli
 - 20: Obeying to easy command
 - 10: Purposeful movement and speech but a lot of mistakes
- I. Awakening without any stimuli
 - 3: Can not tell own name and birth date
 - 2: Disoriented
 - 1: Not so clear
 - 0: Clear