# Effects of Calcium Channel Blocker, Nicardipine, On Intracranial and Cerebral Perfusion Pressure in Experimental Intracerebral Haemorrhage

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**Abstract :** Calcium channel blockers have an important role in the therapy of arterial hypertension and cerebral vasospasm, two phenomena which can be associated with intracerebral haematoma and increased intracranial pressure. The purpose of this s tudy was to investigate the effects of Nicardipine on intracranial and cerebral perfusion pressure in animals with experimental intracranial haematoma formation.

Cerebral perfusion pressure (CPP) was 75.12 5.11 mm Hg in the control group. Intracranial pressure(ICP) showed a significant increase with haematoma formation, but no significant difference was found in CPP. ICP and CPP did not show an y significant difference in the group with slow infusion of nicardipine. However,in the group with intravenous bolus application of nicardipine, there was a significant decrease in CPP.

In conclusion, with the use of calcium blockers for cerebral arterial vasodilatation, the increase in CBF and the antihypertensive effect might also be associated with some negative effects.

**Key words :** Calcium Channel Blocker, Cerebral Haemorrhage, Cerebral perfusion pressure, Intracranial pressure.

## INTRODUCTION

In recent years, calcium channel blockers have had an important role in the treatment of arterial hypertension and cerebral vasospasm (1,3,4,9,13). In general, these two pathological conditions do not develop alone and hypertension is a common cause of spontaneous intracerebral haemorrhage (5, 10,17). Cerebral vasospasm occurs as a result of aneurysmal subarachnoid haemorrhage and is generally associated with intracerebral and/or intraventricular haemorrhage. In addition, an increase in intracranial pressure (ICP) occurs as a result of stroke or mass lesion(9,10).

Calcium channel blockers have an effect of vasodilatation, by preventing $Ca^{++}$ intake through smooth muscle cells and by a direct effect on smooth muscle (1,7,24,26), and it has been shown that, they can increase the cerebral blood flow(CB F) to various degrees and also reduce arterial blood pressure (4,8,9,12,13,18,23). The purpose of this experimental study was to investigate the effects of Nicardipine on ICP and cerebral perfusion pressure (CPP) in intracranial haemorrhage.

## MATERIALS AND METHODS

Thirty New Zealand white rabbits, weights ranging between 2100-3500 g, were used. Anaesthesia was achieved with urethane(1g/kg) intraperitoneally. The femoral artery and vein were canulated with polyethylene catheters containing a mixture of heparin and saline, connected to a pressure transducer to provide a continuous record of blood pressure (NEC San-ei Instruments Ltd., Tokyo, Japan), and for sampling arterial blood gases. The femoral vein was used for infusion of the drugs. Respiration was provided by tracheostomy. On each side of the midline, a 10 mm scalp incision was made behind the coronal suture. Two burr holes were made 5 mm lateral to the midline with an air drill.The dura mater was opened and with a small nerve hook,the subdural space was probed on the right side using the

technique described by Rahimifar(19). For ICP measurement, a 16 G polyethylene catheter, filled with saline, was placed subdurally through this hole, and fixed to the skull around the burr hole with methylmethacrylate cement. The catheter was connected to a pressure transducer (P10E2, Spectramed Inc. California, USA) zeroed at the level of the lateral ventricle. All signals were amplified and displayed on a pressure monitor (Serecust 730, Siemens, Germany). Animals were divided into four groups.

In the control group (n=6), only arterial pressure and ICP were recorded. In the others, 0.5 ml autologous nonheparinised blood taken from the contralateral femoral artery, was slowly injected 5 mm deep into the left frontoparietal area with a 26 G needle via the left burr hole. This hole also was then closed with cement. Arterial and intracranial pressures were recorded in the sham-operated group (n=6) during and after haematoma formation. Nicardipine was not given. During haematoma formation ICP reached its peak value and then reduced to its former value within approximately 2 minutes in all animals. 0.1 mg/kg Nicardipine in normal saline was applied by slow infusion for sixty minutes in the 3rd group (n=9) after haematoma formation, and records were done. In the 4th group (n=9), 0.1 mg/kg intravenous bolus Nicardipine was given after haematoma formation and arterial and intracranial pressures were recorded for 3 minutes. During the study, arterial blood samples were taken from all animals and P aCO2 was measured. At the end of the procedure, the animals were sacrificed by intraarterial KCl injection, the brains removed, fixed in formalin, and slices were examined.

