CROATIAN SOCIETY FOR NEUROVASCULAR DISORDERS OF CROATIAN MEDICAL ASSOCIATION

CROATIAN STROKE SOCIETY

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RECOMMENDATIONS FOR STROKE MANAGEMENT

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Introduction

Acute stroke is the leading cause of disability in the modern society[1]. In developed countries, stroke is the second cause of death[1], and in Croatia it is the leading cause of death for women[2]. Due to modifications of lifestyle and risk factors, and better stroke management, the incidence of stroke in developed countries has decreased and its mortality has been reduced[3,4]. Nevertheless, the treatment of stroke is far from being satisfactory. Over the past decade, acute stroke has finally been recognized as a medical emergency[4,5]. World Federation of Neurology Research Group on Organization and Delivery of Neurological Services has published recommendations for prevention of cerebrovascular diseases.[6] Also, acute stroke treatment, primary and secondary prevention, and rehabilitation at specialized wards have been proved to be effective[7-11]. In the past year, several recommendations for stroke management were published[12-22]. These are recommendations proposed by the Croatian Society for Neurovascular Disorders of the Croatian Medical Association; University Department of Neurology, Sestre milosrdnice University Hospital, which is the Reference Center for Neurovascular Disorders of the Croatian Ministry of Health; and the Croatian Stroke Society.

We provide an overview of the already accepted therapeutic strategies and an evaluation of the evolving new ones.

Table 1 summarizes definitions of the levels of evidence.

Table 1. Levels of evidence and classes of recommendations

Level I: high level of evidence	Source a: primary endpoint from randomized, double-blind study with sufficient sample size Source b: properly performed meta-analysis of qualitatively outstanding randomized trials
Level II: intermediate level of evidence	Source a: randomized, non-blind studies Source b: small randomized trials Source c: predefined secondary endpoints of large randomized trails
Level III: low level of evidence	Source a: a prospective case series with concurrent or historical control Source b: post hoc analyses of randomized trials
Level IV: undetermined level of evidence	Source a: small case series without control, case reports Source b: general agreement despite the lack of scientific evidence from controlled trials

PART I PRIMARY PREVENTION

Primary prevention is aimed at reducing the risk of stroke in asymptomatic people. Lifestyle and several medical conditions have been identified so far as risk factors for stroke. These include eating and drinking habits, smoking, physical activity, hypertension, diabetes mellitus, elevated cholesterol levels, myocardial infarction, atrial fibrillation, and carotid stenosis.

Lifestyle

A report from the Framingham Study(23) indicates that an increased daily consumption of fruits and vegetables may decrease the risk of stroke, including hemorrhagic stroke. Physical activity is inversely related to the risk of stroke. A prospective cohort study[24] of male participants in the Physician Health Study has revealed that vigorous exercise is associated with a decreased risk of stroke. This association is mediated through beneficial effects on body weight, blood pressure, serum cholesterol and glucose tolerance. Apart from these effects, physical activity has shown no direct influence on stroke incidence.

Cohort studies have isolated cigarette smoking as an independent risk factor for ischemic stroke in both men[25] and women[26]. The risks are directly dependent on the consumption of cigarettes and may be as high as 6-fold compared with non-smokers. In both studies, the subjects who had stopped smoking considerably reduced the risk of stroke, i.e. by 50%[27].

A recent case-control study[27] has suggested that moderate alcohol consumption (up to two drinks of liquor, two cans of beer, or two glasses of wine *per* day) would decrease the risk of ischemic stroke. On the contrary, heavy alcohol consumption is associated with an increased risk of both ischemic and hemorrhagic stroke[27].

Stress reaction enhances platelet aggregation. It also activates the renin-angiotensin system and production of angiotensin II leading to a rise in arterial blood pressure. Stress causes higher incidence of cardiovascular and cerebrovascular disorders[28-30]. However, only scarce data exist on the direct connection of stress and stroke[31-37]. Most of these studies are difficult to compare due to different population, different design and due to difficulties in the definition of stress. However, data from these studies could indicate that stress is especially associated with a higher incidence of hemorrhagic stroke. The risk of stroke in general and of ischemic stroke in oral contraceptive (OC) users in particular increases with higher estrogen content of OCs[38]. Whether low dose OCs carry a risk is still being debated, since the present data indicate no increase in the risk in the USA[39], a slightly increased risk in Europe, and a threefold risk in Africa, Asia and Latin America[40]. Such data may be due to either a high prevalence of hypertension and smoking in the non-USA countries, or to some other unknown factors. In the WHO study conducted in developing countries[41], the risk of cerebral hemorrhage was significantly increased among OC users in general. The risk was proven higher with high-dose OCs. It also significantly increased with age (>35 years) and other associated risk factors such as hypertension and smoking. OC use is also associated with a small increase in the risk of subarachnoidal hemorrhage (SAH). This increase is marginal with low-estrogen preparations but is strongly increased with concomitant hypertension[38].

There are numerous observational studies of postmenopausal hormone replacement therapy (HRT) and stroke risk[42-43]. Unfortunately, due to a selection bias that refers to the fact that women prescribed and taking HRT differ in many known and unknown ways from those who do not use HRT, the results cannot be taken as conclusive.

The use of cocaine, especially alkaloidal forms ("crack"), has been associated with an increased occurrence of cerebrovascular disease[44], both ischemic and hemorrhagic forms.

Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke today, and its treatment substantially reduces the risk of stroke. A meta-analysis of 14 randomized trials has shown that a decrease in diastolic blood pressure by merely 5-6 mm Hg in hypertensive patients equals a 42% reduction in stroke incidence[45].

The Systolic Hypertension in the Elderly Program (SHEP)[46] has revealed that the management of isolated systolic hypertension (greater than 160 mm Hg) in patients older than 60 reduces the total incidence of stroke by 36%, and of ICH alone by 50%[47]. The absolute benefit, estimated for a 5-year period, was 30 events *per* 1000 participants[46]. The optimal blood pressure has not yet been confirmed, but there is some concern that a vigorous reduction in blood pressure might be associated with an increased cardiovascular morbidity.

Recently, a reduction in stroke risk was observed in a randomized placebo-controlled trial of an angiotensin-converting enzyme (ACE) inhibitor in a group of high-risk patients that included both hypertensive and non-hypertensive individuals[9].

Diabetes mellitus (DM)

Although DM has been recognized as an independent risk factor for ischemic stroke, it has not yet been established whether strict control of blood glucose can be a factor in stroke prevention. In fact, in patients with type 2 DM, intensive sulphonylurea and/or insulin therapy ameliorated microvascular systemic complications, but not macrovascular ones such as stroke[48].

Hypercholesterolemia

Although former trials[49] did not find strong association between serum cholesterol levels and stroke, two large studies[50-51] have demonstrated that statins (pravastatin and simvastatin) can decrease the risk of stroke for patients with coronary heart disease (CHD). The CARE study has revealed a 32% reduction in the relative risk of stroke with pravastatin therapy[52], and a 24% reduction (28% reduction in cerebrovascular events – stroke and TIAs) with simvastatin in the 4S study[53]. A recent meta-analysis including data from the above trials confirmed a total of 31% reduction in all stroke forms, except for those with fatal outcome[54].

Antithrombotic drugs

Numerous studies have proven aspirin efficacy as a secondary prevention agent[8]. Only a few studies have ever

focused on aspirin as a primary prevention device. In the non-blind British male physician study[55], 5139 physicians were randomly allocated to receive or not receive 500 mg of aspirin daily. There was no difference in the incidence of myocardial infarction (MI), but disabling strokes were more common among those allocated to aspirin. The higher incidence of stroke in the aspirin group was probably due to the higher incidence of hemorrhagic stroke. The Physician's Health Study[56] that included 22 071 male physicians receiving either 325 mg of aspirin or placebo every other day in a randomized double blind, placebo controlled study has shown a 44% risk reduction of MI and a non-significant increase in the risk of stroke. In the subgroup with hemorrhagic strokes, aspirin was associated with an increased risk, with a statistical borderline significance.

In the Nurses' Health Study cohort[57], in which the incidence of stroke in women taking aspirin was monitored, the women taking aspirin had a smaller relative risk of MI, but no alteration in the risk of stroke.

Surgery

The Asymptomatic Carotid Atherosclerosis Study (ACAS)[58] reports that patients with an asymptomatic carotid stenosis greater than 60% had a 5-year relative risk reduction of 53% of ipsilateral stroke if carotid endarterectomy (CEA) was performed. However, the absolute risk reduction was small (5.9% strokes in five years), as was the rate of ipsilateral stroke in the medically treated group (11.0% strokes in five years, or 2.3% annually). These results were assessed with a joint perioperative mortality and morbidity rate of 2.3%. Notably, the rate of complications was 2- to 3-fold when carotid endarterectomy was performed as a secondary prevention procedure[59-60].

