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Prevention of Vasospasm in Subarachnoid Haemorrhage. A Controlled Study with Nimodipine

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Summary

A prospective randomized double blind study was conducted in 70 patients suffering from subarachnoid haemorrhage, due to aneurysm rupture, to determine if the use of nimodipine reduces the severity of ischaemic deficits secondary to vasospasm.

At the end of the study, two patients had severe deficit or died in the treated group, while 10 had a bad outcome in the placebo group. Angiographic vasospasm was not significantly different in its frequency or its severity between the two groups. However, the association of extensive and diffuse vasospasm was less frequent in the nimodipine group.

This study confims the effectiveness of Nimodipine in reducing the occurrence of neurological deficit due to vasospasm, even if this action is not observed in all cases.

Keywords: Subarachnoid haemorrhage; aneurysms; cerebral vasospasm; nimodipine.

Introduction

If the role of vasospasm (VSP) in secondary deterioration of patients with rupture of cerebral aneurysm has been extensively documented, its exact mechanism remains unknown even if the presence of blood around the basal vessels appears to be a prerequisite and if there is a direct relation between the importance of bleeding and the appearance of VSP. As shown by Allen in 1976 [1], extracellular calcium may be the primary cause for contraction of large cerebral arteries. Calcium antagonists have been found experimentally to be potent inhibitors of cerebral VSP [2, 11] and to exert a protecting influence in several models of cerebral ischaemia [10, 15]. Among clinical results the multicentre controlled study published by Allen *et al.* [3] has shown a decrease in mortality or morbidity due to arterial spasm: some open studies demonstrate the same [7, 13].

Our purpose was to confirm or refute these preceding results in a prospective randomized double blind study and to observe if the use of nimidipine reduces the severity of ischaemic deficits secondary to VSP.

Patients and Methods

Patients between 15 and 65 years of age suffering from subarachnoid haemorrhage (SAH) within 72 hours secondary to an aneurysm rupture entered the study. They should correspond to grades I, II, or III on the Hunt and Hess classification, and not present an early complication of SAH (hydrocephalus, significant intracerebral haematoma).

Patients with early operations (prior to day 4) or where treatment has not been started in the first 72 hours were excluded as were patients with arterial hypertension or with cardiac, liver of kidney insufficiency. Another reason for exclusion was the observation of VSP at the first diagnostic angiography when the patient was referred to the Department.

Treatment Evaluation

This protocol has been proposed and approved by the local Committee of Ethics.

Each patient was randomized in a double blind manner: one group (N) receiving nimodipine orally (60 mmg every four hours) and the other a placebo (group P) during a 21-day period. No other vasodilatating substances of β-blockers were used; antifibrinolytic therapy (tranexamic acid 6 g/a day was generally administered, even if its contribution in prolongation of VSP has been extensively discussed [16].

A complete neurological examination was performed before the beginning of treatment and at the end. Any deterioration of the patient's condition during the study was considered regardless of its clinical aspect (motor or sensory disturbances, mental deterioration or worsening of conscious level. Any examination which seemed necessary to evaluate the cause of this modification was carried out (CSF sample, CT scanning and/or angiography).

Radiological Evaluation

On CT scan the importance of bleeding was evaluated according to four aspects: localized or diffuse SAH, cisternal clots, intraventricular blood. CT scan was repeated during the study to distinguish

between the different causes of deterioration (rebleeding, hydrocephalus, haematoma.)

Angiography was performed on day 1 of the patient's admission. A secondary angiogram was made at day 6 before operation, or after the appearance of any neurological deficit.

In evaluating VSP on angiography, three points were considered; frequency, intensity (considered as moderate if arterial diameter was reduced by less than 50%—or severe if the diminution of calibre was greater than 50%), and extension: the VSP was considered as localized if the reduction of vessels calibre concerned only one or two sites, and diffuse if three or more arterial sites showed such a reduction. Diameter of arteries were measured at their narrowest point on internal carotid, middle cerebral, anterior cerebral, pericallosal and basilar arteries.

At the end of treatment, patients were classified according to the Glasgow outcome scale: good results (groups I and II), severe (groups III and IV) or deceased.

Results

Among 170 cases of SAH, 81 satisfied the entry criteria. In reviewing this series, 11 patients were excluded secondarily due to imperfect correlation with the initial criteria (3 cases with significant haematomas, 3 with immediatly VSP, 2 with early surgery and 3 where SAH was not related to a ruptured aneurysm).

