

LACUNAR STROKE - ANTIPLATELET AND ANTICOAGULANT THERAPY FOR SECONDARY PREVENTION

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Abstract. Aim. To assess the therapeutic strategy for secondary prevention in lacunar stroke, according to the underlying mechanism of the cerebral infarct and to determine the recurrence rate of ischemic stroke in patients with lacunar infarct. Lacunar stroke is a small cerebral infarct in the territory of a single perforator artery. The mechanisms that underlie lacunar infarct are various: small vessel disease, atherothrombotic, cardiac and artery-to-artery embolism. **Material and methods.** The study was performed in 1083 patients with lacunar stroke admitted in Ist Clinic of Neurology, "Saint Trinity" Hospital, Iași, during 1.01.1999 - 30.12.2004. The most probable underlying mechanism for the lacunar stroke has been established for each case. A certain therapeutic strategy has been applied for secondary prevention. **Results and discussion.** 163 patients with hypertension have a lacunar stroke due to small vessel disease and the other 489 hypertensive patients had an atherothrombotic lacunar stroke. 219 patients had a probable cardioembolic lacunar stroke. In 94 patients the lacunar stroke was probable due to an artery - to - artery embolism. Aspirin 250 mg was given immediately in 1029 patients and continued for 14 days before changing the patient to a maintenance dose of 75 mg daily for secondary prevention. Clopidogrel 75 mg/day was the option in 54 patients. Anticoagulant therapy was used for selected cases of cardioembolic lacunar stroke. 59 patients (5.5%) had a recurrent stroke. **Conclusions.** The drugs used for acute treatment and for secondary prevention in lacunar stroke must be similar to that used for any other types of ischemic stroke. A high proportion of patients have a recurrent lacunar stroke.

Key words: lacunar stroke, anticoagulants, antiplatelet agents, secondary prevention

Rezumat. Obiectiv. Evaluarea strategiei terapeutice de prevenție secundară în infarctul lacunar, în corelație cu mecanismul de producere al acestuia și determinarea ratei de recurență a infarctului cerebral la pacienții cu infarct lacunar. Ictusul lacunar este un infarct cerebral de dimensiuni mici care survine în teritoriul unei arteriole perforante. Mecanismele care stau la baza producerii infarctelor lacunare sunt variate: boala vaselor mici, aterotrombotic, cardioembolic și embolismul arterio-arterial. **Material și metodă.** Studiul s-a efectuat un lot de 1083 pacienți cu infarcte lacunare, internați în Clinica I Neurologie, Spital „Sf. Treime” Iași, în perioada 1.01.1999 - 30.12.2004. Pentru fiecare caz a fost stabilit cel mai probabil mecanism de producere a infarctului lacunar. În concordanță cu acesta, a fost stabilită o anumită terapie de prevenție secundară a ischemiei cerebrale. **Rezultate și discuții.** 163 pacienți cu hipertensiune arterială au avut infarct lacunar datorat bolii vaselor mici, iar alți 489 pacienți cu hipertensiune arterială au prezentat un infarct lacunar aterotrombotic. 219 pacienți au fost diagnosticați cu un infarct lacunar probabil cardioembolic. La 94 pacienți infarctul lacunar s-a datorat cel mai probabil unei embolii arterio-arteriale. La 1029 pacienți a fost administrat tratament cu aspirină în doză de 250mg/zi în perioada acută și continuat timp de 14 zile, urmat de o doză de menținere de 75 mg/zi pentru prevenția secundară. La 54 pacienți a fost administrat clopidogrel 75mg/zi. Tratamentul anticoagulant a fost administrat la cazurile

selectate de infarct lacunar cardioembolic. La 59 pacienți (5,5%) s-a înregistrat recurența infarctului cerebral. **Concluzii.** Terapia utilizată pentru tratamentul acut și pentru prevenția secundară în infarctul lacunar trebuie să fie similară celei folosite în alte tipuri de ischemie cerebrală. La o proporție importantă de pacienți se înregistrează o recurență a infarctului lacunar.