Recommendations

1. Cigarette smoking should be discouraged (Level II).
2. Heavy use of alcohol should be avoided, whereas moderate consumption should be permitted (Level II).
3. Regular physical activity is recommended (Level II).
4. Increased consumption of fruits and vegetables is recommended (Level III).
5. It is recommended to avoid stress or to learn how to cope with it (Level IV).
6. Avoid high estrogen content of OCs, and avoid OCs in all women older than 35 with concomitant hypertension or smoking habit (Level II).
7. Avoid cocaine (Level IV).
8. Treatment of hypertension is strongly recommended as the most effective means of decreasing morbidity and mortality due to either ischemic or hemorrhagic stroke (Level I). Blood pressure should be kept below 140/85 mm Hg by means of lifestyle modifications and/or pharmacological treatments.
9. Although strict control of glucose levels in DM and high cholesterol levels have not yet been proven to be associated with a decreased risk of stroke in general, it should be encouraged because of the benefits in terms of other diseases (Level III).
10. In coronary patients, statin treatment clearly reduces the risk of stroke (Level II). Statins should be prescribed in patients with CHD and high or moderate cholesterol levels. The benefits of statins probably extend to patients with stroke and high cholesterol levels.
11. There is no scientific support for prescribing aspirin to reduce the risk of stroke in asymptomatic patients (Level I). However, aspirin will reduce the risk of MI in an asymptomatic population.
12. Screening with ultrasound of the brain blood vessels in patients with known risk factors is recommended[61] (Level III).
13. CEA is not recommended for patients with stenosis lesser than 50% (Level I).
14. CEA should be performed in asymptomatic patients with a low surgical risk (<3%) and with life expectancy of at least 5 years (Level II), having stenosis 60%-99% and in centers with joint perioperative complication rate of stroke and death of less than 6% (Level I).

Anticoagulation

Atrial fibrillation (AF)

Atrial fibrillation is a common arrhythmia and an important risk factor for stroke, with established effective therapy for stroke prevention. The annual risk of stroke in unselected patients with nonvalvular atrial fibrillation is 5%, with a wide clinically important variation among subpopulations of AF patients (0.5%-12% *per* year)[20]. Aggregate analysis of several trials[62] shows that oral anticoagulation therapy with vitamin K antagonist, warfarin, reduces the rate of ischemic stroke by 70% compared with untreated patients (AFASAK, SPAF, BAATAF, CAFA, SPINAF). Assessment of the optimal intensity of anticoagulation therapy producing an INR (International Nor-

malized Ratio) between 2.0 and 2.9 reduced the combined incidence rate for both ischemic and hemorrhagic events by 80% when compared with INR below 2.0[63]. When tested with INR above 5.0, the risk of bleeding became unacceptable, whereas no significant reduction in thromboembolism was seen with INR below 2.0. The effect of aspirin was assessed in four separate randomized trials[64]. Aspirin yielded a pooled risk reduction of 21% compared with placebo. In two of these trials, it was proved to be significantly less efficacious than warfarin.

The median age of patients with AF is 75 years. The Framingham Heart Study noted a dramatic increase in stroke risk associated with AF with advancing age, from 1.5% for those aged 50-59 to 23.5% for those aged 80-89[65]. In addition, AF was associated with an OR for death of 1.5 (95% CI 1.2 to 1.8) in men and 1.9 (95% CI 1.5 to 2.2) in women after adjustment for other risk factors. Patients with AF and no other cardiovascular disease aged less than 65 years are at such a low risk that they should not be treated or should be treated with aspirin. Patients over 65 without other risk factors may be considered as being at a moderate risk and therapy could include warfarin or aspirin. The dose of aspirin should be 300 mg a day, because this dosage proved effective in patients with AF.

For patients over 75 years of age, a lower target INR of 2.0 (1.6-2.5) may be more sensible to prevent hemorrhage. However, this lower warfarin level has not been established, and many scientists disregard age and accept a higher INR target of 2.5. Also, there are other patients in whom aspirin might be preferred to warfarin: history of previous hemorrhage, over 80 years of age, unstable anticoagulation control because of poor drug or clinical compliance, history of uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), alcohol abuse and liver disease [66]. In these patients, the risk of hemorrhage may be increased.

Recommendations (Table 2)

1. All patients at a high risk of stroke should be considered for long-term oral anticoagulation therapy (target INR 2.5; range 2.0-3.0) (Level I).
2. Patients aged less than 65 with no cardiovascular disease or patients who are unable to receive anticoagulants should be prescribed aspirin 300 mg *per* day (Level I).
3. Patients over 65 years of age without risk factors could be prescribed either anticoagulants or aspirin 300 mg *per* day (Level III).
4. In patients over 75 years of age, warfarin may be used as an option, with a lower INR (target INR of 2.0; range 1.6-2.5) to decrease the risk of hemorrhage (Level IV).

Table 2. Guidelines for atrial fibrillation management in primary prevention

Age <65 years, no risk factors	Aspirin 300 mg/day
Age <65 years, with risk factors	Warfarin (target INR 2.5; range 2.0-3.0)
Age 65-75 years, no risk factors	Aspirin 300 mg/day or warfarin
Age 65-75 years, with risk factors	Warfarin (target INR 2.5; range 2.0-3.0)
Age >75 years, with or without risk factors	Warfarin (target INR 2.0; range 1.6-2.5)

PART II ORGANIZATION OF STROKE CARE

Stroke as an emergency

Successful stroke care begins with recognizing the stroke as a medical emergency like acute MI. There is a widespread consensus among stroke physicians that the best way to provide early stroke care is to call the emergency medical team (EMT) immediately, and to be transported to an institution where stroke care can be provided at an appropriate level. Despite the high mortality and morbidity rate of stroke, many patients and relatives neither recognize the symptoms of stroke nor realize that seeking treatment is urgent. Various factors are responsible for this delay in patient referral to the hospital, including poor awareness of stroke by both the patient and the family, reluctance to seek emergency medical help, incorrect diagnosis by EMT, and stroke rating as a low emergency by EMTs and family physician. These facts emphasize the need for an ongoing educational program.

The first level of education includes public education[67]. Many patients and their relatives are not aware of the patient having a stroke. Teaching the public to recognize the symptoms and signs of stroke is one of the highest priorities in public medical education, and can be achieved through mass media. The public needs to become aware of two important facts: first, stroke is a treatable condition; and second, there is a legitimate need for stroke victims to be urgently transported to stroke centers.

The second level of education includes physicians. Primary contact with general practitioners may cause delays and prevent the early institution of adequate therapy[66]. Preventive and acute neurological training programs should be included in undergraduate education. For graduate MDs, published guidelines or recommendations (similar to this one) are to be introduced. Evidence need to be actively channelled using multiple strategies such as opinion leadership, academic detailing, computerized reminders, mass media campaigns, or performance feedback such as audits of physician's acquaintance with the problem[67]. Such campaigns would lead to better professional education and motivation of all personnel included in stroke management, from the emergency medicine physicians, nurses, general practitioners, family doctors, neurologists, specialists of internal medicine, and geriatricians to physiotherapists. Medical personnel should be trained to recognize the acute presentations of ischemic stroke, and should be able to cope with the early complications of stroke. Emergency medical teams need to be trained to conduct a focused neurological examination that includes the level of consciousness, presence of focal weakness, presence of seizure activity, and presence of aphasia or other cognitive disturbances. Also, they should be trained to obtain few important facts from the medical history such as exact time of onset, fluctuations of condition, risk factors. They should also be acquainted with the things they should do and should not do in early stroke management. It is particularly important that these professionals understand that they are highly valued and competent partners in providing acute stroke care.

Referral

Stroke patients should be referred to specialized centers such as stroke units[68]. Minimum requirements of such centers include 24-h availability of CT scanning facilities, neurologists or other stroke physicians, presence of other specialized personnel, and adherence to treatment and management guidelines. Stroke centers or stroke units are not stand-alone solutions. They can only work optimally if a well-established referral and rehabilitation network is available. This also includes cooperation with primary care physicians in primary and secondary prevention.

For optimal acute stroke care, it is essential that all stroke patients are immediately referred to the hospital best equipped to provide such care. This is the reason for establishing minimal facilities for centers dealing with stroke. While all stroke patients seem to benefit from stroke unit treatment, certain subgroups of patients will especially benefit in intensive care units[69]. Triage is necessary and recommended by the Stroke Council of the AHA (American Heart Association), American College of Physicians and European *Ad Hoc* Consensus Group.

Stroke units

Stroke care should take place in a stroke unit. A systematic review[7] has shown an 18% reduction in mortality, and a 29% reduction in death occurrence or ADL dependence. A 25% reduction in death occurrence or need for institutional care was noticed in patients treated in a stroke unit compared with those treated on a general medical ward (Level I). In a large randomized Norwegian trail[70] of patient treatments in the acute and subacute condition, mortality was reduced by 46% compared with general ward treatment.

A stroke unit is established as a hospital unit or part of a hospital unit that exclusively or nearly exclusively takes care of stroke patients. The staff and the multidisciplinary approach to the management and care of stroke patients characterize the stroke unit. The core disciplines of such a team are: medicine, nursing, physiotherapy, occupational therapy, speech and language therapy, and social work. The optimal size of a stroke unit in terms of beds has not yet been assessed. Stroke units with as little as six beds have shown effectiveness.

All types of stroke patients benefit from the treatment and rehabilitation in stroke units: males and females, young and elderly, with no difference according to the severity of stroke[68]. Stroke units are available in several categories:

1. The acute stroke unit - is responsible for the admission of acute stroke patients and for the continuance of early treatment for several days but usually less than one week.

2. The combined acute and rehabilitation stroke unit - admitting patients acutely and providing continuing treatment and rehabilitation for several weeks or months if necessary.
3. The rehabilitation stroke unit - admits patients after a delay of one or two weeks and continues treatment and rehabilitation for several weeks or months if necessary.
4. A mobile stroke team - a mobile team offering stroke care and treatment of stroke patients at different wards. Such teams are usually present in hospitals where stroke units are not available.

