CEREBRAL VASOSPASM AND RESOLUTİON WITH NICARDIPINE IN RABBITS

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SUMMARY :

The effects of Nicardipine, a Ca++ channel blocker, on vasoconstriction of rabbit basilar artery in two different conditions, one with a clot contacting the wall of the artery and the other without, were investigated in this study. The Initial diameters of the basilar arteries were measured in all groups. When intracisternal blood was applied, They were found to be 0.35∓0.09 mm in the clot removal group (CR), 0.34+0.13 mm in the clot + Nicardipine group (C+N) and 0.31∓0.07 mm in the clot removal + Nicardipine group (CR+N). Each group showed significant difference when compared with the initial diameter (p<0.001). Mean basilar artery diameter was 0.4∓0.08 mm following CR, 0.52∓0.10 mm following C+N and no significant difference was found between these two conditions and their clot contact conditions. It was 0.79∓0.10 mm in the CR+N group and this was found to be statistically significant when compared with to clot contact cnodition (p<0.001). Therefore, to obtain optimal benefit in subarachnoid haemorrhage the mechanical removal of the clot, even a limited amount, and administration of Nicardipine might be useful.

KEY WORDS

Nicardipine, Rabbit, Vasospasm.

INTRODUCTION

The pathogenesis of cerebral vasospasm which affects the mortality and morbidity of subarachnoid hemorrhage (SAH) is not clear (4,6,7,17,25,26,31) but it is considered to be multifactorial (24,37,39,45). After SAH, endothelial damage and release impairment of endothelium-derived relaxing factor (EDRF) and also vasoconstrictor substances from the blood in the subarachnoid space are all claimed to play an important role in vasospasm (1,2,10,12,13,15,18,22,24,25, 27,29,32,39,42,44). It is thought that these substances produce vasoconstriction by increasing the transmembrane influx of Ca++ (3,11,19,35,38,41). Further, inflammation is also thought to produce vasoconstriction (6,17,23,36).

Since the etiopathogenesis of cerebral vasospasm is not known, treatment is controversial. A number of studies on this subject are evidence of this. The commonest methods include clot removal (16,28,33,42), hypervolemia and hypertension (39), cerebral protection for ischaemia (31), suppression of platelet aggregation, modification of prostaglandin synthesis (6,13), inhibition of TXA2 synthesis and/or stimulation of prostacyclin synthesis (9,13,14,31) and topical, intrathecal or intravenous Ca++ channel blockers (5,8,19,34,35,38,41).

Nicardipine is a Ca++ channel blocker. It protects neural functions by decreasing Ca++ influx in-tracellularly and has important vasodilatory effects (3,11,15,40).

The purpose of this study is to investigate the effects of Nicardipine on vasoconstriction of the basilar artery in rabbits, under two different conditions, one with the clot contacting the wall of the artery and the other not.

MATERIAL AND METHODS

Twenty-eight albino New-Zealand rabbits, weighing from 2.0 to 3.5 kg each, were used for the experiment. Anesthesia was obtained with 1.5 g/kg Urethan intraperitoneally. Following anesthesia the ear vein and femoral artery were catheterised and the artearial blood pressure via the femoral artery was monitored with o polygraph (NEC San-ei instruments Ltd., Tokyo-Japan) and blood was withdrawn to measure arterial PaC02 and pH. Tracheostomy was done with an incision from the mandible to the jugular fossa. The trachea and oesophagus were retracted with a self-retaining retractor and the clivus was exposed via stripping off the musches. The clivus was removed with a dental drill and the cistern containing the basilar artery and its branches was exposed. The dura mater was incised and excised under a surgical microscope (AD Scientific Instruments, Buffalo, New-York). The animals were divided into four groups. The first was the control group (n=6). 0.5 ml nonheparinised autologous blood was administered

intracisternally for 15 minutes in all groups and vasoconstriction of the basilar artery was obtained. In the second group (n=6) the clot was removed and the area was washed with saline solution and left for 60-90 minutes. In the third group (n=8) nicardipine HCI (0.01 mg/ml) (Sandoz, 4. Levent, Istanbul) was applied on the clot for 15-20 minutes. In the fourth group (n=8), the clot was removed and nicardipine HCI (0.01 mg/ml) was applied for 15-20 minutes. Microphotographs were taken at the beginning in all groups, and at the end of each step in groups other than the control group.

