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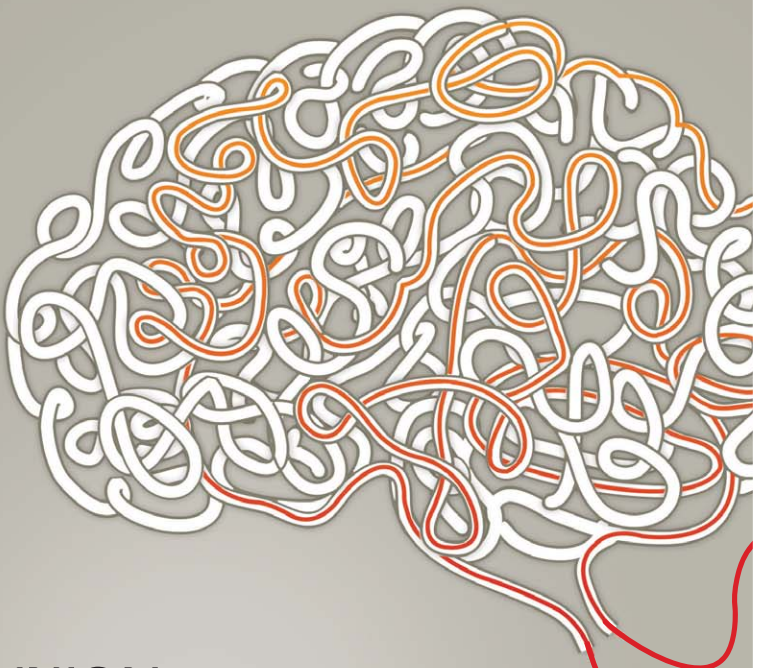

CLINICAL PRACTICE GUIDELINES FOR STROKE

CLINICAL RESEARH CENTER FOR STROKE

뇌졸중임상연구센터
Clinical Research Center For Stroke

CLINICAL RESEARCH CENTER FOR STROKE

Clinical Practice Guidelines for Stroke

[Revision]

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Preamble

Stroke is a major cause of death and disability worldwide. In 2005, WHO reported that stroke accounted for about 5.8 million deaths globally, equivalent to 9.9% of all-cause mortality. In Korea, stroke is the second leading cause of death; however, actual mortality rate has been decreased over the latest decade. Considering that primary prevention, optimal acute care and best secondary prevention play a huge role in clinical outcome, evidence based patient care cannot be too emphasized.

The clinical practice guidelines for stroke aims at providing healthcare professionals with well -summarized evidences in order to help with clinical decision-making process. Therefore, many countries including the United States, European Union, and Asian countries have developed and implemented their own stroke guidelines. However, due to the specificity of unique healthcare system, foreign guidelines cannot be directly applicable in Korea. Hence, the Clinical Research Center for Stroke developed and published the first edition of Clinical Practice Guidelines (CPG) for Stroke in 2009. Afterwards, the Clinical Research Center for Stroke has updated guidelines, reflecting new evidences. Stroke incidence in Korea is on the exponential increase, mainly driven by the fastest increase of elderly population among the Organization for Economic Cooperation and Development (OECD) countries. Therefore, the implementation of stroke guidelines tailored to our healthcare system would be of great importance for efficient stroke care.

The first edition of the Korean CPG was based on the evidences from foreign data and modified to Korean healthcare system. The current updated edition summarized and reflected Korean data in part. As clinical stroke research in Korea is being actively conducted and publications of the results in international journals as well as domestic journals are substantially increasing, we expect that the future guidelines will incorporate even more Korean data.

1. The Epidemiology of Stroke

The World Health Organization (WHO) defines stroke as a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin. Transient ischemic attack (TIA) is defined as focal neurological symptoms but lasting less than 24 hours.