Of these, only the combined acute and rehabilitation stroke units and the rehabilitation stroke unit have proven effective in terms of reduced mortality and handicap[68-71].

Recommendations

1. Stroke patient should be treated in specialized stroke units (Level I).
2. Stroke needs to be considered a medical emergency that requires public education, a referral and treatment network, and fast management.
3. In case stroke happens, the emergency medical team should be called immediately. Patients should be transported by the emergency medical team as fast as possible to qualified centers.

Management in the emergency room (ER)

It is necessary to simultaneously assess vital and neurological functions and begin with treatment of life-threatening circumstances. The therapeutic window is narrow, making time essential for prognosis. There is no need to emphasize how important it is to ascertain the form of stroke by physical and neurological examination combined with diagnostic tests. This is the reason why a stroke patient should be treated as a medical emergency, even when having mild symptoms[13,72,73]. Early assessment of stroke subtypes based on the physical and neurological evaluation, as well as skilled use and interpretation of diagnostic tests, are essential[74].

Once in the hospital, the problem is not resolved and delay may still occur due to the:
- Lack of neuroimaging facilities.
- Admission policies that require placement of patients on general medical wards.
- Standpoint of low urgent level by hospital staff.
- Lack of treatment possibilities for stroke.
- Lack of a stroke specialist, such as a neurologist or some other trained physician with expertise for treatment of stroke in the emergency room.

To have a standard patient care endorsed, one must have strict protocols of management. Some values should be kept individualized, e.g., blood pressure or blood glucose levels. Above all, the ABC (airway, breathing, circulation) procedure must be used and arterial O_2 saturation evaluated using either pulse oximetry or ABGS. As soon as possible, a venous line should be inserted and samples for CBC, blood chemistry and coagulation factors taken. This task divided between physicians and nurses ought to be followed by a specialist's targeted examination.

Questions to be answered in the early patient evaluation are[75]:
- The existence of a life-threatening condition.
- The interval between onset of symptoms and admission.
- The presence of increased intracranial pressure (ICP).
- Concurrent underlying severe illness.
- What is the prognosis?

Emergency diagnostic tests

Diagnostic tests are needed to differentiate between the different types of acute stroke (ischemic, brain hemorrhage, subarachnoid hemorrhage) or to rule out other brain diseases (brain tumors). They are essential to obtain an impression about the underlying cause of brain ischemia (cardiac or carotid disease, risk factors), to provide a basis for physiological monitoring of the stroke patient, and to identify concurrent diseases or involving complications of stroke that may influence prognosis.

Cranial computed tomography (CT)

Computed tomography is the most important initial diagnostic test for assessment of cerebral hemorrhage and for distinguishing cerebral infarction from other lesions that may produce focal neurological signs (brain tumors, infections or contusions and extradural/subdural hematoma). CT signs of early ischemia can be detected as early as 2 h after stroke onset[76], but they may also develop later. It is sometimes possible to visualize an arterial clot (hyperdensity in the affected artery) or occlusion, which may

identify the underlying cause of the stroke[12]. The detection of early changes such as edema (swelling), hypodensity or blurring of normal structures is possible in about 50%-60% of ischemic stroke patients that are examined in the acute phase[77]. If present, these may indicate that the ischemic injury is more serious. They are also associated with poor outcome and may predict hemorrhagic transformation[76].

Magnetic resonance imaging (MRI)

MRI is more sensitive, but it has not yet reached the level of standard procedure in most centers. Modern MRI techniques such as diffusion and perfusion MRI and magnetic resonance angiography (MRA) require major resources that are currently not available in Croatia.

Cerebrospinal fluid (CSF) analysis

Lumbar puncture and CSF analysis may sometimes be needed in dubious findings of CT scan or in vasculitis. It may differentiate between subarachnoidal hemorrhage and infection, and may be useful in patients with subarachnoidal hemorrhage and negative CT findings[78,79]. It is necessary in centers with no possibility of CT scanning to calculate Allen score, which is 90% accurate in the identification of hemorrhage[80].

Other emergency tests

Electrocardiogram

It should be performed in all stroke patients because of the high incidence of heart condition in stroke patients. Stroke and acute myocardial infarction may occur at the same time. Hemispheric stroke may cause dysrhythmias and heart failures. Frequently, dysrhythmias are the cause of embolic strokes.

Ultrasound studies

Several types of ultrasound equipment may be used in stroke diagnosis. The B mode scan gives information on the morphology of extracranial arteries, while Doppler ultrasound can be used to visualize blood flow. Duplex and color duplex machines combine both facilities. Transcranial Doppler (TCD) ultrasound can be used to investigate the blood flow within the basal intracranial arteries and other vessels that are not accessible to other methods[81,82], and may even enhance drug therapy[83].

In skilled hands, an ultrasound scan may suggest the cause of stroke such as occlusion of the carotid, middle cerebral or vertebrobasilar arteries and intra- or extracranial stenosis, or extracranial artery dissection in some cases[84-88]. It may provide additional information on the cause of stroke (emboli detection[89], or visualization of aneurysm). In SAH, it is inevitable in detection and monitoring of vasospasm[90] and of therapeutic effect[91].

Other ultrasound studies include transthoracic and transesophageal echocardiography to screen for cardiogenic emboli, but these tests are usually not performed in the ER. However, it seems to be useful to have these studies available in the first 24 h after stroke onset.

Laboratory tests

Laboratory tests include CBC and coagulation parameters, electrolyte status, hepatic and renal function check, and basic markers of infarction.

Recommendations

1. Cranial computed tomography (CT) is the most important diagnostic tool in patients with suspected stroke.
2. Early evaluation of physiological parameters, blood chemistry and hematology, and of cardiac function is recommended in the management of acute stroke patients. This also includes ECG, pulse oximetry and chest X-ray.
3. Ultrasound of extra- and intracranial vessels, modern MR techniques, cardiac ultrasound and specific hematologic and serologic tests for rare causes of stroke should be performed early after stroke, but should not delay general or specific treatment.

PART III ACUTE STROKE MANAGEMENT

It can be said that therapy for acute stroke has three pillars. The first group can be addressed as general therapy. It deals with the management of all underlying serious medical conditions that need to be revised immediately. Then, there is specific therapy that is directed against aspects of stroke pathogenesis. It effects either recanalization of the vessel occlusion or neuroprotection that is directed against several mechanisms of neural injury that occurs after brain ischemia. In hemorrhagic stroke, the mechanism of bleeding is to be determined and considered for acute surgical treatment. The third area of stroke treatment deals with complications occurring as sequels of acute stroke. These conditions can be divided into those of the neurologic origin (secondary hemorrhage, space occupying edema, seizures) and those not allied with neurologic condition of the patient (infections, decubitus ulcers, deep vein thrombosis or pulmonary embolism).

Monitoring of vital functions

To monitor vital functions and neurologic condition accurately, frequent checks have to be made. Vital functions of particular interest are: blood pressure, pulse rate, body temperature, blood gases, and blood glucose levels. The objective way to assess the neurologic status is the use of neurological scales such as the NIH-Stroke Scale, Scandinavian Stroke Scale, Glasgow Coma Scale, and others. Additional tests will have to be performed in some patients. In patients with a pre-existing cardiac disease, history of dysrhythmias and unstable blood pressure, on-line ECG monitoring is recommended. To monitor the respiratory action, cardiac electrodes or clinical evaluation can be used. Most of the time, conventional blood pressure monitoring proves adequate, however, when needed automatic inflatable units or mobile 24-h our blood pressure devices should be available. Respiratory status is verified through pulse oximetry or blood gases. Occasionally, central venous pressure *via* central venous catheter will be indispensable in specialized wards. The same catheter can also estimate other information like intravascular volume, cardiac function and compliance with the venous system.

GENERAL STROKE TREATMENT

It is not always neurological illness that is crucial for the prognosis of certain patients, but concurrent underlying medical conditions that are almost always present. It has already been agreed upon "general treatment" as a foundation for early stroke patient management[13,17,22,72]. It includes respiratory and cardiac monitoring, blood pressure control, treatment of elevated intracranial pressure, fluid and metabolic management, metabolic surveillance and fluid administration. Also, there is seizure treatment, deep vein thrombosis and pulmonary embolism prophylaxis, infection control – especially aspiration pneumonia and prevention of decubitus ulcers.

General stroke treatment is equally applied in specialized units as in general hospital wards. Despite this, the prognosis for patients treated in stroke units is better when early therapeutic actions are taken immediately.

Pulmonary function and airway protection

Normal respiratory function with adequate blood oxygenation is required for stroke management, primarily because of preservation of metabolic turnover in the marginal zone of infarction, the so-called penumbra. Still, there are no data obtained from prospective clinical trails to corroborate this assumption. Oxygenation of the blood is improved by the administration of 2-4 l O_2/min *via* a nasal tube.

In patients with seizures following hemispheric or hemorrhagic stroke, a plugged airway may be present. In patients with chronic obstructive airway disease, pulmonary dysfunction may occur during exacerbation. Ventilation may be particularly compromised during sleep.

