Lyubertsy mortality study of patients
after cerebral stroke or transient ischemic attack (LIS-2): design and evaluation of drug therapy

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Aim

Research of social, demographic and anamnestic characteristics of patients that have survived cerebral stroke as well as the medical treatment received by the patients before the reference stroke in the hospital and at discharge within the framework of the stroke register entitled as LIS-2 (Lubertsy study of mortality in patients who have survived stroke).

Material and methods

All the patients (637 people) admitted to the Lyubertsy District Hospital № 2 due to stroke from January 2009 to December 2010 were enrolled into the study.

Results

36% were men and 64% were women with mean age of 70.99±9.6 years old. 554 (87.0%) patients had history of hypertension and 155 (24.3%) a history of atrial fibrillation. 147 (23.1%) patients had previous stroke. Hospital mortality was 21.8% (139 patients died with mean age of 72.7±9.6 years old). At discharge, 374 (75%) patients were prescribed ACE inhibitors, 421 (85%) antiplatelet agents, 4 (1%) warfarin. Statin treatment was recommended to 3 (1%) patients.

Conclusion

We revealed low frequency of prescription of drugs with proven effects on prognosis in patients with risk factors before the reference stroke and in patients discharged from the hospital after stroke.

Key words

Stroke, risk factors prevalence, medical treatment, register

Cerebral stroke is the leading cause of mortality in a majority of developed countries [1]. Patients who survive an acute period of stroke are at high risk of recurrent strokes and have a poor life prognosis [2,3]. However, evidence-based data clearly testify that some concrete medical preparations can significantly improve this prognosis [4].

Cerebral stroke risk factors in general coincide with other cardiovascular disease risk factors, firstly with those of coronary artery disease (CAD). Stroke pathogenesis, especially of its most prevalent type – ischemic stroke (cerebral infarction) due to athero-thrombosis, is similar to that one of myocardial infarction (MI) [5,6].

This apparently determines similarity of approaches to the primary and secondary stroke and CAD prevention. It is not surprising that the principal drug groups that have demonstrated their effectiveness in secondary stroke prevention to a great extent coincide with medications used for the secondary CAD prevention. First of all these drugs are antiplatelet, antihypertensive and hypolipidemic agents.

Different clinical guidelines present the basic principles for primary and secondary stroke prevention; among them the guidelines promulgated conjointly by the American Heart Association and American Stroke Association are of special interest [7,8]. It is well known that real clinical practice does not always follow modern clinical guidelines. For example, the large-scale international epidemiological study PURE (Prospective Urban and Rural Epidemiological) study revealed that a majority of patients surviving stroke do not receive therapy that could really extend their life [9]. Respectively, life prognosis of patients in conditions of real clinical practice can significantly differ from the one registered in large-scale controlled trials.

All these impose a necessity of evaluation of real stroke patients' care situation, determination of their life prognosis in conditions of such treatment as well as main factors affecting it. Development of a register, providing evaluation of received treatment quality and patients survival rate during more or less long time period, is known to be the best way of overcoming this problem.

There were a number of cerebral stroke registers established in our country, however, almost all of them were organized in accordance with a similar protocol and were aimed at evaluation of stroke morbidity, its risk factors and in-hospital mortality [10–14]. Efforts to estimate long-term outcomes of a treatment were non-systemized and did not meet the requirements of modern research in survival rate evaluation [13]. Estimation of risk factors influencing mortality rate was not performed within a framework of the above mentioned registers.

The main objective of our cerebral stroke register, called LIS-2 (study of mortality among patients survived cerebral stroke in Lyubertsy district), was the assessment of actual therapy received by the patients and its influence on long-term disease outcomes. This article presents the design of the study, characteristics of the patients enrolled into it, and the treatment prescribed before the reference stroke during hospitalization and after discharge.

Materials and methods

The LIS-2 study is a register of patients admitted to the Lyubertsy District Hospital № 2 (LDH № 2) for cerebral stroke or transient ischemic attack (TIA) in 2009-2011.