In Korea, the annual stroke mortality rate substantially decreased by 28.3% over the first decade of the 21st century, which might be attributed to the improvement of risk factor control and acute stroke care. However, stroke is still a major cause of death. According to the 2010 vital statistics in Korea, stroke accounted for 26,517 death (53.2 per 100,000) , indicating that roughly one stroke-related death occurs in every 20 minutes. Stroke is the second leading cause of death after cancer, but takes the first place when analyzed by mortality per organ basis. Even with the substantial decrease during the last decade, the stroke mortality in Korea still remains at a high level compared to other OECD countries.

Whereas stroke mortality is decreasing, the overall stroke occurrence is increasing due to the population aging in Korea. Although stroke incidence data from a representative population-based cohort study are not available, a study, based on the 2004 insurance claim database of the Korean Health Insurance Review Agency and national death certificate data, showed that about 105,000 Korean people experienced a new or recurrent stroke in 2004, suggesting that one stroke occurs in every 5 minutes in Korea. The estimated stroke incidence was 216 per 100,000 person-years (women, 220/100,000 person-years; men, 213/100,000 person-years), and the incidence skyrocketed in the elderly (20/100,000 person-years in population aged $\leq$44 years and 3,297/100,000 person-years in those aged $\geq$85 years). The overall incidence was greater in women than in men because women were consisted of more elderly population. However, when stratified by age, the incidence was greater in men than in women across all age groups. Given the current rate of population aging, the stroke incidence in Korea is expected to increase by 3 folds in 2030, suggesting that immediate nationwide actions is mandatory.

Regarding stroke subtypes, the proportion of ischemic stroke is increasing while hemorrhagic stroke is decreasing. According to the reports analyzing - insurance claim database of the Korean Health Insurance Review Agency, ischemic stroke accounted for 64.7% and hemorrhagic stroke 35.3% in 2000, while ischemic stroke accounted for 76.1% and hemorrhagic stroke 23.9% in 2009. Data on ischemic stroke subtypes from nationwide representative population are not available. However, a hospital-based stroke registry data based on more than 36,000 patients admitted to training hospitals showed that large artery atherosclerosis (36.1%) was the most common subtype, followed by small vessel occlusion (25.4%) and cardioembolism (17.1%). Of note, the proportion of cardioembolism has increased, accounting for up to 20% in recent years, whereas the proportion of small vessel occlusion has decreased.
The estimated stroke prevalence is about 795,000 in Korea. According to the 2005 Korean National Health and Nutrition Examination Survey, the age-standardized prevalence of stroke diagnosed by physicians was 15.9 per 1,000 (men, 16.44 per 1,000; women, 15.39 per 1,000). When stratified by age, the stroke prevalence steeply increased after the 50s: for every 1,000 people, 6.53 in the 40s, 24.26 in the 50s, 57.96 in the 60s, and 67.45 in the 70s. Not only due to the overall increase of stroke occurrence attributed to population aging but also due to the increase of disabled stroke survivors from the decrease in stroke fatality, stroke will result in a great socioeconomic burden in the next decades. The nationwide cost data for stroke care was estimated to be over 3.7 trillion Korean Won in 2005. According to the WHO-Global Burden of Disease Project measuring regional and global burdens of hundreds of diseases and injuries with the metric of DALY (disability-adjusted life years) lost, about 344,000 healthy life years are being lost to stroke in Korea.

2. Scope

The Korean CPG for stroke covers the primary stroke prevention, acute stroke management including early rehabilitation, and secondary stroke

prevention. Strokes in children and specific surgical treatments are not included. Among stroke subtypes, ischemic stroke is primarily focused. Intracerebral hemorrhage is also included, but subarachnoid hemorrhage is excluded. However, the current updated CPG includes issues on unruptured aneurysm in the primary stroke prevention.

3. Objectives

The current CPG aims to provide systematically developed statements to help physicians of neurology, neurosurgery, rehabilitation, internal medicine, family medicine, neuroradiology, and neurointervention with decision-making process in specific clinical circumstances. However, the current guidelines cannot give specific recommendations for individual patient care; the ultimate management decision should be made by responsible physicians, taking into account of specific factors in individual patient. The current CPG, therefore, does not have any intention to restrict clinical practice, nor to serve as a reference for the insurance reimbursement. In particular, it should not be used to make legal judgment of treatment decisions made on a specific patient in a specific clinical situation.

