Effect of nicardipine, a calcium antagonist in therapy of patients with acute ischemic stroke*

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We studied the effect of nicardipine, a calcium antagonist, on neurologic deficit and mortality in 50 patients with acute ischemic stroke. For prophylaxis, all patients were given aspirin (300 mg/day) and 25 of these patients also received nicardipine (30-60 mg/day). Neurologic status of the patients were assessed with a modified Mathew scale on days 1,7,14,21 and 28 of treatment. Both groups showed a significant improvement on these consecutive assessments. However, there was not a significant difference between the Mathew sum scores of the two groups. 5 patients from nicardipine group and 1 patient from control group died during the study period. There was no significant difference between the two groups in mortality, either. [Turk J Med Res 1993; 11(6): 289-294]

Key Words Nicardipine, Stroke

In acute cerebral ischemia, blocking the calcium influx into the neurons and thus preventing the neuronal death due to the failure of energy dependent membrane pumps and increasing the cerebral blood flow (CBF) are two main strategies to protect the "ischemic penumbra" from irreversible damage (1-4).

In the experimental studies, calcium antagonists are shown both to limit the accumulation of calcium in neurons and to increase the CBF by relaxation of vascular smooth muscle (5-11).

A calcium antagonist, nimodipine from the "1,4 dihydropiridine" group has been the subject of many experimental and human studies, and has been reported to have a positive effect on neurological outcome in cerebral ischemia (12-16). However, human studies on the efficacy of "nicardipine", another calcium antagonist from the same group, are very limited. Rosenbaum et al have reported favourable outcome with nicardipine in their patients whereas a control group was not included in this study (17). In our study, the effect of nicardipine on functional improvement and mortality was investigasted in patients with cerebral ischemia and the results were compared with those of a control group.

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MATERIALS AND METHODS

50 consecutive patients admitted to the Bakırköy State Hospital for Psychiatric and Neurological diseases. First Neurologic Clinic, within 48 hours after the onset of symptoms of cerebral stroke, that had a confirmed finding of an infarction area either on their initial or follow up CT's were included in this study, whereas patients with lacunar infacts, hemorrhages and transient ischemic attacks were excluded. Besides, patients with cerebral ischemia that had uncontrolled diabetes, recent myocardial infarction, malignant and diseases, hepatic and renal insufficiency were also not included.

25 patients in the study group received nicardipine 30-60 mg/dy (in 3 equally divided doses) and aspirin 300 mg/day, while the 25 patients in the control group received only aspirin 300 mg/day. The patients were randomly assigned in either group.

No calcium antagonists other than nicardipine was used and no patient in the control group used nicardipine or any other calcium antagonist. Antihypertensives, antibiotics and cardiotonics were used as needed. All patients received also physiotherapy.

Table 1. Modified Mathew Scale

A. Mentation	
Level of conciousness	
Fully conscious	8
Lethargic	6
Obtunded	4
Stuporous	2
Comatose	0
Orientation	
Fully oriented time, space and person	6
Oriented x 2	4
Oriented x 1	2
Disoriented	0
B. Speech	
Normal	23
Dysarthria	
Mild	21
Severe	18
Sensory aphasia understands one-step commands	15
understands two-step commands	12
Motor aphasia	10
Mixed aphasia	5
Speechless	0
C. Cranial Nerves	
Homonymous Hemianopia	
Intact	3
Mild	2
Moderate	1
Severe	0
Conjugate deviation of eyes	
Intact	3
Mild	2
Moderate	1
Severe	0
Facial weakness	
Intact	3
Mild	
Moderate	1
Severe	0
D. Motor Power*	
Normal strength	5
Contracts against resistance	4
Elevates against gravity	3
Gravity eliminated	2
Flicker	1
No movement	
E. Disability-status scale	
Normal	28
Mild impairment	21
Moderate impairment	17
Moderately severe imp.	12
Severe impairment	7
Death	0
F. Reflexes	
Normal	3
Asymetric or pathologic	2
Clonus	1
No reflexes elicited	0
G. Sensation	
Normal	3
Mild sensory abnormality	2
Severe sensory abnormality	1
No response to pain	0

* Each limb was assessed separately.