The results were thus analized in 70 cases (31 receiving Nimodipine—group N; 39 receiving placebo—group P). Among the 11 cases with secondary exclusion, 8 were of the first group (nimodipine) and 3 of the second (placebo).

1. Comparability of Treatment Groups

Both groups were comparable with regard to age, sex, weight and height (Tab. 1). Other factors such as the date of inclusion (Table 2), clinical grade at first examination (Table 3) site of aneurysm (Table 4) and time of surgery (Table 5) were also similar.

The presence of blood in the basal subarachnoid space was equally distributed in the two groups (Table 6).

Table 1. *Demographic Data*

	Group N	Group P
N	31	39
Age (years)	44.3 ± 13.2	45.6 ± 12.8
Sex	14 M, 17 F	16 M, 23 F
Weight (kg)	64.6 ± 11.6	66.5 ± 14.2
Height (cm)	162 ± 8	163 ± 8

Table 2. *Time of Inclusion in the Study/*SAH

	Group N	Group P	Total
< 24 h	22 (71%)	30 (77%)	52 (74%)
< 48 h	7 (23%)	6 (15%)	13 (19%)
< 72 h	2 (6%)	3 (8%)	5 (7%)
N	31	39	

Table 3. *Hunt and Hess Grade at Time of Inclusion*

	Group N	Group P	Total
I	6 (19%)	3 (8%)	9 (13%)
II	21 (68%)	28 (72%)	49 (70%)
III	4 (13%)	8 (20%)	12 (17%)

Table 4. *Site of Aneurysms*

	Group N	Group P
Anterior communicating A.	14 (45.1%)	17 (43.6%)
Internal carotid A.	8 (25.8%)	10 (25.6%)
MCA	5 (16.1%)	8 (20.5%)
Others	4 (12.9%)	4 (10.2%)
N	31	39

Table 5. *Time of Surgery (Aneurysm Clipping)*

	Group N	Group P
Operated between day 4 and 10	12	13
Operated after day 10	10	13
Not operated	9	13
N	31	39

Table 6. *Extent of Bleeding on Initial CT Scan*

	Group N	Group P
Local	1	0
Diffuse	23 (74%)	30 (77%)
Cisterns	18 (58%)	27 (69%)
Intra-ventricular	11 (35%)	8 (20%)

2. Patients with Deficit

Neurological deficit was observed in 29 cases of group P (74.4%) and in 18 cases of group N (58.1%); this difference is not statistically significant.

Deficit was directly related to VSP in 11 cases of group P (28.2%) and in 4 cases of group N (12.9%). In 3 of group N and 6 cases of group P (15.4%) VSP was associated with other complications (infection, hydrocephalus, thromboembolism in group N, and 3 rebleedings, 2 thromboembolisms and one hydrocephalus in group P).

Patients with neurological deficit but without VSP were observed in 11 cases of group N (35.5%) and 12 of group P (30.8%).

3. Angiographic Vasospasm

It was observed in 14 cases in group N (52%) and in 25 in group P (+ 3 post-operative) (72%). This difference even if noticeable, is not statistically significant.

Severity of VSP inside each group was equally distributed with 23% of moderate and 29% of severe in group N, while in group P 36% of moderate and 33% of severe spasm were noted.

The distribution of extension of VSP (Table 7) revealed a lower percentage of diffuse VSP in group N (36%) compared to group P (60%); however, this difference is not statistically significant ($p < 0{,}20$).

If one compares the patients with severe and diffuse VSP to other groups (Table 8), the percentage of patients in group N is 21%, and in group P 44%. As above, this differences is not statistically significant ($p < 0.20$), probably due to the small number of patients in each group.

4. Results at the End of the Study

When considering patients where deficit was directly related to VSP, 10 among the 39 of group P were considered as having severe results. Only 2 among 31 of group N had the same results. (Table 9).

Nimodipine has a significant effect ($p < 0.05$) in the prognosis of ischaemic deficit due to VSP. The difference is even more significant if patients where VSP was associated with other complications were also taken into account (3 patients of group N had severe result compared with 13 in group P).

5. Tolerance

No side effect has been noted during treatment. Biological functions have been tested regularly and there is no difference between the two groups. No modification of blood pressure has been observed during the study.