Cuvinte cheie: infarct lacunar, anticoagulante, antiagregante, prevenție secundară

INTRODUCTION

Lacunar stroke is a cerebral infarct that occurs in the territory of a single perforator artery. The mechanism that underlies lacunar infarct is presumed to be the small vessel disease (1, 2). The nature of this microangiopathy includes lipohyalinosis secondary to the effects of hypertension, micro-atheroma of the perforator artery (1, 2) and, less common, emboli from heart or large vessels (3). Lacunar infarcts are more frequent in patients with chronic hypertension, diabetes, hyperlipidemia, or smoking, disease considered as vascular risk factors. A lacunar stroke may present as pure motor hemiparesis, sensorimotor stroke, pure sensory loss, dysarthria-clumsy hand syndrome, or ataxic-hemiparesis.

Many lacunar strokes may be clinically silent or have other clinical presentations.

The prognosis for recovery with lacunar stroke is generally better than with other types of stroke, but the risk for a recurrent stroke remains. For these reasons secondary prevention strategies of the disease from progressing to a completed stroke or to prevent another stroke (recurrence) is needed and beneficial. (5).

Current opinions favor using antiplatelet therapy or conservative management rather than thrombolytic therapy for lacunar infarct (6). It needs to be emphasized that there are two phases

in prevention: first phase is focused on prevention of acute recurrent stroke and the second is designed for long term secondary prevention.

For cerebrovascular patients alone, antiplatelet therapy reduced risk of secondary stroke, myocardial infarction and vascular death by 22%. In the International Stroke Trial, 24% of patients had lacunar stroke and have been treated with either aspirin or heparin. There was no evidence to support any change in the likelihood of being dead or dependent at 6 months, for both antiplatelet and anticoagulant therapy. A meta-analysis of two large studies has shown that aspirin statistically significantly reduced the risk of having a recurrent stroke within 14-28 days. Risk reduction was 7 ‰ (4). Effects of early aspirin were beneficial on “death without further stroke” (4 ‰ risk reduction) and on “death or dependency” respectively (12 ‰ risk reduction). In high risk patients, aspirin reduces the risk in nonfatal stroke by 31%.

Although, a wide range of doses are mentioned for aspirin in clinical trials (between 75-1300 mg), the complications of aspirin increase with higher doses. Low doses of aspirin, between 50-325 mg a day are thus recommended (7). The Antiplatelet Trialists’ meta-analysis found no conclusive evidence that any other antiplatelet regimen was significantly more effective than aspirin (8).

LACUNAR STROKE - ANTIPLATELET AND ANTICOAGULANT THERAPY

Anticoagulant therapy was evaluated in the Chinese Acute Stroke Trial, which failed to find specific evidence to support the use of this therapy in lacunar infarct. However, heparin can be considered for patient with lacunar stroke and fluctuating deficit. Low-molecular-weight heparin can be used in patients who are at low risk for embolic disease and are awaiting carotid or cardiac ultrasound. For patients with atrial fibrillation and specific risk factors, warfarin should be administered (international normalized ratio – INR – in the 2 to 3 range), unless there is a specific contraindication for that medication (9). Even the risk of hemorrhagic transformation or edema in patients with lacunar stroke is extremely low, anticoagulant therapy is not supposed to be given routinely in lacunar infarct (4).

Apart from risk factor modification, long term secondary prevention implies the use of antiplatelet therapy. Aspirin remains the most efficacious treatment in secondary prevention. Ticlopidine, which inhibits ADP dependent fibrinogen binding, was shown to have a significant protective effect in patients with recent thrombo-embolic stroke with a relative risk reduction of 21% in stroke, myocardial infarction and vascular death (8). The side effects of ticlopidine are serious and it has a modest increase in efficacy over aspirin. Therefore is generally not considered a first line antiplatelet agent for stroke prevention but may be useful in patients who cannot tolerate aspirin. The recommended dose is 250 mg po bid.

The use of Clopidogrel, an antiplatelet agent similar to ticlopidine in mechanism of action *versus* Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial has shown a relative risk reduction of 8.7% within stroke, myocardial infarction and vascular death. Dipyridamole impairs platelet function by inhibiting phosphodiesterase. The combination of dipyridamole plus aspirin has an outcome of a 37% relative risk reduction within stroke compared to placebo (10). Compared with aspirin alone, the combination therapy is leads to a 23% relative risk reduction in stroke. The second European Stroke Prevention Study (ESPS-2) randomized 6602 patients with a recent transient ischemic attack or ischemic stroke. Dipyridamole and aspirin mono-therapy had an independent and significant effect in preventing the recurrence of stroke with relative risk reductions of 16% and 18% respectively (8).