Early endotracheal intubation is recommended in the event of a pathologic respiratory pattern. Stroke types that may lead to this condition are: extensive vertebrobasilar and hemispheric infarction, large intracranial hemorrhages, and unconscious patient at high risk of aspiration pneumonia. The prognosis of stroke patients undergoing intubation is thus better than usually thought, with a one-year survival rate of almost one-third[92,93]. Before intubation, the general prognosis, coexisting life-threatening medical conditions and patient family consent must be considered and obtained.

Cardiac care

Cardiac arrhythmias may occur secondary to stroke. Significant alterations in the ST segments and T wave on ECG may appear in the acute phase and mimic myocardial ischemia[94]. Cardiac enzymes may be elevated after

stroke[95]. Every stroke patient should have an initial ECG. However, not all cardiac phenomena after cerebral ischemia should be regarded as secondary. The coexistence of myocardial infarction (MI) and stroke is possible, sometimes MI presents in the clinically silent form.

The main goal in stroke management is to obtain an optimal cardiac output while maintaining a high normal BP and normal heart rate. Central venous pressure should be maintained at approximately 8-10 cm H_2O. Central venous pressure monitoring is valuable in the prevention of volume deficiency or overload. The intravascular volume must be kept stable. Dobutamine is an inotropic agent with the advantage of increasing cardiac output without major effect on heart rate or blood pressure. Dopamine is useful in patients with hypotension or renal insufficiency. Increases in cardiac output may enhance cerebral perfusion in the areas with autoregulative capacity breakdown due to cerebral ischemia.

Normal cardiac rhythm should be restored by drugs, cardioversion or pacemaker care in cooperation with specialists of internal medicine or cardiologists.

Blood pressure (BP) management

BP monitoring and treatment are crucial. Many patients with acute infarcts have elevated BP. Cerebral perfusion in patients with advanced carotid stenosis depends on mild hypertension. Blood flow autoregulation may be defective in the areas of evolving infarction, and the flow in the penumbra zone therefore becomes passively dependent on the mean arterial pressure. A drop in BP must therefore be avoided if an adequate cerebral perfusion pressure is to be maintained. A target systolic BP of 180 mm Hg and diastolic BP of 100-105 mm Hg are recommended in patients with prior hypertension. In other cases, mild hypertension is desirable (160-180/90-100 mm Hg). Extremely high BP levels should be treated. Systolic values over 220 mm Hg or diastolic values over 120 mm Hg are indications for early drug treatment (Table 3). The reduction in BP should not be too vigorous. There are only a few other indications for immediate antihypertensive therapy in the first hour after symptom onset. Treatment may be appropriate in the setting of acute myocardial ischemia (although extreme lowering of BP is detrimental in patients with MI, cardiac insufficiency, acute renal failure, or acute hypertensive encephalopathy). Non-ischemic causes of stroke, such as subarachnoid hemorrhage or intracerebral hemorrhage, also are indications for antihypertensive treatment.

The effects of oral nifedipine, still frequently used in Europe and Croatia (due to the lack of span of iv treatments) may be rapid and excessive. Its use is discouraged[20]. Oral captopril (6.25-12.5 mg) or labetalol (10 mg) may be used instead. Intravenous urapidil is being used increasingly in this situation. Sodium nitroprusside is sometimes recommended despite some major side effects, such as reflex tachycardia and coronary artery ischemia[20].

Glucose metabolism

Many stroke patients are diabetics. Diabetes mellitus is sometimes detected only after an ischemic infarction has developed. Both hypoglycemia and hyperglycemia can have unfavorable effects in patients with increased ICP. Serum

Table 3. Antihypertensive treatment in acute ischemic stroke

Systolic BP <220 mm Hg Diastolic BP <120 mm Hg	Do not treat
Systolic BP slightly increased when measured 15 min apart Diastolic BP >120 mm Hg	Nitroglycerin 5 mg IV or 10 mg po Sodium nitroprusside 1-2 mg iv (rarely needed)
Systolic BP <220 mm Hg Diastolic BP 110-120 mm Hg or Both when measured repeatedly	Nifedipine 10 mg sl* Captopril 6.25-12.5 mg po Labetalol 5-20 mg iv** Clonidine 0.15-0.3 mg iv or sc Urapidil 10-50 mg iv followed by 4-8 mg/h iv Dihydralazine 5 mg iv and metoprolol 10 mg iv

*Nifedipine may cause an overly rapid decline of BP
**Avoid in patients with asthma, cardiac failure, severe conduction abnormalities and bradycardia

glucose level should be kept between 7.8 and 10[96]. Therefore, temporary administration of insulin may be necessary. A blood glucose of 10 mmol/l or higher requires immediate insulin titration. Unless the blood glucose is known, no carbohydrate concentrate should be given to a stroke patient. Hypoglycemia may mimic acute ischemic infarction. Hypoglycemia should be directly countered by an infusion of 10%-20% glucose, preferably *via* a central venous line.

Body temperature

Fever negatively affects the neurologic stroke outcome[97,98]. Infection is a risk factor for stroke, and many patients develop an infection after stroke[99]. Fever increases the infarct size, due to enhanced metabolism and greater production of toxic amino acids. Therefore, elevated temperature (>37.5 °C) in stroke patients should be treated although there are no prospective data to support this concept. Antipyretics such as paracetamol and early use of antibiotics are usually recommended in case of apparent bacterial infection.

Fluid and electrolyte management

In hemorrhagic stroke or SAH, serious electrolyte abnormalities are frequent. Contrary, in ischemic stroke they can rarely be found. A balanced fluid and electrolyte status should be kept to avoid plasma volume contraction, raised hematocrit, and impairment in the blood rheologic properties. Electrolytes should be monitored daily and substituted accordingly. Uncontrolled volume replacement may increase cerebral edema, or lead to pulmonary edema and cardiac failure. A venous approach is needed for initial fluid management and blood sampling. If larger volumes of fluids need to be replaced or solutions with high osmolality are used, placement of a central venous catheter is recommended.

Recommendations

1. Neurological status and vital functions should be monitored.
2. Glucose and body temperature should be monitored and corrected, if elevated (Level III).
3. Monitoring and correction of electrolyte disturbances are advised.
4. Secure airways and oxygen to patients with severe acute stroke (Level III).
5. Do not treat hypertension in patients with ischemic stroke, unless they have critically elevated BP levels (Level III).

SPECIFIC TREATMENT IN ISCHEMIC STROKE

Thrombolytic therapy

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA), 0.9 mg/kg body weight given within 3 h after stroke onset to patients with acute ischemic stroke) significantly improves the outcome of stroke[100]. There is evidence that thrombolysis may also work up to 6 h after stroke onset in carefully identified patients[101]. In Europe, doubt about its risk-benefit ratio exists, which is preventing some centers from actively promoting the treatment. Caution is advised before giving intravenous rt-PA to patients with severe stroke (NIH Stroke Scale >22) and extended early infarction signs[102]. In centers where thrombolytic therapy is offered, it should only be given if a physician who has expertise in the diagnosis of stroke has established the diagnosis (Table 4). Secondly, brain CT should be assessed by physicians who have expertise in identifying major early infarct signs, which may represent a contraindication for iv thrombolysis. Thrombolytic therapy should not be given unless the emergency ancillary care and the facilities to handle bleeding complications are readily available.

Table 4. Indications for thrombolytic treatment with rt-PA

1	Ischemic stroke within 180 minutes
2	NIHSS of neurologic deficit
3	CT brain scan without intracranial bleeding
4	Age >18 years

Due to the high risk of major bleeding and possible risk of death, the risks and potential benefits of rt-PA should be discussed with the patients and their families before the treatment is initiated. Recognition of early infarct signs and strict adherence to exclusion criteria (Table 5) are essential.

Intravenous streptokinase has been shown to be associated with an unacceptable risk of hemorrhage and death[103-106]. Its use is strongly discouraged.

Intra-arterial thrombolytic therapy with prourokinase was associated with better outcome[10]. The treatment is

only available in selected centers and requires superselective angiography[107].

Intra-arterial treatment with urokinase or rt-PA showed good results in acute basilar occlusion [107,108]. It is available in selected centers. Due to the small number of basilar occlusions, no randomized trials have been conducted.

Table 5. Contraindications for rt-PA thrombolytic treatment

1	Brain CT signs of intracranial hemorrhage
2	Brain CT or MR signs of acute stroke
3	Small (NIHSS <4) or large (NIHSS >22) neurologic deficit or quick symptom regression
4	Clinical evidence of SAH, but brain CT negative
5	History of intracranial bleeding, arteriovenous malformations, aneurysm or brain tumor
6	Stroke or head trauma within 3 months
7	Systolic BP <185 mm Hg or diastolic BP >110 mm Hg
8	Arterial catheterization at the site that is not compressible or lumbar puncture within a week
9	Operation or major injury within two weeks
10	Gastrointestinal bleeding or urinary tract bleeding within three weeks
11	Platelets >100 000
12	APTV exceeding control values due to heparin treatment within 48 hours
13	Oral anticoagulation treatment, PV >15 or INR >1.7
14	Seizure as initial stroke presentation
15	Glucose levels <2.78 or >22.2 mmol/l
16	Recent myocardial infarction, bacterial endocarditis or pericarditis
17	Pregnancy

Defibrinogenating enzymes

Ancrod, a defibrinogenating enzyme, has been shown to improve outcome after acute ischemic stroke, if given within 3 h after stroke onset and over 5 days[110].