Table 7. *Extension of Radiological Vasospasm*

	Group N	Group P
Localized	9	10
Diffuse	5	15
	36%	60%

Table 8. *Distribution of Intensity and Extension of Radiological Vasospasm*

		Group N	Group P
Localized	moderate	5	7
	severe	4	3
Diffuse	moderate	2	4
	severe	3	11
		21%*	44%*
Total		14	25

* Not statistically significant.

Table 9. *Mortality and Morbidity Due to Spasm.* Results at end of treatment (day 21)

Neurological deficit due to		N (31)	P (39)
Spasm associated to other causes	good	2	3
	severe	0	0
	death	1	3
Spasm alone	good	2	1
	severe	0	6
		2*	10*
	death	2 (6,4%)	4 (25.6%)

Severe: groups 3, 4 Glasgow outcome scale

* $p < 0.05$

Discussion

Our study suggests that nimodipine may be efficient against VSP post SAH by diminishing its frequency (but the difference between our two groups has not been statistically significant), and by reducing the

severity of ischaemic deficit. Two patients in the group treated had severe deficit or died while 10 patients had a bad outcome in the placebo group. The difference is even more evident if one adds the cases where bad results were related not to VSP alone, but to VSP associated with other causes.

These results are similar to those of Allen *et al.*[3]. In their series, 8 out of 60 patients either died or had severe deficit at the end of the day 21 treatment period in the placebo group, while 1 of the 56 patients given nimodipine fell into the severe outcome category.

Some non-prospective, non-randomized studies seem to corroborate these conclusions. Ljunggren[12, 13] has compared two series of aneurysms with early operations, one without nimodipine (137 cases) and the second with local and intravenous administration. Neurological deficit due to VSP occurs in 13% of the patients of the first series and in only 3% in the second.

In a study by Auer[7], 65 patients with ruptured aneurysms were operated upon within 48 to 72 hours after SAH and were treated with intra- and post-operative nimodipine. Transient symptoms of ischaemia were noted in two patients and irreversible neurological deficit occurred in two other patients.

Nimodipine, if reducing the frequency of ischaemic deficits due to VSP, did not completely prevent the occurrence of such deficits in our series (6% of bad outcome) as in the one by Allen[11]. As suggested by these authors, the doses used in the preliminary studies may not have been sufficient to achieve the maximum effect.

In our series, the dose was approximately three times higher than that of Allen *et al.* Based on our experience, it would be appear that 360 mmg daily is necessary to ensure a permanent efficient plasma level. However, higher doses did not significantly modify our results as compared to those of Allen.

One may conclude that alternative means of administration would produce bettwe results. Auer[5] has insisted on the bettwer outcome observed with a combination of topical intravenous administration; the increased effectiveness, according to Auer, could be due to an immediate high concentration of the drug locally and to higher plasma levels of nimodipine (2 to 3 times higher).

Nimodipine did not modify significantly the frequency of finding radiological VSP nor its intensity on angiography performed at the end of the first week in our series. No other clinical studies have dealt with the effect on calibre of large arteries as seen by angiography.

In the experimental work of Espinosa *et al.*[8] radiological vasospasm is quite as frequent in a treated group as in a placebo one. The average in diminution of the calibre of large vessels is not significantly different in those two groups. Nosko[14] *et al.* drew the same conclusions even if the doses of nimodipine were increased (12 ml/kg every 8 hours).

The reduced frequency of extensive and severe VSP, even if not statistically significant in our series, nevertheless is noteworthy; the same observation has been made in the work of Espinosa *et al.*[8] where VSP controlateral to the clot side was markedly reduced, as if calcium inhibitors were able to control the occurrence of VSP only when CSF concentration of vasoactive substances around the vessels was not too high. The possibility of nimodipine finally acting to reduce extensive and severe VSP remains however questionnable.

The prevention of ischaemic deficits despite radiological VSP, suggests the probability of a peripheral vascular action: this has been supported by the experimental work of Auer *et al.*[4] and by a clinical study where dilatation of the small resistance (pial arteries) to infusion of nimodipine has been observed during EC-IC by-pass[6]. The same author has noted a cross correlation between vessel size and percentage of dilatation during topical administration. Improvement in pial circulation may be a mechanism for the prevention of focal ischaemia.

In conclusion, this study confirms the effectiveness of nimodipine in reducing the occurrence of neurological deficit due to VSP, even if this action is not observed in all cases. Due to the imperfection of oral administration (low bioavailability) difficulty of a constant plasma level, limitation in comatous patient, a further study using intravenous administration may be useful, especially in evaluating curative action on established VSP.

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