This study is aimed to assess the therapeutic strategy for secondary prevention in lacunar stroke, according to the underlying mechanism of the cerebral infarct and another study goal was to determine the recurrence rate of ischemic stroke in patients with lacunar infarct.

SUBJECTS AND METHODS

This study is part of a larger trial, aimed to assess various features in lacunar stroke: epidemiological, pathophysiological, clinical, radiological, evolutive and therapeutical aspects. The study was conducted in the 1st Clinic of Neurology, “Saint Trinity” Hospital,

Iași city, during 1.01.1999 - 30.12.2004. The group consisted of 1083 patients with lacunar stroke. For each patient has been established the most probable underlying mechanism for the lacunar stroke. This was done taking into account the risk factors profile and the laboratory, cardiological, neurovascular and imaging tests results. Depending on the cause and mechanism established for each case, a certain therapeutic strategy has been applied. The next step was to choose an efficacious therapy for the secondary prevention of ischaemic stroke. Antiplatelet or anticoagulant agents were the treatment options.

Another study goal was to determine the recurrence rate of ischemic stroke in patients with lacunar infarct. The recurrence was defined by a brutal installation of a new neurological deficit, occurring after a period of neurological stabilization or amelioration for at least 24 hours, which was not due to mass effect, edema or haemorrhagic transformation of initial stroke.

RESULTS AND DISCUSSION

Among the 1083 patients with lacunar stroke, 652 had hypertension (60%). In 163 cases hypertension was the only risk factor for stroke (25%). In 489 patients (75%) hypertension was associated with other vascular risk factors (one or more) as follows:

- ✓ diabetes mellitus in 150 cases (30.6%);
- ✓ obesity in 61 cases (12.5%);
- ✓ alcohol abuse in 38 patients (7.8%);
- ✓ carotid artery disease in 286 cases (58.5%).

In the subgroup of patients with hypertension as the only risk factor (163 cases), small-vessel disease has been considered the underlying mechanism for the lacunar stroke. In the 489 cases in which hypertension were associated with other risk factors, it was presumed that the atherothrombotic arterial disease has been responsible for the lacunar stroke (fig.1).

The patients with acute lacunar stroke and small-vessel disease or atherothrombotic arterial disease were given aspirin 250 mg within the first 48 hours of ischaemic event, and daily for the next 2-4 weeks. Aspirin was continued thereafter in a dose of 75 mg daily for secondary prevention. This treatment was not suitable for 54 patients with duodenal ulcer or allergic to aspirin. Those patients were given clopidogrel in a dose of 75 mg daily.

Among patients 219 (20%) had an embolic cardiac disease as the only vascular risk factor: 110 patients had chronic nonvalvular atrial fibrillation, other cardiac arrhythmias in 67 cases, mitral valve disease in 9 patients; 15 patients had aortic stenosis and in 2 cases had aortic insufficiency; 16 patients had dilatative cardiomyopathy (fig.1). Embolism from the heart as a cause of lacunar stroke was considered in these patients. The brutal onset of the neurological symptoms in relationship with the sudden occlusion of the perforating artery also suggested this mechanism. Multiple lacunar infarcts are detected in 30% patients with cardiac arrhythmias, thus being an argument for the cardioembolic mechanism (3).

LACUNAR STROKE - ANTIPLATELET AND ANTICOAGULANT THERAPY

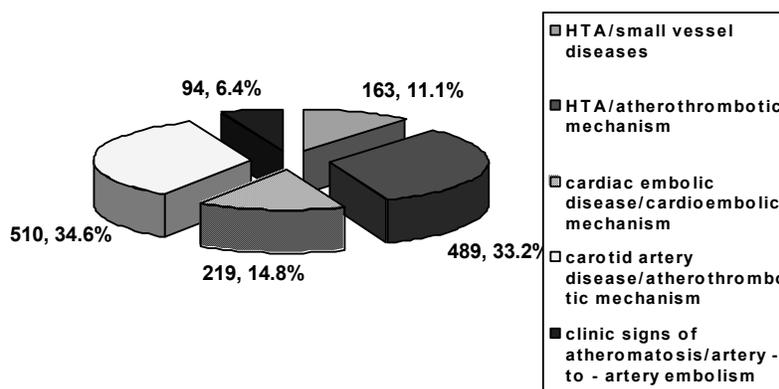


Fig. 1 Risk factors and mechanisms in lacunar stroke

For this subgroup of 219 patients with lacunar stroke of presumed cardioembolic origin, the aspirin was considered for the first 0-14 days. Anticoagulant agents were not used in the acute phase because immediate systemic anticoagulants increase the rate of symptomatic intracranial haemorrhage. Low-molecular-weight heparins were used in 41 patients to reduce the risk for deep vein thrombosis and symptomatic pulmonary embolism after stroke. 88 patients were switched to oral anticoagulant therapy with acenocumarol after the first 3-14 days. This decision depends on the assessment of the risk of re-embolisation in each case. The dose of acenocumarol ranged between 1- 4 mg daily.