Recommendations for centers offering thrombolysis

1. Intravenous rt-PA (0.9 mg/kg; maximum of 90 mg) with 10% of the dose given as a bolus, followed by an infusion over 60 min, is recommended within 3 h of onset of ischemic stroke (Level I), if indications and contraindications are strictly followed (Tables 4 and 5).
2. The benefit from the use of iv rt-PA for acute ischemic stroke between 3 and 6 h from stroke onset is only present in selected patients (Level I).
3. Thrombolysis with iv rt-PA is not recommended when the time of stroke onset cannot be determined; this includes patients whose strokes are recognized upon awaking.
4. Thrombolysis with iv streptokinase, outside the setting of a clinical investigation, is dangerous and not indicated for the management of patients with ischemic stroke (Level I).
5. Thrombolysis with other iv drugs is not recommended due to insufficient data.
6. Intra-arterial treatment of acute middle cerebral artery M1 occlusion in a 6-h time window using prourokinase results in a significantly improved outcome (Level I).
7. Acute basilar occlusion may be treated with intra-arterial therapy in selected centers (Level IV).
8. Ancrod given in a 3-h time window significantly improves outcome after acute ischemic stroke (Level I).

Platelet inhibitors

Two large randomized, non-blind, intervention studies[118,111] have shown that aspirin given within 48 h after stroke reduces mortality and recurrent stroke minimally, but statistically significantly. Up to now, it is not clear if the positive effect of early aspirin is due to the effect on the infarct itself or to the prevention of recurrent infarction. A recent meta-analysis[112] has shown that the prompt use of aspirin should be routinely considered for all patients with suspected acute ischemic stroke (even when CT scan is not available), mainly to reduce the risk of early recurrence.

Early anticoagulation

Although early heparin treatment has been frequently used in the treatment of acute ischemic stroke, it has not proved overall benefit due to the higher rate of hemorrhagic complications. None of the trials performed over the past years has proved the influence of heparin on stroke outcome or recurrent stroke reduction[113]. Also, low-molecular-weight heparins and heparinoids (LMWHs) were analyzed in a systematic meta-analysis[114]. LMWHs reduce venous thromboem-

bolic events in patients with acute ischemic stroke and increase the risk of extracranial bleeding. A nonsignificant reduction in combined death and disability, and nonsignificant increases in case fatality and symptomatic intracranial hemorrhage were also observed. There is a general agreement that heparins should not be used in the routine management of patients with ischemic stroke. Most investigators agree that heparin is only indicated in selected patients (Table 6). Contraindications for treatment with heparin include large infarcts (>50% MCA territory), uncontrollable arterial hypertension, and advanced microvascular changes in the brain.

Table 6. Indications for heparin treatment after stroke

1	Stroke due to cardioembolism with high risk of reembolization (artificial valves, atrial fibrillation, MI with mural thrombi, left atrial thrombosis)
2	Coagulopathies such as protein C and S deficiency, APC-resistance
3	Symptomatic dissection of extracranial arteries
4	Symptomatic extracranial and intracranial stenosis
5	Symptomatic internal carotid stenosis prior to operation
6	Crescendo TIAs or stroke in progression
7	Sinus venous thrombosis

Hemodilution

There is no proof of hemodilution therapy as clinically beneficial. At the same time, a possibility of excess brain edema exists making the decision difficult[93,115-117].

Neuroprotection

There is no proof that any neuroprotective agent influences stroke outcome[118,119]. There is no recommendation to treat ischemic stroke patients with neuroprotective agents.

Recommendations

1. There is no recommendation for general use of heparin, low molecular heparin or heparinoids after ischemic stroke (Level I).
2. Full dose heparin may be used in selected indications (Table 6) (Level IV).
3. Aspirin (100-300 mg *per* day) may be given after stroke to an unselected population, even without CT scan (Level I).
4. Hemodilution therapy is not recommended in the management of ischemic stroke patients (Level I).
5. Neuroprotective drugs are not recommended in ischemic stroke patients (Level I).

SPECIFIC TREATMENT IN HEMORRHAGIC STROKE

The classic presentation of intracerebral hemorrhage (ICH) is sudden onset of a focal neurologic deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness and elevated blood pressure. The early progression of the neurologic deficit in many patients with ICH is frequently due to the ongoing bleeding and enlargement of the hematoma during the first few hours[120].

Specific treatment is oriented to determination of bleeding mechanisms and the possibility of surgical treatment. Clinicians try to determine the likely cause of the hemorrhage according to its location in the brain as seen on the CT scan, the presence of structural abnormalities as seen in brain imaging, associated medical conditions such as hypertension, and the patient's age. Hemorrhages that originate in the putamen, globus pallidus, thalamus, internal capsule, deep periventricular white matter, pons and cerebellum, particularly in a patient with known hypertension, are often attributed to hypertensive small-vessel disease. Contrary, lobar hemorrhages in the very old subjects are often thought to be due to amyloid angiopathy. These assumptions may be incorrect. A majority of patients with lobar hemorrhage have hypertension. Some vascular malformations may also be the cause of deep lobar hemorrhage. If angiography is to be done, the timing will depend on the clinician's judgment. It is dependent of the clinical condition of the patient and the neurosurgeon's judgment of surgical emergency, if surgery is really needed.

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), if available, have emerged as additional useful tools for detecting structural abnormalities such as malformations and aneurysms[120]. Although MRI may miss small aneurysms and vascular malformations, it is superior to CT and angiography in detecting cavernous malformations. Angiography is still the gold standard in detecting aneurysms.

Recommendations

1. Angiography should be considered for all patients without a clear cause of hemorrhage who are surgical candidates, particularly young, normotensive patients who are clinically stable (Level IV).
2. Angiography is not required for older hypertensive patients who have a hemorrhage in the basal ganglia, thalamus, cerebellum or brain stem, and in whom CT findings do not suggest a structural lesion. Most elderly patients with deep hemorrhage die or have severe morbidity related to the hemorrhage and are not candidates for angiography (Level IV).
3. Timing of cerebral angiography depends on the patient's clinical condition and the neurosurgeon's judgment concerning surgical emergency, if surgery is really needed.
4. MRI and MRA are helpful and may obviate the need for contrast cerebral angiography in selected patients. They should also be considered when searching for cavernous malformations in normotensive patients presenting with lobar hemorrhages and normal angiographic results, who are surgical candidates (Level IV).

Medical management

Four small randomized trials of medical therapy for ICH have been conducted[116,121,123,126]: steroid *versus* placebo treatment[122,123)], hemodilution *versus* best medical therapy[116], and glycerol *versus* placebo[123]. None of the 4 studies has shown any significant benefit for the three therapies. In the study testing steroids[121], patients who were treated with steroids were more likely to develop infections than those treated with placebo.

Recommendation

1. Corticosteroids are not recommended due to possible side effects and increased development of secondary infections (Level II)

Vasospasm after SAH

Cerebral vasospasm is a delayed narrowing of large capacity arteries at the base of the brain after SAH, often associated with radiographic or cerebral blood flow evidence of diminished perfusion in the distal territory of the affected artery. Angiographic vasospasm has a typical temporal course, with onset 3 to 5 days after the hemorrhage; maximal vasospasm is expected at 5 to 14 days, and gradual resolution over 2 to 4 weeks[124]. In about one half of cases, vasospasm is manifested by the occurrence of a delayed neurologic ischemic deficit, which may resolve or progress to cerebral infarction (with acute or subacute development of focal or generalized symptoms)[125]. The incidence of angiographic vasospasm is over 50%, with symptomatic vasospasm in 32% of patients[126]. Therefore, TCD is a valuable tool for detection of vasospasm and timing of angiography.

Recommendation

1. Nimodipine is recommended to reduce poor outcome related to vasospasm, while complications and side effects of the drug are minimal (Level I)[127,128]. Other calcium antagonists given orally or intravenously are of uncertain value (Level I)[129,130].
2. Worse hypertension, hypervolemia and hemodilution are recommended for prevention and treatment of ischemic complications from vasospasm (Level III)[131,132].
3. Intracisternal fibrinolysis and antioxidant and anti-inflammatory agents are of uncertain value (Level III)[133].
4. Transluminal angioplasty is recommended for the treatment of vasospasm in patients in whom conventional therapy has failed (Level IV)[134,135].

Hyponatremia/Volume contraction

The reported incidence of hyponatremia following SAH ranges from 10% to 34%. It usually develops several days after the hemorrhage (3rd to 15th day after SAH) and is more common in patients with poor clinical grade[136]. Hyponatremia has been attributed to inadequate secretion of antidiuretic hormone. Hyponatremia lowers the level of consciousness, leads to muscular weakness, seizures and coma. Dehydration along with hypotension increases the risk of vasospasm[137]. Although the incidence of hyponatremia was not altered by the administration of large volumes of fluid or of fludrocortisone[138], hyponatremia is usually too mild to produce symptoms. Therefore, aggressive measures to correct hyponatremia appear unwarranted, especially if they lead to volume contraction.

Recommendations

1. Management of hyponatremia after SAH is recommended to emphasize the need to prevent volume contraction; management should include intravascular administration of isotonic fluids (Level III).
2. Hypotonic fluids should be avoided as they may contribute to hyponatremia; fluid restriction should not be instituted to treat hyponatremia (Level IV).