All the consecutive patients admitted to the LDH № 2 for stroke (ischemic or hemorrhagic) or TIA from 01.01.2009 to 31.12.2011 were enrolled into the register. Those in whom diagnosis of stroke or TIA at admission was not confirmed were not included.

Stroke was diagnosed on the grounds of typical clinical features and specific neurological signs. Such methods of the brain visualization as computer tomography (CT) and magnetic resonance imaging (MRI) were carried out in singular cases in 2009–2010 due to technical capability of the hospital. The patients were examined in accordance with the current health economic standards of medical care. A stroke, a patient was admitted for, was regarded as the reference stroke. Data received at case history analysis concerning patient's history and status at hospitalization, treatment tactics and medications prescribed at discharge from hospital were entered onto a special standardized chart and then in an electronic database.

Prospective part of the study designated for discharged patients consists of several stages. At the first stage telephone contact with a patient or his relatives is obtained. In cases of lethal outcome after discharge from hospital, the cause of death is determined as precisely as possible. At the second stage patients are invited for the control examination, laboratory assays (blood count, lipid profile analysis, electrocardiogram (ECG)) and completion of questionnaires. If a patient can not attend a doctor by himself, a general practitioner visits him at home, registers ECG and lipid profile indices by a rapid test method using the CardioCheck analyzer; all received data are

filled in the standardized chart and the electronic database.

This article presents analyzed data from medical records of the patients admitted to hospital from 01.01.2009 to 31.12.2010.

Results

A total of 637 patients [230 (36.0%) men and 407 (64.0%) women] were admitted to the LDH № 2 for stroke or TIA from 01.01.2009 to 31.12.2010. Ischemic stroke was diagnosed in 558 (87.6%) patients, TIA in 55 (8.6%) and hemorrhagic stroke in 24 (3.8%) patients.

Mean age was 71.0±9.6 years old, youngest age was 25 and oldest 99 years (Figure 1). It is important to note that primarily patients above 60 years old were hospitalized due to stroke in 2009-2010. 567 (89.0%) patients were retirees and 207 (32.5%) were disabled.

We analyzed history of cardiovascular disease (CVD) and their risk factors in our patients (Table 1). According to medical records data 84 (13.2%) patients were smoking; 70 (11.0%) abused alcohol; and 63 (9.9%) were previously diagnosed with hyperlipidemia, with the total cholesterol level during hospitalization higher than 4,5 mmol/L in 329 (52.9%) patients. 120 (18.8%) patients had obesity; 142 (22.3%) were overweight; the weight of 100 (15.7%) patients was normal; and, in 275 (43%) cases, anthropometric indices were not completely indicated. 554 (87%) patients had a history of arterial hypertension; 155 (24.3%) a history of atrial fibrillation (AF), with 117 patients (75.4% of all the AF patients) having permanent AF, 27 (17.4%) paroxysmal AF, 2 (1.3%) persistent

AF, and 9 (5.8%) paroxysm of unknown duration. 80 (12.6%) had previous MI; 4 (0.5%) patients had undergone percutaneous coronary intervention with stent placement, with a similar number of patients having had coronary artery bypass surgery. 137 (21.5%) patients had diabetes mellitus type 2. The reference stroke was a recurrent one in 147 (23.1%) patients. 13 (2.0%) patients had a history of TIA.

In-hospital mortality was 21.8% [n=139; mean age 72.7±9.6 years old; 43 (30.9%) men and 96 (69.1%) women], 498 (78.2%) patients were discharged for out-patient follow-up.

129 (92.8%) patients of all the deceased were retired persons, 47 (33.8%) were disabled. 109 (78.4%) deceased persons had hypertension, 50 (36.0%) had AF, 16 (11.5%) had previous MI, and 32 (23.0%) had diabetes (Table 2). The reference stroke was the recurrent one in 35 (25.2%) deceased patients.

