Therapeutic Trial of Nimodipine in Good Condition SAH Patients With Clipped Aneurysms at the Same Location

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Abstract: Since 1993, we have been using nimodipine in patients admitted to hospital before the fifth day of their initial subarachnoid haemorrhage. During this period, 84 patients were treated surgically and among them, 34 were admitted to our study of nimodipine groups. We have tried to investigate the benefits of nimodipine when added to routine medical therapy against vasospasm, in patients whose preoperative and peroperative conditions were similar, and aneurysms were at the same location. For this purpose, we constructed nimodipine and control groups for anterior communicating artery, internal carotid artery, and middle cerebral artery aneurysms. Patients chosen for the control groups, had been treated before 1993 with the same approach, but without nimodipine. We analysed early postoperative grades, angiographic and computerized tomographic appearances, and outcomes at the third postoperative month. In anterior communicating artery aneurysm patients, there were significant differences between nimodipine and control groups for these parameters, but the outcome ($p<0.05$). Inversely, there was no significant difference in internal carotid and middle cerebral artery aneurysm patients for any of the parameters.

Key words: Cerebral aneurysm, intravascular volume expansion, ischaemia, nimodipine, subarachnoid haemorrhage.

INTRODUCTION

Rebleeding and ischaemic neurological deterioration of delayed onset are the two most frequent deleterious complications in patients who have survived rupture of an intracranial aneurysm (11). Early surgical intervention improves the overall outcome by reducing the rate of rebleeding (5), but a precise definition of the underlying pathophysiology of arterial vasospasm remains elusive, as does an effective treatment (13). A variety of pharmacological agents and therapeutic protocols have been proposed to prevent and treat vasospasm or limit its effects, including modification of surgery timing, with delayed or, inversely, very early surgical procedure; washing of the cerebral cisterns; vascular volume expansion; and intrathecal corticotherapy consisting of dopamine, theophylline-isuprel combination, and papaverine (9). The use of calcium antagonists started in 1983 after the publication of Allen et al: (1), and has became widely used, but later, controversial reports about their efficacy accumulated (9, 12). In these reports, the efficacy of calcium antagonists was investigated according to oral or intravenous applications, or usage in early or delayed surgery, good or poor grade patients, and alone or with other therapeutic protocols.

We have been using nimodipine for two years while still using other measures against vasospasm, and have approached nimodipine therapy from a different point of view. We investigated the benefits of adding nimodipine to routine therapy for vasospasm by comparing groups of patients with aneurysms at the same location, and similar preoperative or perioperative condition.

MATERIALS AND METHODS

We try to operate patients with aneurysms as early as possible. As soon as the subarachnoid haemorrhage diagnosis is confirmed by CT(or lumbar puncture if CT scan is negative), we assume that the patient may have an aneurysm. In addition to routine medical therapy, we maintain central venous pressure above 5 cmH_2O and arterial blood

pressure between 140 and 160 mmHg. Since 1993 we have been using nimodipine in patients admitted to hospital before the sixth day of SAH. The initial dose of nimodipine is 0.25 µg/kg/min by continuous intravenous infusion administered via an infusion pump. After 2 hours, the dose is increased to 0.5µg/kg/min, and continued for 7 to 10 days after the SAH and, if the patient undergoes surgery late, for 2 to 3 days after the operation. After intravenous treatment, oral administration (60 mg every 4 hours) is continued for up to 21 days after the ictus.

Since 1993, 129 patients were diagnosed as subarachnoid haemorrhage, and 84 were treated surgically. Among these, 59 were admitted in the first 5 days of SAH, and treated with nimodipine in addition to other therapy for vasospasm. Thirty-four patients who were included in our study as the nimodipine group, had aneurysm or aneurysms at only one location. Their preoperative neurological grades were I to III according to WFNS grading scale (15). We compared these groups with similar groups of patients who had been treated before 1993. Nimodipine was used in 14 patients with aneurysms of the anterior communicating artery (ACoA), 10 internal carotid artery (ICA) , and 10 middle cerebral artery (MCA). The number of patients in the control groups of these locations was 11, 10, and 13 respectively.