The measurements of PaCO2 and pH were done with the autoanalyzer (Stat Profile Analyzer, Nova Biomedical-Waltham, Massachusetts). In order to find the changes in arterial diameters a measurement was made with to formula: Arterial diameter measured on photographs in mm/Magnification degree of the microskope.
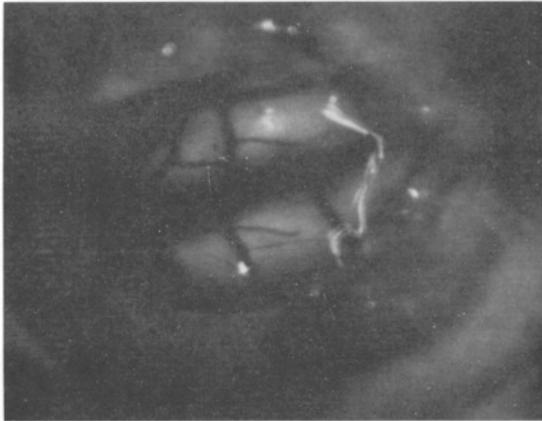
Student's t-test was used for statistical analysis.

RESULTS

The physiological parameters of the experimental group are shown in Table 1. The mean basilar artery was found to be 0.82 mm in the control group. No significant difference was found between the initial arterial diameters of all groups. In the 2nd, 3rd and 4th groups to which intracisternal blood was applied, the mean artery diameters were determined as 0.32 ∓ 0.09 mm, 0.34 ∓ 0.13 mm and 0.31 ∓ 0.07 mm respectively. A significant degree of vaso-contriction was found when each was compared with their initial diameter and the control group ($p < 0.001$).

Mean artery diameter was $0.41 + 0.08$ mm after clot removal and there was no significant difference when compared with clot presence (Fig 1). It was 0.52 ∓ 0.10 mm in the clot+Nicardipine group and moderate vasodilatation was determined when compared with clot presence, but no significant difference was found (Fig 2).

Fig 1 : Microphotographic representation of basiler artery in the clot removal group. a) No intracisternal blood. b) 15 minutes after intracisternal blood clot. c) 90 minutes after clotremoval.

Mean artery diameter was 0.79 ∓ 0.10 mm in the clot removal+Nicardipine group, significant vasodilatation was found when compared with clot presence ($p < 0.001$) (Fig 3)

Mean arterial diameters of all groups are shown graphically in (Fig 4).

Fig 2 : a) Microphotographic representation of basilar artery in the clot+Nicardipine group. a) No intracisternal blood.

Fig 2 : b) 15 minutes after intracisternal blood clot,

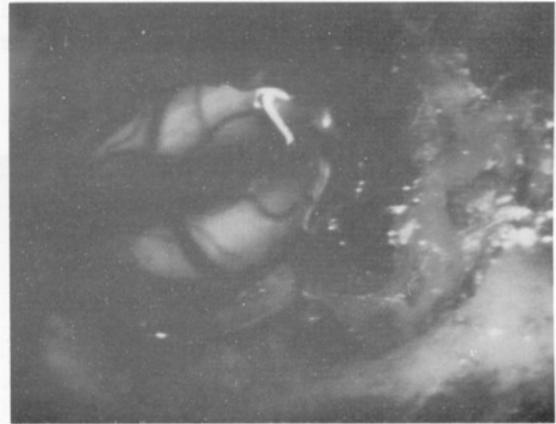Fig 2 : c) 15 minutes after clot+Nicardipine.

Fig 3 : b) Microphotographic representation of basilar artery in the clot removal+Nicardipine group.
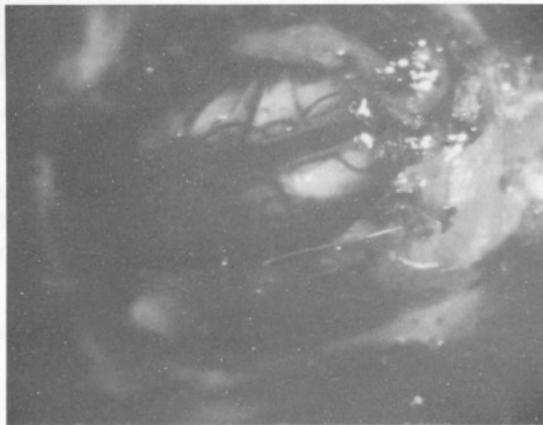

Fig 3 : b) 15 minutes after intracisternal blood clot.

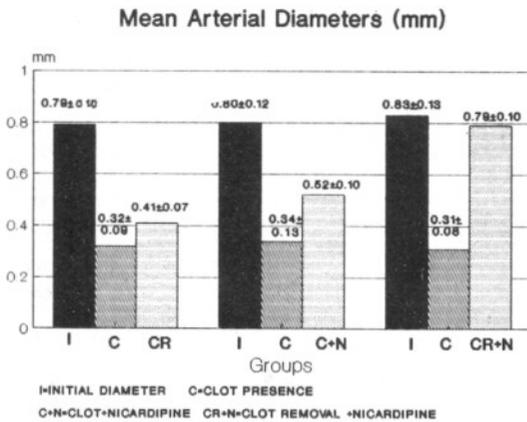Fig 3 : c) 15 minutes after clot removal+Nicardipine.