## RESULTS

Mean arterial blood pressure(MABP) was 85.21 + 6.40 mm Hg in the control group. An increase in arterial pressure was observed in all groups during the haematoma formation process (Table I). These values were statistically significant compared with MABP prior to haematoma ($p<0.05$). A slight decrease in MABP observed after slow infusion of Nicardipine, was not significant, but there was a significant decrease after intravenous bolus of Nicardipine. It was also significant compared with MABP be fore the haematoma process($p<0.001$) and also before Nicardipine bolus injection($p<0.05$). PaCO2 ranged between 28-33 mm Hg in all animals.

**Table I: MABP, ICP and CPP values in the SICB and IVCB groups.**

| | MABP | ICP | CPP |
|---|---|---|---|
| SICP Initial | 84.00±4.33 | 8.77±1.78 | 75.66±3.84 |
| Grup | | | |
| TLP | 92.88±4.64 | 28.22±6.36 | 64.33±6.91 |
| 10 sec. later | 84.55±3.60 | 14.85±2.14 | 70.11±5.10 |
| 30 sec. later | 81.00±1.87 | 9.55±1.58 | 71.44±2.29 |
| 60 sec. later | 80.22±2.63 | 9.11±1.61 | 70.66±2.73 |
| SICB beginning | 77.33±3.70 | 8.88±1.36 | 68.33±3.87 |
| 5 min. later | 74.66±8.03 | 9.55±1.74 | 65.22±8.34 |
| 10 min. later | 75.88±6.43 | 9.33±1.58 | 66.55±6.52 |
| 30 min. later | 75.88±6.02 | 9.00±1.22 | 66.77±6.61 |
| 60 min. later | 75.55±6.52 | 9.55±1.23 | 66.22±6.30 |
| IVCB Initial | 84.33±6.34 | 8.44±1.42 | 73.33±5.31 |
| Group | | | |
| TLP | 95.00±2.82 | 27.55±7.95 | 67.55±8.53 |
| 10 sec. later | 89.11±4.88 | 21.33±7.22 | 67.77±10.59 |
| 30 sec. later | 82.11±3.68 | 11.55±2.12 | 70.55±4.61 |
| 60 sec. later | 81.00±4.18 | 10.33±1.58 | 70.66±4.24 |
| IVCB beginning | 79.66±4.42 | 10.22±1.39 | 68.77±7.34 |
| 30 sec. later | 66.22±7.27 | 14.11±2.20 | 51.88±7.49 |
| 60 sec. later | 66.55±6.72 | 15.11±3.29 | 51.55±8.76 |
| 120 sec. later | 66.55±6.72 | 15.11±3.29 | 51.55±8.76 |
| 300 sec. later | 66.32±5.86 | 13.88±2.36 | 52.44±7.28 |

(MABP: mean arterial blood pressure, ICP: intracranial pressure, CPP: cerebral perfusion pressure, SICB: slow infusion calcium blocker, IVCB: intravenous bolus calcium blocker, TLP: time lesion production, sec.: second, min.: minute)

When the brains were examined, although equal volumes of blood had been injected, it was seen that intracerebral haematomas of various sizes occurred. There were some haematomas with a surface collection of blood, and in addition, intraventricular haematomas were found in some animals.

In the control group, ICP remained stable during the one hour period of study. At the beginning of induction of intracranial haemorrhage, ICP rose acutely,with a peak occurring within 10-20 seconds. Following the peak, there was an immediat e decrease within 60 seconds, but ICP generally stayed a little over the control group levels (Fig.1/A). There was no significant difference in the slow Nicardipine infused group during the 60 minute period (Table I). No statistical difference was found when the results were compared with the values obtained before haematoma and the controls(Fig.1/B). Following intravenous Nicardipine injection, the mean ICP was 14.11 + 2.20 mmHg at 30 seconds, and 15.77 + 3.56 mmHg at 60 seconds later. These results when compared with the control group and ICP values before Nicardipine injection, it were significantly high ($p<0.001$). Then a slight decrease was observed in ICP, but it was above normal values.