Neurologic outcome of the patients were assessed with a modified Mathew scale (Table 1) (18) on days 1,7,14,21 and 28 of treatment.

The analysis of parametric data (i.e. the sum scores of Mathew scale, and age) was performed with use of a t-test. Non-parametric data analysis was made with a chi-square test.

RESULTS

Demographic data of the patients including the risk factors are shown in Table 2. The two groups were comparable in sex distribution (chi2:0.739) Risk factors such as diabetes mellitus, ischemic heart disease, rheumatic heart disease, hypertension, heart deficiency, cigarette and alcohol use were also comparable (p>0,05), while the mean age of the study group (66.52±8.14) was found to be significantly higher than the mean age of the control group (59.52±11.4) (p:0.016).

Follow-up of the patients in the treatment group with Mathew scale on days 7,14,21 and 28 revealed a significant improvement in the neurological status of the patients (p:0.003, p<0.01, p:0.012 and p<0.001 respectively).

Similarly, the Mathew sum scores recorded on the same days increased significantly in the control group, (p 0.001 for each examination) However, the comparison of the initial and follow-up Mathew sum

Table 2. Demographic and historical data of the patients

	Nicardipine	Control
Number of patients	25	25
Sex		
Female	13	9
Male	12	16
Age (meaniSD)	66.52±8.14	59.52±11.4
Risk factors		
Hypertension	15	8
Diabetes	2	
Ischemic heart disease	3	2
Rheumatic heart disease	—	1
Cardiac deficiency	5	2
Smoking	8	10
Alcohol	—	2

Table 3. Mathew scores of the control and treatment group

	Nicardipine	Control	P
Initial	57.4±19.2	59.6±20.2	0.689
Day 7	64.3+19.1	65.5±20.3	0.848
Day 14	70.8+20.5	71.7±20.4	0.889
Day 21	72.7±25.0	76.0+20.4	0.632
Day 28	80.7±19.9	78.0±19.9	0.672

Table 4. Causes of death in nicardipine and control groups

	Sex	Age	Cause of death	Initial Mathew score	Day of death
Nicardipine					
Patient 1	F	79	Heart deficiency	43	22
Patient 2	M	50	Myocardial inf.	37	12
Patient 3	M	73	Progression	55	25
Patient 4	F	67	Progression	39	8
Patient 5	M	64	Heart deficiency	58	22
Control					
Patient 6	F	67	Pneumonia	54	16

scores revealed no significant difference between the two groups. (p:0.689, p:0.848, p. 0.889, p:0.632, p. 0.672 respectively) (Table 3) (Figure 1).

6 patients died, 1 patient had myocardial infarction and 3 of the 5 patients externated on day 21 and invited for the last assessment did not come and thus quit the study. So the results of 40 patients that completed the 28 days treatment period were taken into consideration.

5 of the 6 patients that died during the study were from the nicardipine group. The causes of death are shown in Table 4. Two of these Six patients had died from the progression of neurologic deficit. Four of these deaths were due to the cardiac problems. The mortality rates were not significantly different between the two groups, (chi^2: 3.48, p:0.6190) While the patients who died hat lower Mathew scores than the ones who survived, the difference was again negligible (p:0.14).