Carotid artery disease was diagnosed in 510 patients (47%), including 18 cases with carotid artery stenosis. In 96 cases carotid artery disease was the only risk factor (fig.1). It was associated with one or more other factors in 414 cases as follows:

- ✓ hypertension and other factors in 181 cases (43.7%),
- ✓ hypertension in 105 patients (25.4%),
- ✓ diabetes mellitus in 10 cases (2.4%),
- ✓ diabetes and other factors in 60 cases (14.5%),
- ✓ alcohol abuse in 36 patients (8.7%),
- ✓ obesity in 43 cases (10.4%).

In the cases with stenotic or non-stenotic carotid artery plaques, an artery-to-artery embolic mechanism was considered. A similar mechanism was taken into account for 9 patients with vertebral bruits and lacunar stroke in vertebrobasilar territory.

There was another group of 94 patients (9%) without hypertension, without cardiac or arterial embolic sources, but with clinical signs of atheromatosis (fig.1). Isolated risk factors or associated with the other ones were: diabetes mellitus, obesity, cigarette smoking and hyperlipidaemia. The

mechanisms by which these factors, in different association, cause a lacunar stroke are uncertain, but are probably multifactorial (increased platelet aggregability, reduced fibrinolytic activity, increased fibrinogen concentration), leading to an atherothrombotic mechanism for the lacunar stroke in

these cases. It seems reasonable to conclude that aspirin is effective in secondary prevention in all these patients too (tabel 1). Control of risk factors should be added to antiplatelet or anticoagulant therapy in secondary prevention, an important issue being the management of blood pressure (11).

Table 1. Lacunar stroke - Antiplatelet and anticoagulant therapy for secondary prevention

	Drugs	patients number/ 0 - 14 days	patients number/ over 14 days
Antiplatelet therapy	Aspirin	1029 (95.1%)	941 (86.9%)
	Clopidogrel	54 (4.9%)	54 (4.9%)
Anticoagulant therapy	Oral anticoagulants	-	88 (8.2%)
	Low molecular heparins	41 (39.9)	-

It is known that the seven day risk of stroke is between 8-12% (12). We found that a recurrent stroke occurred in 36 cases (16 %) among the 219 patients with cardiac sources of embolism and in 23 (14%) among 163 hypertensive patients. The recurrent stroke occurred in the next 3 years after the index stroke. The patient who had suffered a recurrent stroke under therapy with aspirin, were switched to clopidogrel. This treatment strategy was settled in accordance to evidence-based guidelines for drug selection; clopidogrel is commonly used as a drug of second choice once a patient has suffered a cerebrovascular event under therapy with aspirin.

Even in literature it is mentioned that lacunar infarction may have the lowest recurrence rate (7), most of our

patients with recurrent stroke (41 cases, 70%) had another lacunar stroke and the rest suffered a territorial infarct. Long term data suggest that up to 25% of patients with lacunar infarcts have a second stroke within 5 years (2). A far higher risk of subsequent stroke than has conventionally been appreciated is now associated with lacunar stroke (12), therefore it is considered a risk factor for a new ischemic stroke. This is especially true for patients with non-small-vessel disease lacunar stroke (13).

CONCLUSIONS

For each treatment option chosen, there is no tendency for the patients with lacunar infarct to get on worse than other types of ischemic stroke.

As long as the antiplatelet or anticoagulant therapy efficiency is similar to that obtained in other types

LACUNAR STROKE - ANTIPLATELET AND ANTICOAGULANT THERAPY

of ischemic stroke, there are no reasons to consider lacunar stroke as a particular group regarding the therapeutic strategies. Therefore the drugs used for acute treatment and for secondary prevention must be similar to that used for any other types of ischemic stroke.

In this study, a high proportion of patients have a recurrent lacunar stroke, therefore the prevention of the lacunar stroke may be considered less than an ideal one.

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