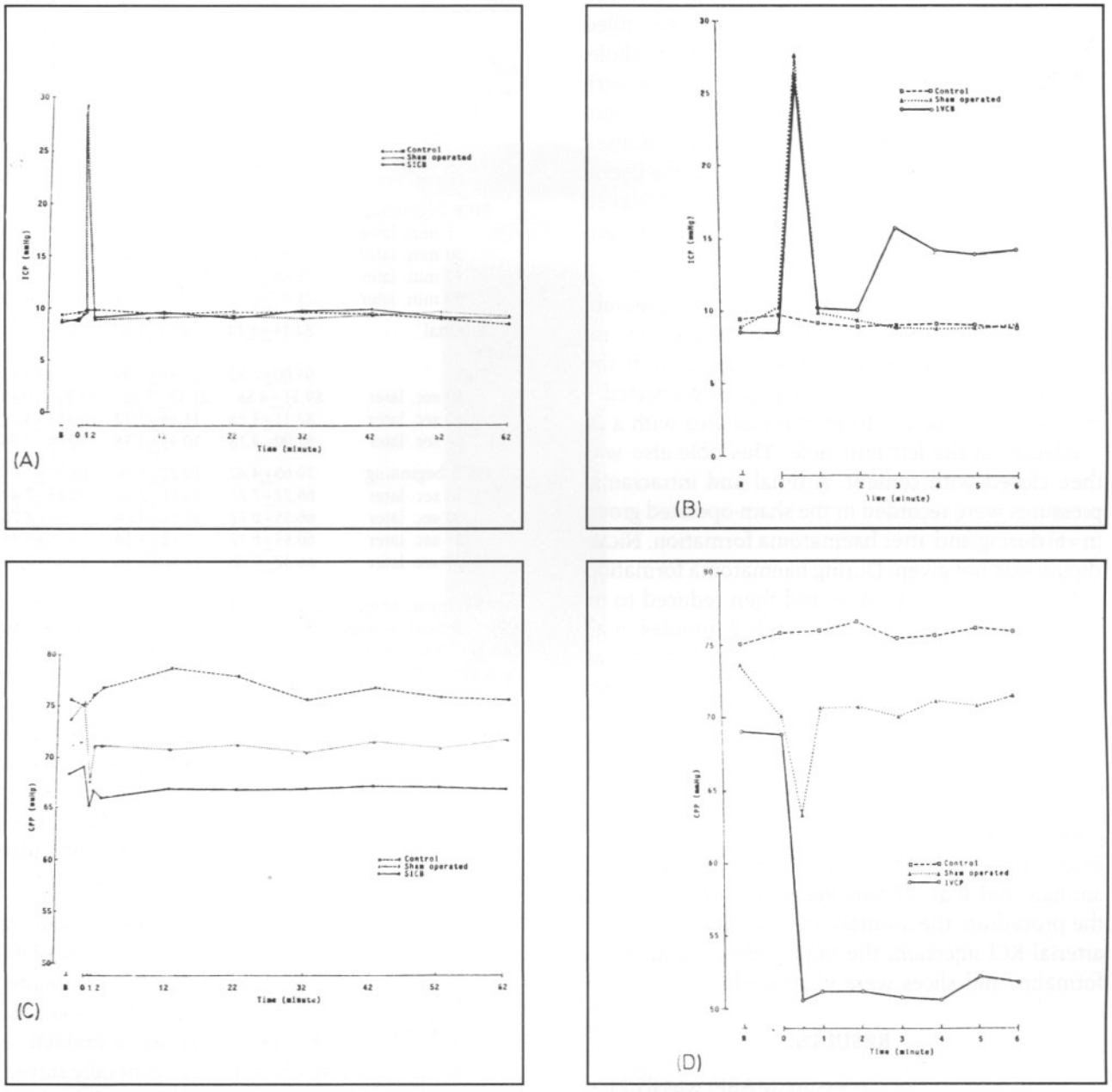


*Fig. 1 : Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) measurements in the groups with slow infusion and intravenous bolus injection of calcium blockers. Time 0 indicates time of lesion production. Time 2 indicates time of calcium blocker application. A and C : ICP and CPP changes in the slow infusion Nicardipine group. B and D : ICP and CPP in the intravenous bolus injection Nicardipine group.*