In the study group, no adverse effects that would cause discontinuation of treatment was encountered. However, normotensive subjects tended to be hypoten-

Table 5. Systolic and diastolic blood pressures of the patients

	Day 1	Day 7	Day 28
Systolic BP (mmHg)			
Nicardipine	154±29.4	128.3+21.5	138.8±19
Control	134±21	126.3±20.2	123.5±21.9
Diastolic BP (mmHg)			
Nicardipine	85.6±16.5	75.7+12	76.5±13.2
Control	81.6±13.4	77.1 ±14	75.7±13.8

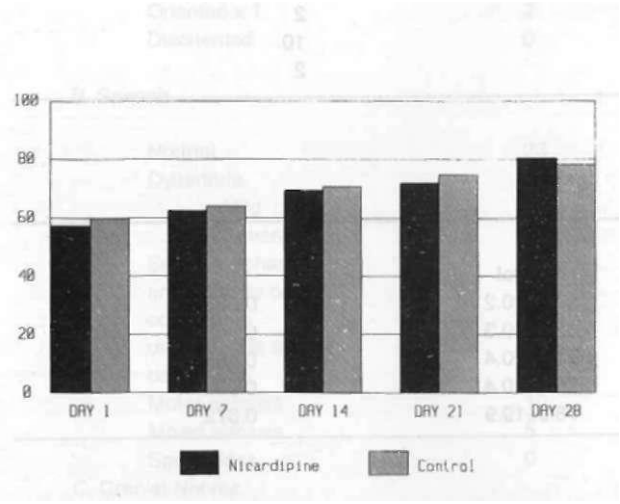

Figure 1. Mathew scale sums of the patients.

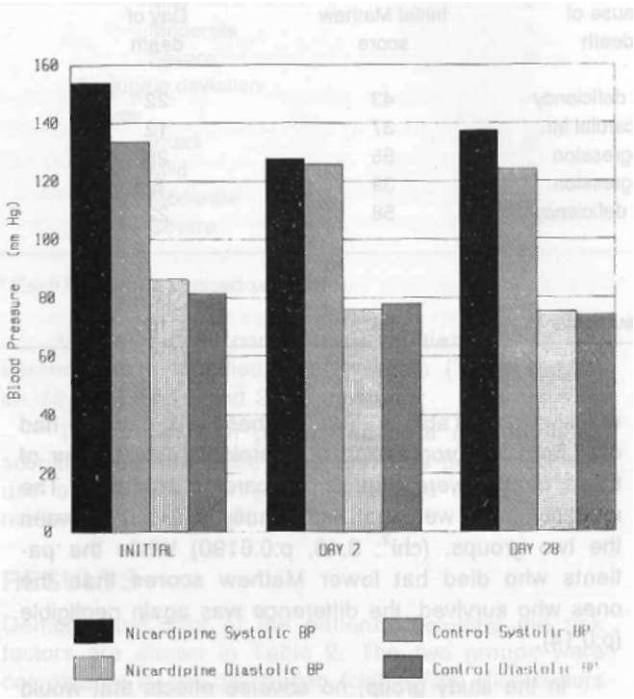

Figure 2. Blood pressure values of the patients

sive with nicardipine, so these patients received doses less than 650 mg/day. Similarly, systolic blood pressure of the hypertensive patients decreased significantly on days 7($p<0.001$) and 28 ($p:0.02$). Diastolic pressures also decreased significantly on the same days ($p: 0.001$ $p:0.012$ respectively). There was also a decrease in the systolic and diastolic blood pressures of the control patients, but the difference was not statistically significant ($p>0.01$). (Table 1) (Figure 2).

DISCUSSION

The theraupetic effects of various calcium antagonists on the cerebral ischemia has been the subject of many experimental and clinical studies. Some of the animal experiments have failed to show a positive effect of calcium antagonists in increasing CBF and improving the neurological outcome (19-24). On the other hand, a calcium antagonist, nimodipine, from the "1,4 dihydropiridine group" has been reported to reduce the ischemic volume in the rats treated before or after the ischemia in two distinct studies (10,28). Nicardipine, another calcium antagonist from the same group has also been reported to be effective when used before ischemia (6,8,11,25-27) or both (5,9).