Our aim was to investigate whether nimodipine had any additional benefit when used together with other routine therapeutic approaches. For this purpose, we examined changes between the preoperative and early postoperative grades of patients, incidence of arterial spasms on postoperative angiograms, incidence of cerebral infarcts on postoperative computerized tomographic (CT) scans, and outcomes at 3 months postoperatively in the nimodipine and control groups which had been established according to presence of aneurysms in the same locations. Assessment of observed differences between the groups for these variables was done by chi-square and Fisher's exact test. A p value of 0.05 or less was considered significant.

All patients underwent CT scanning after admission. This was repeated if there was any clinical deterioration and routinely before discharge. Four-vessel cerebral digital subtraction angiography was performed before and seven days after the operation in each case. These angiograms were evaluated for obliteration of the aneurysm, cerebral arterial spasm, and possible inclusion of a major arterial branch in the clip.

The outcomes at 3 months postoperatively, assessed using a three point scale (19), were categorized as; independent (full neurological recovery or minimal to moderate disability); dependent (severe disability or vegetative state), and dead.

RESULTS

Neurological status:

Postoperative grades of all 14 patients who had ACoA aneurysm and had been treated with nimodipine were the same as the preoperative grades, or better. But in the control group, four (36%) of 11 patients had no improvement, or were worse. The difference between the postoperative grades of these groups was statistically significant ($p<0.05$). In MCA aneurysms, only two (20%) of 10 patients who had been treated with nimodipine, had no improvement, or were worse, while five (38%) of the 13 control patients were still in high grades. Among patients with ICA aneurysms, two (20%) of 10 cases from the nimodipine group had no improvement, on the other hand, four (40%) of ten control patients were still in high grades. Although nimodipine groups showed better results, the differences between the nimodipine and control groups for ICA and MCA aneurysms had no statistical significance. But when all three locations were combined, the observed difference between the nimodipine and control groups became significant ($p<0.05$).

Angiographic spasm:

In patients with ACoA aneurysms, angiospasm was observed in only one (7%) nimodipine patient against six (55%) control patients. The difference was significant($P<0.05$). For ICA aneurysm, two (20%) nimodipine and five (50%) control patients, and for MCA aneurysm, two (20%) nimodipine and eight (62%) control patients had postoperative angiospasms. The nimodipine groups seemed to have less angiospasm for ICA and MCA locations. However, this was not proven statistically. Also when all three locations were examined together, the nimodipine groups had significantly lower angiospasm rates than the control groups ($p<0.05$).

Cerebral infarct on CT:

Among ACoA aneurysm patients, one (7%) from the nimodipine and five (45%) from the control group had cerebral infarct on postoperative CT scans. The number of cerebral infarct in the nimodipine and control groups with ICA and MCA aneurysms were 3 (30%) and 7 (70%), and 2 (15%) and 6 (46%),

Table I: Summary of nimodipine trial.

	ACoA		ICA		MCA		TOTAL	
	Nimodipine n=14	Control n=11	Nimodipine n=10	Control n=10	Nimodipine n=10	Control n=13	Nimodipine n=34	Control n=34
sex								
male	9	7	3	5	3	5	15	17
female	5	4	7	5	7	8	19	17
age	50.28+13.52	52.18+10.52	51.30+8.44	49.70+11.25	47.00+12.74	47.76+10.24	49.61+11.78	49.76+10.47
bleeding type								
WL	2	1			1	2	3	3
minor	11	8	10	7	5	6	26	21
moderate		1			3	1	3	2
major	1	1		1		2	1	4
no bleeding				2	1	2	1	4
preop.grade(WFNS)								
I	9	8	7	6	7	11	23	25
II	4	2	2	1	1		7	3
III	1	1	1	3	2	2	4	6
postop.grade(WFNS)	***						***	
I	13	7	7	6	7	8	27	21
II								
III	1	3	3	4	2	5	6	12
IV		1						1
V								
exitus					*1		1	
preoperative spasm								
present	8	7	7	8	9	10	24	25
absent	6	4	3	2	1	3	10	9
postoperative spasm	***						***	
present	13	5	8	5	8	7	29	17
absent	1	6	2	5	2	6	5	17
preoperative CT								
Fisher (4)I	2	3	2	3	1	4	5	10
" II	6	2	2	2	2	5	10	9
" III	5	3	4	4	4	2	13	9
" IV	1	3	2	1	3	2	6	6
infarct				**(1)		**(1)		**(2)
postoperative CT	***						***	
infarct(+)	1	5	3	4	2	6	6	15
infarct(-)	13	6	7	6	8	7	28	19
outcome at 3 months								
independent	13	7	7	6	7	8	27	21
dependent	1	4	3	4	2	5	6	13
dead					1		1	
nimodipine day	2.35+2.23		1.40+2.50		1.50+1.26		1.82+2.08	
surgery day	7.14+3.91	13.54+8.12	4.40+2.83	16.30+11.01	6.9+3.87	13.46+9.89	6.26+3.71	14.32+9.50
temporary clippage	8	3	0	2	2	5	10	10
cisternal papaverine	all	all	all	all	all	all	all	all