Mean Arterial Diameters (mm)

mm

- 0.79±0.10
- 0.32±0.09
- 0.41±0.07
- 0.80±0.12
- 0.34±0.13
- 0.52±0.10
- 0.83±0.13
- 0.31±0.08
- 0.79±0.10

Groups

I=INITIAL DIAMETER   C=CLOT PRESENCE
C+N=CLOT+NICARDIPINE   CR+N=CLOT REMOVAL +NICARDIPINE

Fig 4 : Mean arterial diameters.

DISCUSSION

In experimental studies, in general vasospasm is produced with autologous blood application intacisternally. Blood is either put into the cistern surgically (6,9,11,14,16,17,22) or via injection and catheretisation (1,3,4,5,18,26). In this study vasoconstriction was obtained after introduction of autologous blood into the cistern. After clot removal, an increase in the diameter of the basilar artery was determined, but it was not significant. Some authors claimed that clot removal in the first 24-48 hours might prevent chronic vasospasm (16,28,33,42). Inagawa suggested that this improvement in vasospasm was not of a significant degree and in addition, multifactorial effects were required (20,21). On the contrary, Ohta wrote that early clot removal had the risk of severe brain aedema and bleeding due to retraction and was not effective in the prevention of vasospasm (30). Wakayabashi reported that severe vasospasm developed on the side opposite to the operative approach in patients with the pterional approach (44).

After administration of Nicardipine without clot removal, some improvement was observed in vasospasm, but it was not enough. This might be due to dense clot presence in the space. But after SAH, the blood does not always show diffuse distribution in the subarachnoid space, it may be local and dense. Lewis reported that intrathecal Nicardipine administration did not produce any significant benefit (23). It was considered that blood clots on the adventitial surface might cause a disturbance of vessel wall nutrition and the vessel wall penetration of intrathecally administered compound might be impaired in a similar manner.

Extensive influx of $Ca++$ into the smooth mus-

cle cells of the cerebral vessels produce vasoconstriction (8,12). Nicardipine, a $Ca++$ channel blocker, hinders this influx, thus the contractile activity due to $Ca++$ and ischemia might be prevented (3,39). In addition, the direct relaxation effect of nicardipine on smooth muscles and inhibition of platelet aggregation has been shown (15,40). Following nicardipine administration after clot removal, there was significant resolution in vasospasm in this study. Ohman and Heiskanen reported that early surgical intervention in association with $Ca++$ channel blockers had given excellent results(34).

In consclusion, although the etiopathogenesis is still unclear, it seems that vasodilatatory agents will continue to be used for the resolution of vasospasm of the cerebral arteries which tend to respond with vasocostriction, when they meet blood. Our results showed that administration of $Ca++$ channel blockers could produce limited benefit when a clot was present, but administration of $Ca++$ channel blockers following clot removal could resolve the vasospasm. Therefore after SAH, administration of $Ca++$ channel blockers seems to have a more beneficial effect on the resolution of vasospasm when used in association with the removal of as much of the clot as possible.

Table 1 : Physiological parameters

	MABP (mmHg)	PaCO$_2$ (mmHg)	PH
Control	87+4	34.2+0.4	7.38+2.91
Clot removal	85+4	37.0+2.4	7.40+3.21
Clot + Nicardipine	79+2	36.6+1.8	7.39+3.60
Clot removal + Nicardipine	79+5	37.2+1.0	7.40+0.02

(MABP : Mean arterial blood pressure, PaCO$_2$ Arterial partial pressure of carbon dioxide, mean∓SEM)

Tablo 2 : Mean arterial diameters (mean∓SEM) (mm)

	No Intracis-Ternal blood	Intracisternal blood	After procedure
Control	0.82∓017	–	–
	(0.58–1.00)		
Clot removal	0.79∓0.10	0.32∓0.09	0.41∓0.07
	(0.56–1.00)	(0.20–0.45)	(0.35–0.55)
Clot + Nicardipine	0.80∓0.12	0.34∓0.13	0.52∓0.10
	(0.62–0.84)	(0.17–0.50)	(0.34–0.63)
Clot removal + Nicardipine	0.83∓0.132	0.31∓0.07	0.79∓0.10
	(0.63–0.95)	(0.22–0.44)	(0.62–0.91)

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