Surgical therapy

Hematoma treatment

The ideal goals of surgical treatment of ICH should be to remove as much blood clot as quickly as possible with the least amount of brain trauma from the surgery itself. If possible, surgery should also remove the underlying cause of ICH, such as an arteriovenous malformation, and prevent complications of ICH such as hydrocephalus and mass effect of the blood clot. The decision on when and what to operate still remains controversial due to the lack of data from randomized clinical trials. So far, there is an overall agreement based on the evidence available from known researches[19].

Recommendations

1. Patients with small hemorrhages (<10 cm^3) or minimal neurologic deficit should not be surgically treated (Level II).
2. Patients with a GCS score <4 should not be surgically treated (Level II). However, these patients will be surgical candidates if they have simultaneous cerebellar hemorrhage within brain stem.
3. Patients with cerebellar hemorrhage >3 cm who are neurologically deteriorating or who have brain stem compression and hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (Level III).
4. ICH associated with a structural lesion such as an aneurysm, arteriovenous malformation or cavernous angioma may be removed if the patient has a chance for good outcome and the structural vascular lesion is surgically accessible (Level III).
5. Young patients with a moderate or large lobar hemorrhage who are clinically deteriorating (Level II).

Hydrocephalus

The etiology of acute ventriculomegaly after SAH is usually obstructive hydrocephalus caused by intraventricular blood. Acute hydrocephalus (ventricular enlargement within 72 hours) is noted in 20%-27% of patients surviving the ictus of SAH, with a greater frequency among poor-grade patients. Ventriculostomy has been associated with an increased rate of recurrent hemorrhage after SAH and may also be complicated by meningitis/ventriculitis[139,140]. Chronic ventriculomegaly occurs in 14%-60% of patients within 30 days from SAH[141].

Recommendations

1. Acute (obstructive) hydrocephalus ventriculostomy is recommended, although it may be associated with increased recurrent hemorrhage and infection (Level IV).
2. Chronic (communicating) hydrocephalus is a frequent occurrence after SAH. Temporary or permanent cerebrospinal diversion is recommended in symptomatic patients (Level IV).

Surgical treatment of aneurysm

Recommendations

1. Surgical clipping is recommended to reduce the rate of rebleeding after aneurysmal SAH (Level III)[142].
2. Early referral to specialized centers is recommended. Early surgery reduces the risk of recurrent hemorrhaging after SAH and is recommended for the good grade patient (Hunt and Hess 1 or 2) with uncomplicated aneurysm. For other clinical situations, either early or delayed surgery is recommended, depending on the specific clinical situation (Level II)[143,144].
3. Complete surgical obliteration of the aneurysm is recommended whenever possible, since wrapped or coated aneurysms or incompletely clipped aneurysms probably have an increased risk of recurrent hemorrhage (Level IV)[145].

Measures of prevention of recurrent hemorrhage after SAH

Recommendations

1. Regulated bed rest or antihypertensive therapy both are frequently included in overall treatment of patients with SAH; these measures should be combined with other definitive measures to prevent recurrent hemorrhage (Level I)[146].

2. Carotid ligation is of indeterminate value in preventing rebleeding (Level I)[147].
3. Antifibrinolytic therapy to prevent recurrent hemorrhage is recommended in certain clinical situations, e.g., patients with a low risk of vasospasm and/or beneficial effect of delaying surgery (Level I). However, antifibrinolytic therapy has been associated with a higher rate of cerebral ischemia, resulting in no benefit in terms of overall outcome. Future studies are recommended to determine whether a combination of antifibrinolytic therapy with other treatments to reduce vasospasm will be beneficial.[148].
4. Intraluminal coils and balloon-coils can promote aneurysmal thrombosis in a majority of cases, although long-term occlusion remains indeterminate[149].

Treatment of increased intracranial pressure (ICP) and brain edema

Ischemic brain edema

Cytotoxic brain edema occurs during the first 24-48 h after ischemic infarcts. In younger patients, brain edema and elevated ICP may become a major complication and may lead to herniation and death[150]. These patients usually show a rapid decline in consciousness and develop signs of herniation 2-4 days after the onset of symptoms. Outcome is fatal in the majority of these patients, with a mortality of about 80% with standard treatment[150,151].

Medical therapy

The basic management of elevated intracranial pressure following stroke includes 30° upright position and the patients should not be turned to either side during the first 24 h. The level of sedation must be controlled and adjusted if necessary to avoid pain and anxiety. Body temperature should be normalized. Osmotherapy with intravenous mannitol (25-50 g every 3-6 h) is the first medical treatment to be used if the signs of space-occupying edema occur. It should not be given for longer than 2 days or in emergency situations (for example, decompensated ICP). Mannitol is cleared by the kidney and acts as an osmotic diuretic. Electrolyte disturbance and hypovolemia are complications of osmotherapy with mannitol. During osmotherapy, plasma osmolality should not exceed 330 mOsm/kg. Short-term increases of osmolality seem to be more effective in reducing ICP compared with continuous high osmolality. Osmotherapy is only effective for 48-72 h. Hypotonic and glucose-containing solutions should be avoided as replacement fluids. Dexamethasone and other corticosteroids are not useful for brain edema treatment after stroke.

Intravenous barbiturates can decrease ICP by lowering cerebral blood volume. A parallel decrease in the mean arterial pressure may lead to a decrease of the cerebral perfusion pressure. Therefore, an effective therapy with barbiturates depends on reliable on-line monitoring of ICP and mean arterial pressure. The injection of barbiturate is stopped when a burst-suppression pattern is reached[75].

Decompressive surgery

Malignant middle cerebral artery (MCA) infarction

Space-occupying hemispheric infarction, the so-called malignant MCA infarction, has a high mortality and morbidity even with optimal conservative treatment. More than 80% of these patients die despite maximal conservative treatment. In selected cases, hemicraniectomy may be lifesaving and may improve outcome[150,151].

Cerebellar infarction

Cerebellar territorial infarction has a good clinical course even without aggressive treatment. However, in some cases with space-occupying cerebellar infarction, comatose patients have a mortality of about 80% if treated conservatively. This mortality is due to the development of occlusive hydrocephalus or direct brainstem compression. In these patients, decompressive surgery of the posterior fossa is significantly superior to ventriculostomy[151,152]. It should be noted that these are the results of open small- or medium-sized case series, so data from a controlled, randomized trial are needed.

Recommendations

1. Osmotherapy is recommended for patients whose condition is deteriorating secondary to increased intracranial pressure, including those with herniation syndromes (Level III).
2. Surgical decompression and evacuation of large cerebellar infarction compressing the brain stem is justified (Level III).
3. Surgical decompression and evacuation of a large hemispheric infarction can be a lifesaving measure. Survivors may have a residual neurologic deficit that allows an independent life (Level III).

Hemorrhagic brain edema

Osmotherapy

The first medical line of defense is osmotherapy. However, it should not be used prophylactically. Mannitol 20% (0.25-0.5 g/kg every 4 h) is reserved for patients with type B ICP waves, progressively increasing ICP values, or clinical deterioration associated with mass effect. Due to rebound phenomenon, mannitol is recommended for only ≤5 days. To maintain the osmotic gradient, furosemide (10 mg for 2-8 h) may be administered simultaneously with osmotherapy. Serum osmolality should be measured twice a day in patients receiving osmotherapy and targeted to ≤310 mOsmol/L.

Hyperventilation

Hypobaria causes cerebral vasoconstriction. Reduction of cerebral blood flow is almost immediate, although peak ICP reduction may take up to 30 minutes after pCO_2 has changed. Reduction of pCO_2 to 35-30 mm Hg, which is best achieved by raising ventilation rate at a constant tidal volume (12-14 ml/kg), lowers ICP by 25%-30% in most patients.

Muscle relaxants

Neuromuscular paralysis in combination with adequate sedation can reduce elevated ICP by preventing increases in intrathoracic and venous pressure associated with coughing, straining, suctioning, or "bucking" the ventilator (Level III). Nondepolarizing agents such as vecuronium or pancuronium with only minor histamine liberation and ganglion-blocking effects are preferred in this situation. Patients with critically elevated ICP should be pretreated with a bolus of a muscle relaxant before airway suctioning.

Sedation

Many patients who are delirious or stuporous are agitated. Hyperactivity is distressing to patients and may lead to self-injury or may increase ICP. Prudent use of minor and major tranquilizers is recommended, e.g., short-acting benzodiazepines or propofol[19]. Analgesics and neuroleptics can be added if necessary.

Recommendations

1. Osmotherapy with mannitol is reserved for patients deteriorating due to severe brain edema (Level IV).
2. Steroids are avoided because multiple potential side effects exceed the potential benefit (Level II).
3. Hyperventilation at constant tidal volume is recommended to lower ICP (Level III).
4. Muscle relaxants in combination with sedation are recommended to reduce increased ICP by preventing increases in intrathoracic and venous pressure associated with coughing, straining, suction or "bucking" the ventilator (Level III).

PREVENTION AND TREATMENT OF POST-STROKE COMPLICATIONS

Aspiration and pneumonia

One of the most important risks in the early phase after stroke is pneumonia. It accounts for 15%-25% of stroke deaths. Pneumonia may be caused by aspiration[153] or may be hypostatic in origin due to poor coughing and immobilization. To reduce the risk of aspiration pneumonia in patients with reduced consciousness, or with impaired gag reflexes or with swallowing disturbances, nasogastric feeding may be introduced. Hypostatic pneumonia may be prevented by frequent changes of the patient's position in bed and pulmonary physical therapy.