Estimation of medical treatment received by the patients before the reference stroke, in hospital and therapy prescribed at discharge

Estimation of the treatment before the reference stroke revealed that 265 (41.6%) patients received antihypertensive therapy as follows: angiotensin-converting-enzyme (ACE) inhibitors in 195 (74%) patients, β-blockers in 68 (25.7%), and calcium channel blockers in 53 (8.3%) patients. 43 (6.8%) patients were prescribed antiplatelet agents, 4 (0.6%) patients (or 2.6% of 155 patients with AF history) warfarin. 6 (0.9%) patients used anti-cholesterol drugs.

The most frequently prescribed drugs in hospital were: cinnarizine in 444 (69.7%) patients, gamma-
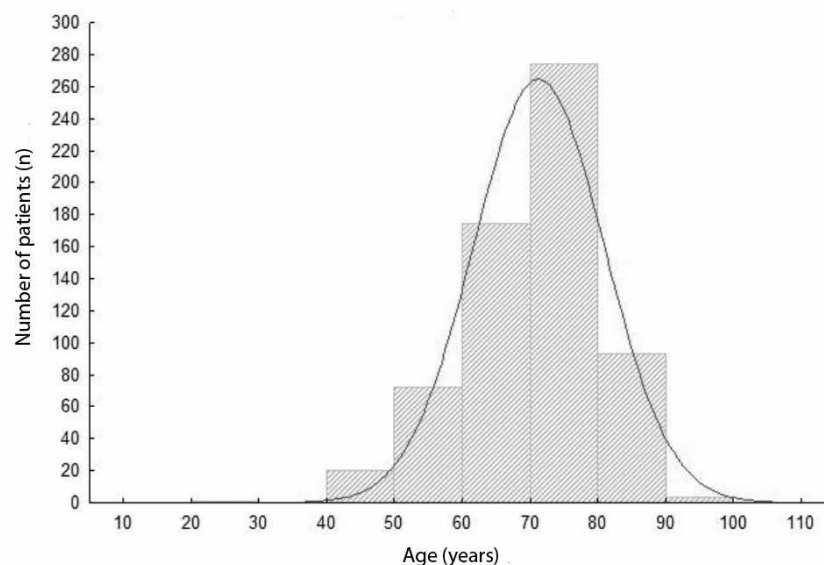

Figure 1. **Age distribution of patients enrolled in the LIS-2 register (n=637)**

aminobutyric acid (Aminalon) in 438 (68.8%), ACE inhibitors in 432 (67.8%), acetyl salicylic acid in 392 (61.5%), and papaverine in 347 (54.5%) patients. 4 (0.6%) patients received warfarin. Statins were not administrated at all.

We also analysed recommendations for discharged patients (n=498). ACE inhibitors were recommended to 374 (75.1%) patients and calcium channel blockers as an antihypertensive drug to 10 (2.0%) patients. The most frequently prescribed diuretic was indapamide (n=125; 25.1%). Antiplatelet agents (acetyl salicylic acid) were prescribed to 421 (84.5%) patients, warfarin to 4 (1%) patients. 3 (0.6%) patients were recommended statins. Such medications as vinpocetine and piracetam were prescribed more often (n=346; 69.6% and n=300; 60.2%, respectively).

Discussion

The LIS-2 register is a limited register, key factor of which is the diagnosis of stroke or TIA in patients admitted to the neurology unit of a municipal hospital. This register has a number of limitations due to difficulties in diagnosis verification, because such methods as CT or MRI were used in singular cases; besides, patients with stroke or TIA predominantly admitted to the hospital were of elderly age (above 60 years old). Due to difficulties in diagnosis verification, and taking into account similar approach to primary and secondary stroke and TIA prevention, we included in the register both patients with diagnosis of TIA and stroke.

A lot of publications and discussions are devoted to the problem of implementation of evidence-based recommendations in clinical practice [15–17]. Primarily the problem is of current interest in terms of secondary stroke prevention, what has been demonstrated in a number of trials including the above mentioned international epidemiological PURE study [9].