ACoA= anterior communicating artery, ICA= internal carotid artery, MCA= middle cerebral artery, WFNS= World Federation of Neurosurgeons.

*=This case died from severe brain oedema due to postoperative infarct.

**=Patients who had cisternal blood and infarct on CT scans.

***= $p<0.05$.

Except mean surgery day, the peoperative clinical conditions for nimodipine and control patients were similar. There were significant differences between nimodipine and control groups for ACoA aneurysms when postoperative grade, postoperative angiospasm, and computerized tomographic infarct findings were analysed. The outcome at 3 months did not differ statistically in any group.

respectively. Although the difference for ACoA aneurysm patients was significant, this was not valid for ICA and MCA aneurysm patients. But when all three locations were analysed together, the nimodipine groups had a statistically lower rate of infarct.

Outcome at 3 months postoperatively:

Among ACoA aneurysm patients, thirteen (93%) from the nimodipine and seven (64%) from the control group, were independent while no patient died in either group. The number of independent patients with ICA aneurysm was seven (70%) in the nimodipine and six (60%) in the control group. Also no patients died. But one(10%) MCA aneurysm case from the nimodipine group died while seven (70%) from the nimodipine and eight (62%) from the control group were independent. Statistical analysis of the outcomes between nimodipine and control groups in each aneurysm location revealed no significant difference($p>0.05$).

DISCUSSION

Early intraoperative removal of blood-contaminated cerebrospinal fluid and clots has been suggested as a way to reduce vasospasm and delayed ischaemia, but this has been disputed (8,16). The most successful approach for the treatment of delayed cerebral ischaemia has been the use of intravascular volume expansion (18). It appears that the efficiency of vascular volume expansion could be explained by the haemodilution phenomenon, and by limitation of the cerebral vascular autoregulation deregulation phenomenon. The obtained results vary between 73 and 85% good and excellent (6, 9, 14, 17). But since the publication of Allen et al, calcium antagonists have gained the favour of neurosurgeons. However, there are many controversial reports about its efficacy. Most clinical and laboratory studies have demonstrated that nimodipine neither reverses nor prevents angiographic arterial narrowing after SAH(1, 7, 10). Instead, it seems to dilate the intraparenchymal arterioles of the brain and promote leptomeningeal circulation (2). Nimodipine may also function by improving red blood cell deformability and exerting an antiplatelet aggregating effect (3). Best results are obtained when intravenous perfusion is used in association with cisternal injection, giving 75% good results. Even if nimodipine seems to have demonstrated its efficiency when used alone, recent studies show that its addition to vascular volume expansion does not improve the outcome (9).

Our study revealed that the early postoperative grades of patients with ACoA aneurysm were better than those of the control group. Also the incidence of postoperative angiographic spasm and cerebral infarct on CT scans was significantly lower in the nimodipine group. This positive effect for patients with ACoA aneurysm may partly be due to the protection of dissected numerous thin perforating branches by nimodipine prophylaxis. But these favourable results were not observed in patients with ICA and MCA aneurysms. Although the nimodipine group with ACoA aneurysm did better in the early postoperative period, there was no significant difference between whole groups of patients for outcomes at 3 months postoperatively. Another important result was the difference between the operative timing of patients. We were able to operate nimodipine patients earlier since the fluctuations in their neurological status were rare. This condition may reduce mortality from rebleeding by giving patients the chance of early surgery.

In summary, according to our study, even if nimodipine seems to have favourable results only for ACoA aneurysm patients, its usage for all aneurysms may be reasonable due to its effect in shortening the preoperative period.

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