Urinary tract infection

Urinary tract infection may develop due to urinary retention in the early stroke phase. Urinary incontinence is a frequent stroke complication leading to the use of indwelling catheters. Intermittent catheterization is not always feasible in the setting of severe stroke and may contribute to decubitus ulcer. Suprapubic catheters are considered to carry a lower risk of infection. Acidification may reduce the risk of infection. Once urinary infection is seen, appropriate antibiotics should be started. However, there is no need for prophylactic antibiotics or treatment of catheter colonization.

Pulmonary embolism (deep vein thrombosis)

Pulmonary embolism may be the cause of 5% of stroke deaths. Early mobilization and use of subcutaneous heparin or molecular weight heparin can reduce the risk of deep venous thrombosis and pulmonary embolism. However, this effect seems to be counterbalanced by an increase in hemorrhagic complications[109]. Nevertheless, prophylaxis with subcutaneous low-dose heparin (7 500-10 000 IU every 12 h) has been recommended for bedridden stroke patients. Tachypnea and pain are sensitive signs of

pulmonary embolism. Examination of the lower extremities should be performed daily to detect signs of deep vein thrombosis. Physical therapy and support stockings are suggested as an alternative.

Decubitus ulcers

Frequent turning of immobilized patients is useful for prevention of decubitus. The skin of incontinent patients must be kept dry. For patients at a particularly high risk, an air- or fluid-filled mattress system should be used. If the decubitus does not respond to conservative therapy, antibiotic therapy may be justified for several days, preceding definitive surgical debridement.

Seizures

Partial or secondary generalized epileptic seizures may occur in the acute stroke phase. Diazepam (10-20 mg iv) followed by carbamazepine po is the treatment of choice.

Recommendations

1. Administration of heparin or low molecular weight heparin is recommended in bedridden stroke patients to reduce the number of deep vein thromboses and pulmonary embolisms, however, there is a risk of additional intracranial bleeding (Level I).
2. Infections after stroke should be treated with antibiotics and antipyretics. Aspiration pneumonia may be prevented by nasogastric feeding.
3. Early mobilization is helpful to prevent numerous complications after stroke: aspiration and hypostatic pneumonia, deep vein thrombosis and decubitus ulcers.
4. In seizure recurrence, administration of anticonvulsants is recommended (Level III).
5. Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended.

PART IV NEUROREHABILITATION

Early stroke rehabilitation is a key consideration in acute stroke management. A patient suffering from stroke often has severe impairments and functional limitations in action and perception. More than 40% of stroke survivors remain dependent upon others for their activities of daily living, about 25% are hospitalized, 10% are unable to walk, and 66% cannot return to work[156]. Some studies have suggested that early physical therapy helps in functional improvement and reduces the number of patients who are left dependent after stroke[157]. The principal aims of stroke rehabilitation should be to prevent contractures and embolism, optimize treatment associated with specific medical problems and provide psychological support to patients and families.

Early rehabilitation

Almost half of all stroke patients need active rehabilitation services. Rehabilitation should be started as soon as possible, even in comatose patients, who benefit from proper positioning and range-of-motion exercise. This means that the stroke patient should immediately be brought to a hospital with such facilities not only because of acute diagnosis and therapy but also because of early rehabilitation. The intensity of the rehabilitation program depends on the status of the patient and the degree of disability. If the patient is unconscious, the rehabilitation is passive to prevent contractions and joint pain, and to prevent distress for the patient when movement is restarted after immobilization. With passive rehabilitation, one can also minimize the risk of decubitus ulcers and pneumonia. All joints on the paralyzed side are moved through the full range of motion several times a day (3-4 times at least). Patients rarely need to be immobilized in bed for more than 1 or 2 days after a stroke unless they have a major decrease in their level of consciousness. Prolonged immobilization and hemiplegia carry a risk of deep vein thrombosis and complication of pulmonary embolism. After 2 or 3 days, most patients who are alert can be moved out of bed with safety and placed in either a wheel-chair or fixed chair for a good part of the day.

Rehabilitation programs

Early and adequate prediction of functional recovery after stroke is important in order to facilitate proper discharge planning, anticipate the need for home adjustments and community support, and set realistic and attainable goals for treatment. Important predictors for functional recovery after stroke are: disability on admis-

sion, sitting balance, severity of paralysis, urinary incontinence, level of consciousness within 18 hours post-stroke, and age. The assessment of the patient's situation includes evaluation of intellectual impairment including specific cognitive deficits such as aphasia, agnosia, apraxia, mood motivation, and degree of motor weakness, sensory loss and visual loss. Other problems that influence the patient's ability to respond to rehabilitation include financial burden, chances of return to activities and work, ability to live at home, sexual function, and need of other people's help. Ideally, the multidisciplinary stroke team who provide for adequate rehabilitation for stroke victims, consists of a stroke physician, nurses experienced in stroke management, a physiotherapist trained in stroke rehabilitation, an occupational therapist skilled in stroke care, a speech therapist familiar with speech problems in stroke, a neuropsychologist accustomed to stroke rehabilitation, and a social worker. Unfortunately, most hospitals treating stroke patients do not have all of these specially trained stroke experts. Still, it remains unclear which part of the expert care is mostly ameliorating stroke prognosis. Among the factors, involvement of active family participation, special staff education, early start of treatment or intensity of treatment are most prominent. Several lines of evidence suggest that intensity of treatment is a key aspect of stroke rehabilitation[155,157].The progress of the patient needs to be followed on a daily basis, by different members of the rehabilitation program. The patients and members of their families should be taken to be members of the stroke team. They should be taught the principles of stroke rehabilitation, so that they can actively participate in it. As soon as the patient's condition allows it, they should visit their home, and if they need longer rehabilitation period, they should be transferred to a special rehabilitation hospital. At the same time, the documentation of the patient and the progress in rehabilitation should be transferred too.

The recovery of the neurologic deficit occurs fastest during the first three months after the onset of symptoms. This is also the optimal time for rehabilitation. Still, active rehabilitation should be continued for as long as needed as part of a long-term rehabilitation program. Such a program includes twice a year a series of 15-20 physiotherapy sessions. This is to guarantee that the functional status, which has been achieved during the acute rehabilitation program, is sustained. If maintenance of the recovery is in jeopardy, an active rehabilitation program is needed, and sometimes it is reasonable to readmit the patient for a more intensive inpatient rehabilitation period.

Rehabilitation programs do not change the neurologic deficit, but patients can become ambulatory and largely independent. Of more importance is the fact that a majority of patients are able to be at home and do not require nursing home care. A better outcome of stroke is of benefit in both human and economic terms.

Recommendations

1. Rehabilitation should be initiated early after stroke (Level I).
2. Every patient should have access to evaluation for rehabilitation (Level III).
3. Rehabilitation services should be provided by a multidisciplinary team (Level III).

PART V SECONDARY PREVENTION

Secondary prevention means treatment and rehabilitation of patients who have had a stroke or transient ischemic attack, in order to prevent recurrent stroke. Secondary prevention also means identification and treatment of persons at a very high risk of developing stroke to prevent stroke occurrence. Secondary prevention can extend overall survival, improve quality of life, decrease the need of surgical procedures, and reduce the incidence of subsequent strokes. Secondary prevention comprises changing of lifestyle: quitting smoking, increasing physical activity, reducing body weight, changing eating habits, etc., treatment of concomitant diseases: hypertension, diabetes, elevated plasma lipids, cardiac diseases, atrial fibrillation, etc.; prescribing drugs for secondary prevention of ischemic stroke and surgical interventions: carotid endarterectomy and angioplasty[158]. Changing of lifestyle, treating of concomitant disease, and surgical interventions are measures of secondary prevention for ischemic as well as for hemorrhagic stroke, while prescribing antiplatelet and anticoagulant drugs are reserved only for secondary prevention of ischemic stroke.

Changing of lifestyle and treatment of concomitant diseases are described in Part I. Primary prevention. Everything that is said there could and must be applied in secondary prevention.

DRUGS FOR SECONDARY PREVENTION OF ISCHEMIC STROKE

ANTIPLATELET DRUGS

In the secondary prevention of ischemic stroke, antiplatelet drugs are prescribed, most often acetylsalicylic acid, ticlopidine, clopidogrel and dipyridamole.

Acetylsalicylic acid

Acetylsalicylic acid is a drug that has been in use for more than 100 years, and it is the best studied medical therapy for preventing stroke. The Antiplatelet Trialists' Collaboration performed a meta-analysis of 145 trials involving 51,144 patients allocated to antiplatelet therapy[159]. They found a 25% (20%-28%) reduction in stroke risk among patients receiving acetylsalicylic acid. The optimal dose of acetylsalicylic acid has not yet been defined. Usually, the dose of acetylsalicylic acid is defined as low (<160 mg), medium (160-325 mg) and high (500-1500 mg) dose. It has been debated that low doses could be more effective than medium or high doses because the production of prostacyclin by the endothelial cells may be partially preserved[160]. In European countries, acetylsalicylic acid is mainly prescribed in low and medium doses[161], while in the United States acetylsalicylic acid is mainly prescribed in high doses[162]. However, studies that compared the effects of various doses of acetylsalicylic acid have failed to show differences in stroke recurrence between low and medium doses[163] or between medium and high doses[164]. According to the findings of the Antiplatelet Trialists' Collaboration[159], the most widely tested were doses between 160 and 325 mg *per* day, and these doses may be most beneficial. However, there also exists evidence that doses of 30 and 50 mg daily are effective[163-165]. It seems that acetylsalicylic acid in any daily dose, 30 mg or higher, leads to moderate but significant reduction of stroke. A major side effect of acetylsalicylic acid therapy is bleeding. The rate of severe hemorrhages (those requiring blood transfusion or hospitalization) is not dose-dependent. However, higher doses increase the incidence of gastrointestinal side effects, e.g., indigestion, heartburn, nausea, vomiting. The recommended dose of acetylsalicylic acid therefore should be between 50 and 325 mg[166].