The reasons for this are various and include clinical inertness, presence of controversial data, incompatibility of clinical guidelines made for different nosologies [17–18]. Perhaps, in case of stroke, one such reason is absence of evident clinical effect of drugs that proved their positive effect on a patients' life prognosis.

Numerous stroke registers organized in Russia almost did not concern the problem of prescribing medications with proven effect. The first results of the LIS-2 study have demonstrated rather low frequency of the prescription of the main drug groups with proven positive influence on patients' life prognosis. It should be noted that the frequency of using different groups of drugs varied significantly: so, while antiplatelet agents and ACE inhibitors / angiotensin receptor blockers were recommended to the majority of patients at their discharge from hospital (84.5 and 75.1%, respectively), such medicines as statins and anticoagulants were in fact prescribed almost to no one. It should be mentioned that according to re-

Table 1. **Clinical and anamnestic characteristics of the patients** (n=637)

Clinical and anamnestic risk factors	Yes	No	Not known
Smoking, n (%) / Курение, n (%)	84 (13.2)	496 (77.9)	57 (8.9)
Alcohol abuse, n (%)	70 (11.0)	510 (80.1)	57 (8.9)
Hypertension, n (%)	554 (87.0)	41 (6.4)	42 (6.6)
Diabetes mellitus, n (%)	137 (21.5)	489 (76.8)	11 (1.7)
Atrial fibrillation, n (%)	155 (24.3)	460 (6.3)	22 (3.5)
Previous stroke, n (%)	147 (23.1)	80 (12.6)	78 (12.2)
Previous transient ischemic attack, n (%)	13 (2)	410 (64.4)	214 (33.6)
Previous myocardial infarction, n (%)	80 (12.6%)	499 (78.3%)	58 (9.1%)

Table 2. **Comparative analysis of survived and deceased in-hospital patients**

Parameter	The deceased during hospitalization (n=139)	The discharged (n=498)	P
Mean age, years / Средний возраст, лет	72.7±9.6	70.5±9.6	0.02
Stroke risk factors			
Smoking, n (%)	10 (7.2)	74 (14.9)	0.02
Alcohol abuse, n (%)	12 (8.6)	58 (11.6)	0.32
Hypertension, n (%)	109 (78.4)	445 (89.4)	0.0007
Atrial fibrillation, n (%)	50 (36.0)	105 (21.1)	0.0003
Diabetes mellitus, n (%)	32 (23.0)	105 (21.1)	0.06
History of CVD			
Previous stroke, n (%)	35 (25.2)	112 (22.5)	0.51
Previous myocardial infarction, n (%)	16 (11.5)	64 (12.9)	0.23

cent guidelines, statins are indicated for all patients surviving ischemic stroke and indirect anticoagulants (if not contraindicated) for all patients with AF, who made according to LIS-2 data about 24.3%.

We only estimated drugs prescription in hospital and at discharge according to nothing else but medical documentation data. In the following actual medical treatment of the survived patients is to be assessed with the help of special questionnaires at repeated visits, which will provide significantly more objective estimation of the treatment quality.

There is one more problem of implementation of evidence-based recommendations in clinical practice. It is known that randomized controlled trials (RCT), on which recent clinical guidelines are based, are carried out on accurately selected groups of patients. Such patients not always conform to typical patients with variety of concomitant diseases and often extremely older (these patients are oftentimes excluded from studies). So, it is disputable if drugs that have proven their positive effect in an RCT would similarly act in real practice. Modern registers technically allow estimation of a drug's influence on disease outcomes, as it was demonstrated in the similar by its design LIS study that included patients survived acute MI [19–21]. We hope that the LIS-2 study will also let estimate effect of some drugs on long-term outcomes of the disease.

Conclusion

The register of patients with cerebral stroke was created in Lyubertsy district (Moscow Region). Data from the register show that drug therapy used in secondary prevention of cerebral stroke does not conform well to current clinical guidelines. Monitoring of a disease's long-term outcomes in the register will identify the key factors that determine long-term prognosis for life and in particular the role of drug therapy.

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