CPP was 75.12 + 5.11 mmHg in the control group. There was no significant reduction in CPP as detected during the haematoma process. After slow infusion of Nicardipine, a minimum reduction in CPP was observed (Fig.1/C), which was not significant. In one animal there was a significant decrease in MABP and this caused an important reduction in CPP. Following intravenous bolus Nicardipine injection, CPP was 51.88 + 7.49 mmHg at 30 and 60 seconds respectively(Fig.1/D). When this decrease was compared with CPP before Nicardipine injection, it was found to be statistically significant ($p<0.005$). This decrease in CPP continued for three minutes.

## DISCUSSION

Calcium channel blockers have the effect of vasodilatation by both preventing Ca input needed for vasoconstriction and directly affecting the vessel wall (9,21,26). Besides they inhibit vasoconstriction of cerebral vessels in the presence of vasoactive agents (1), thus increasing CBF. Blood constitutes intracranial volume both with brain and cerebrospinal fluid. For this reason, increased intracranial volume also might increase ICP. If the intracranial volume is increased by haematoma or o edema, it might play an important role in the disturbance of compensatory mechanisms and further increase intracranial hypertension. The effects of calcium blockers on ICP are variable and can show differences according to dose and application . In our study, following intracranial haematoma formation Nicardipine in the same dose, was applied in two groups of animals, but in different ways. Slow infusion of Nicardipine did not produce any significant difference in CPP and ICP. Similar results have been reported by. Hadley et al. (7) in patients with increased ICP due to infarct, and Gaab et al. (6) in patients with head injury, reported that infusion of Ca antagonists did not produce a significant increase in ICP. Robinson et al. (20) showed that no significant dilatation occurred in venous capacitance vessels and increases in ICP were small when Nifedipine was used. However, Tateishi et al.(25) claimed that oral Nifedipine increased ICP to a significant degree in a small group of patients.

We observed a significant increase in ICP and a significant decrease in CPP in the animals receiving bolus Nicardipine. Decreased CPP is due to not only decreased arterial pressure but also to an increase in ICP as a result of cerebral vasodila tation. Variations of PaCO2 recorded at frequent intervals in these animals, did not show any relation with changes in ICP. Bedford et al. (2) showed significant increases in ICP with intravenous bolus Verapamil in patients with brain tumour. Wusten et al. (27) claimed similar results with intravenous Nifedipine. In addition Nishikawa et al. (16) showed that lumbar cerebrospinal fluid pressure increased 50-90% with intravenous Nicardipine in patients without any neurological disease.

The brain of a rabbit is approximately 0.3-0.5% of its body weight and can tolerate a 0.5-1 $cm^3$ haematoma mass(11). ICP showed a rapid increase and decrease in a short period during the formation of intracranial haemorrhage in this study . Nath et al.(14,15) reported similar results in their two studies. Kaneko et al. (10) stated that the haematoma reached its maximum size in 10-20 minutes, might expanse with effort and oedema occurring within 7-8 hours. Contrary to the increase in ICP, no significant decrease in CPP was observed in our animals in the same period, due to the increase in arterial blood pressure during haematoma formation. Furthermore, isch aemic damage and CBF decrease was claimed with lesion formation in early periods (22). These varying results are the basis of the controversy over early surgical intervention. Also, it is not easy to explain late oedema formation. We found an increase of IC P and a decrease of CPP 8 hours later in rabbits with intracerebral haemorrhage in our unpublished study. But it is difficult to say whether oedema increases ICP and decreases CPP , or the decrease in arterial pressure due to various mechanisms decreases CPP and aggravates oedema.

No significant effect on ICP and CPP , and a slight reduction in arterial blood pressure might seem safe in animals with a slow infusion of Nicardipine, but particularly in hypertensive patients , there are some risks of getting optimal effect. It has been claimed that Nicardipine produces a slight reduction in arterial pressure, but high doses cause, a significant decrease (4,24). In conclusion, when calcium blockers are used for cerebral arterial vasodilatation, the increase in CBF and antihypertensive effect might be associated with some negative effects making careful monitoring neccessary in hypertensive patients with high ICP.

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