Gelmers et al have reported significant improvement of neurologic disability and reduced mortality with nimodipine in two different clinical studies (12,13). Pad et al have reported similar results (25). Pozilli et al have measured the CBF of 7 ischemic stroke patients with SPECT and Xenon 133 inhalation before and 30 minutes after nimodipine infusion. They have found an increase in CBF in ischemic penumbra, while there was no change in the center of the lesion and intact brain tissue (16). Hakim et al have reported some increase in CBF of ischemic zone in their study with PET. However the clinical outcome was not affected (16). Heiss et al have reported no change in the ischemic zone whereas the metabolic activity increased in the normal brain tissue (14).

Patients operated for extracranial anastomosis were given nicardipine with local injections into the cerebral vessels were dilated and cerebral p02 had increased (30). In hypocapnia, on the other hand, nicar-

dipine did not change the vascular reactivity significantly (31). In a study, where the efficacy of the nicardipine treatment was assessed with SEP, it was shown to reduce the neuronal function in the ischemic region (32).

Rosenbaum et al have reported favorable outcome in their patient with nicardipine infusion for 72 hours and oral use for 30 days (30 mg tid) (27). However, the lack of a control group in this study makes it impossible to prove the superiority of nicardipine to the standard or placebo treatment.

In our previous study with nicardipine, we compared the neurological outcome of 25 patients treated with aspirin. There was no significant difference between the two groups (33). In this study, patients in the treatment group received both aspirin and nicardipine, while patients in the control group received again only aspirin. Both groups showed a significant improvement, but there was no significant difference between the two groups.

Due to the risk of hypotension we encountered in our patients, nicardipine was administered at lower doses (30-60 mg/day), than that suggested as optimal dosage (i.e. 60 mg/day). Rosenbaum et al have also reported hypotension in some of their patients (17).

Patients in the nicardipine group were significantly older than the control group, which arouse the question of the effect of old age on the outcome. However, in our previous study where the two groups were comparable in all demographic features including age, nicardipine was not found to be superior to our standard profilactic treatment (33).

5 patients from the nicardipine and 1 from the control group died during our study. The common characteristics of these patients were initially low Mathew scores and the presence of cardiovascular risk factors. Gelmers has reported more significant improvement in patients with low Mathew scores (13) while we observed the opposite in our patients.

In conclusion, with the lower doses we had to use because of the risk of hypotension, we found no difference between the two groups in favor of nicardipine. Also, the lack of a control group in a previous study with positive results puts forth the necessity of making further investigations before accepting nicardipine as a promising agent in the treatment of ischemic stroke patients.

Akut tıkayıcı inmeli hastaların tedavisinde bir kalsiyum antagonisti olan nicardipine'in etkinliği

Akut tıkayıcı inme geçiren 50 hastada bir kalsiyum antagonisti olan nicardipine'in nörolojik işlev kayıpları ve mortaliteye etkisini araştırdık. Tüm hastalara 300 mg/gün aspirin verilirken, hastaların 25'ine oral olarak 30-60 mg/gün arasında değişen dozlarda dicardipine verildi. Hastaların nörolojik durumları başlangıç, 7,14,21 ve 28. günlerde Mathew ölçeği ile değerlendirildi. Her iki grupta başlangıca göre 7,14,21 ve 28. günlerde anlamlı bir düzelme bulundu. Ancak İki grubun başlangıç, 7,14,21 ve 28. gündeki Mathew ölçek skorları arasında anlamlı bir fark yoktu. Çalışma sırasında nicardipine grubundan 5, kontrol grubundan 1 hasta kaydedildi. İki grubun mortalitesi arasında da anlamlı bir fark yoktu. Çalışma sırasında nicardipine grubundan 5, kontrol grubundan 1 hasta kaydedildi. İki grubun mortalitesi crasında da anlamlı bir fark yoktu. (X^2: 3.48 p:0.619) [Turk J Med Res 1993; 11(6):289-294]

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