Ticlopidine

Ticlopidine is a thienopyridine derivative that inhibits the adenosine diphosphate pathway of platelet aggregation. In the Canadian American Ticlopidine Study (CATS), ticlopidine (500 mg/day) showed a risk reduction for stroke by 33.5% compared to placebo[167]. In the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine (500 mg/day) in intention-to-treat analysis showed a reduction of 21% compared with acetylsalicylic acid (1300 mg/day) for fatal and nonfatal stroke[168]. Ticlopidine, therefore, compares better to acetylsalicylic acid in the secondary prevention of ischemic stroke. A major disadvantage of ticlopidine are gastrointestinal side effects: diarrhea, dyspepsia and bleeding, skin rashes and bone marrow side effects: neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura. Most of these side effects occur in the first three months, but thrombotic thrombocytopenic purpura can occur even after the first three months[169,170]. Ticlopidine is a drug with more side effects than acetylsalicylic acid, and it is also more expensive.

Clopidogrel*

Clopidogrel is a new thienopyridine derivative, chemically related to ticlopidine. The Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study compared the effects of 75 mg clopidogrel and 325 mg acetylsalicylic acid once daily in reducing the composite endpoint of ischemic stroke, MI, or vascular death in 19,185 patients, and found a significant 8.7 % relative reduction in events in favor of clopidogrel[171]. Clopidogrel is slightly but significantly more effective than medium-dose acetylsalicylic acid. The side effects of clopidogrel and acetylsalicylic acid were similar. Recently, an article was published on 11 cases of thrombotic thrombocytopenic purpura associated with clopidogrel use[172]. Clopidogrel is the agent of choice in patients with contraindications or adverse effects to acetylsalicylic acid, and may be more effective in higher risk patients[173]. However, clopidogrel is more expensive than acetylsalicylic acid.

* Drug not registered in Croatia

Dipyridamole*

Dipyridamole is an antiplatelet agent with inhibition of cyclic nucleotide phosphodiesterase and blockage of the uptake of adenosine[174]. Four trials investigated whether the combination of dipyridamole plus acetylsalicylic acid is superior to acetylsalicylic acid alone and all had negative findings[175-178]. The European Stroke Prevention Study II[165] analyzed 6602 patients with stroke or TIA who were randomized to acetylsalicylic acid alone (50 mg daily), extended-release dipyridamole alone (400 mg daily), acetylsalicylic acid plus extended-release dipyridamole (50 + 400 mg daily), or placebo. The risk reduction in stroke events in the acetylsalicylic acid plus dipyridamole group (37%) was significantly higher than in either the acetylsalicylic acid group (18.1%) or dipyridamole group (16.3%). Although this study was viewed with some criticism, the results of the statistically adequately powered study clearly demonstrate the superiority of the combined treatment: acetylsalicylic acid (25 mg) plus extended-release dipyridamole (200 mg) twice daily.

Recommendations

1. Low- or medium-dose acetylsalicylic acid (50-325 mg) should be given as first-choice agent to reduce recurrence of ischemic stroke (Level I). Alternatively, where available, a combination of acetylsalicylic acid (25 mg) and dipyridamole (200 mg) twice daily may be given as first choice therapy (Level I).
2. Ticlopidine is in some aspects superior to acetylsalicylic acid in secondary prevention of ischemic stroke (Level I). Owing to the side effects of ticlopidine, it should be prescribed only to patients who cannot take acetylsalicylic acid (Level I).
3. Clopidogrel is slightly more effective than acetylsalicylic acid (Level I). It may be prescribed as first choice therapy or when acetylsalicylic acid is not tolerated or effective, and in special situations such as high-risk patients (Level III).
4. Patients starting treatment with thienopyridine derivatives should receive clopidogrel instead of ticlopidine because it has fewer side effects (Level I). Patients who have already been receiving ticlopidine for a long time should be maintained on this regimen because the most severe side effects (neutropenia and rash) occur at the beginning of treatment.
5. Patients who do not tolerate acetylsalicylic acid, ticlopidine or clopidogrel may be treated with dipyridamole (ret., 2x200 mg daily; Level I).

Anticoagulants after cardioembolic ischemic stroke

Oral anticoagulation with maintaining of International Normalized Ratio (INR) between 2.0-3.0 reduces the risk of recurrent stroke in patients with atrial fibrillation and recent ischemic stroke[163]. Oral anticoagulation therapy should also be considered for the many well established potential causes of embolism. Although evidence from randomized trials is still lacking, long-term anticoagulants are routinely used in patients with mechanical prosthetic valves. In this setting, a higher target of an INR of between 3.0 and 4.0 is recommended[179]. Long-term anticoagulation with an INR of 2-3 in patients with rheumatic valvular heart disease, MI, heart failure, cardiomyopathy, arrhythmia other than AF, or patent foramen ovale may be indicated.

Recommendations

1. Oral anticoagulation (INR 2.0-3.0) is indicated after ischemic stroke associated with atrial fibrillation (Level I).
2. Patients with mechanical prosthetic valves should receive long-term anticoagulation therapy with a target INR between 3.0 and 4.0 (Level III).
3. Patients with confirmed cardioembolic stroke should receive anticoagulation if the risk of recurrence is high, with a target INR between 2.0 and 3.0 (Level III).

SURGERY

Carotid endarterectomy

The North American Symptomatic Carotid Endarterectomy Trial Collaboration (NASCET)[59] and European Carotid Surgery Trial (ECST)[60] found carotid endarterectomy to be effective in symptomatic patients with ipsilateral carotid stenosis greater than 70%. Although these trials used different methods to measure stenosis, it is possible to predict the percentage of stenosis from one me-

* Drug not registered in Croatia

thod to another, and there is little difference in their ability to predict ipsilateral stroke.

In the NASCET, patients who underwent carotid endarterectomy had an absolute reduction of 17% in the risk of ipsilateral stroke at 2 years. The authors therefore warn that the benefit of surgical procedure diminishes when perioperative complications exceed 2.1%, and that it vanishes entirely when the rate approaches 10%. Although the rate of perioperative complications in the ECST was higher (7.5% of deaths, disabling stroke, or any stroke producing symptoms for more than 7 days), surgery-allocated patients still had a significant absolute risk reduction of 6.5 % in ipsilateral stroke and a relative reduction of 39%. The recent NASCET analysis of surgery for symptomatic patients with less than 70% stenosis revealed an absolute risk reduction of 6.5% and a relative risk reduction of 29% in patients with 50%-69% stenosis allocated for surgery[180].

Angioplasty and stenting

Carotid percutaneous transluminal angioplasty is a potentially valuable technique. Its advantages over carotid endarterectomy are short hospital stays, avoidance of general anesthesia and surgical incision, and ability to treat surgically inaccessible sites such as internal carotid artery stenosis at the base of the skull. Moreover, carotid percutaneous transluminal angioplasty and stenting may be the most effective means of treating restenosis after initial carotid endarterectomy [182]. Since this procedure has only recently been used, the principal problem is that data on long-term follow-up and comparison with carotid endarterectomy are not yet available. Randomized trials are planned. In the meantime, carotid percutaneous transluminal angioplasty may be considered as an experimental alternative to carotid endarterectomy. The results of the Carotid and Vertebral Artery Transluminal Angioplasty Study, the first randomized comparison of angioplasty and carotid endarterectomy, were presented at several conferences but have not yet been published.

Recommendations

1. Carotid endarterectomy is indicated for symptomatic patients with stenosis of 70%-99%, but only in centers with a perioperative complication rate (all strokes and death) less than 6% (Level I).
2. Carotid endarterectomy may be indicated for some patients with stenosis of 50%-69% without a severe neurologic deficit. This is also valid only for centers with a perioperative complication rate (all strokes and death) less than 6%. The subgroup of patients most likely to benefit from surgery are males with recent hemispheric symptoms (Level I).
3. Carotid endarterectomy is not recommended in patients with stenosis less than 50% (Level I).
4. Carotid endarterectomy should not be performed in centers not exhibiting low complication rates equal to those in NASCET and ECST.
5. Carotid endarterectomy may be indicated for some patients with stenosis of 60%-99%. Only patients with a low surgical risk (<3%) and with a life expectancy of at least 5 years are likely to benefit from surgery (Level II)
6. Carotid PTA with or without stenting may be performed in patients with contraindications for carotid endarterectomy (Level IV).
7. Carotid percutaneous transluminal angioplasty with or without stenting may be indicated in patients with stenosis at surgically inaccessible sites (Level IV).
8. Carotid percutaneous transluminal angioplasty and stenting may be indicated in patients with restenosis after initial carotid endarterectomy (Level IV).

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