4. Development Process

1) Topic Selections

These guidelines consist of three domains: primary stroke prevention, acute stroke management, and secondary stroke prevention. The items of each domain were selected by the Guidelines Development Task Force Team (TFT) in May 2006, and then approved by the Steering Committee through intensive review and revision. The Writing Committee, organized for each

domain, determined the final items, taking into account the healthcare system in Korea.

2) Formulating Guidelines

The TFT devised the CPG development manual. Referencing the CPG development manual, the Writing Committee reviewed all available foreign guidelines and selected four guidelines: those of the American Stroke Association (ASA), the European Union Stroke Initiative (EUSI), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of Physician (RCP). Then, the recommendations of these guidelines were summarized, and the evidences for the recommendations were collected by search and review of all the relevant articles. The level of evidence and the grade of recommendation for each statement in the current guidelines were determined according to the suggested format of the US Agency for Health Care Policy and Research (currently the Agency for Healthcare Research and Quality, AHRG) in 1993. Additional literature search and review process was performed to include new important evidences emerged after the publications of the four selected foreign guidelines, and the Writing Committee updated the new evidences in the Korean CPG.

The first edition published in 2009 reflected the evidences published until June 30, 2007. Afterwards, we have updated the guidelines for specific topics where new important evidences should be included. In the 2012 edition, 'asymptomatic carotid artery stenosis' and 'aspirin on primary prevention of stroke' were updated and 'public awareness and education' was newly added in the guidelines for primary stroke prevention. 'Antithrombotic therapy for noncardioembolic stroke or transient ischemic stroke' and 'extracranial carotid artery stenosis' were updated in the guidelines for secondary stroke prevention. The current 2013 edition updated 'atrial fibrillation' and newly added 'screening tests of unruptured intracranial aneurysm' and 'the treatment of unruptured intracranial aneurysm' in the guidelines for primary stroke prevention, and updated

'intravenous thrombolysis' and 'intra-arterial thrombolysis' in the guidelines for acute stroke management. The updated and added topics in detail were published as articles. The Korean GPC provides recommendations from four foreign guidelines as well as our recommendations for readers' comparison and understanding of diverse guidelines. Each of foreign guidelines differs in the definitions of the grade of recommendation and the level of evidence. Accordingly, in order to avoid readers' confusion and maintain unity with our guidelines we modified the grade of recommendation and the level of evidence of foreign recommendations based on the formulation adopted in our guidelines in the 2009 first edition. However, the modification process can even further increase confusion and have a risk of misinterpretation, therefore, to better reflect the original meaning in context, we used the recommendations and level of evidences from foreign guidelines without modificationin the editions thereafter. Moreover, with the decision by the Steering Committee, the modifications in the first edition were changed back into the original style based on specific its evidence and recommendation strategy.

3) Selection of Writing Committee Members

The Steering Committee chose a chair for each of the three domains of primary stroke prevention, acute stroke management, and secondary stroke prevention. Each chair organized writing members based on their specialty with the approval from the Steering Committee.

4) Writing Process

Under the leadership of each chair, writing committee members developed the contents and recommendations for each topic. Disagreements among writing committee members were resolved by consensus. The chair reviewed and submitted the first draft to the Steering Committee.

5) Review by the Steering Committee

The Steering Committee reviewed the first draft and recommended revision if necessary. The revised draft by the Writing Committee was submitted, reviewed, and approved by the Steering Committee.

6) Review by an External Specialist

The draft approved by the Steering Committee was sent to external reviewers who were recommended by relevant academic societies. The suggestions of external reviewers were considered and reflected in the final document.

7) Guideline update

The Steering Committee and the Writing Committees are consistently monitoring new evidences and selecting topics for which guideline updates are needed. The Steering Committee makes the final decision for the guideline update and selection of writing chairs and members. The process for update adheres to the updated protocol developed by the Guideline Development TFT. The updated topics are included in the CPG, and also published in articles that describe the evidences of the updates in detail.

5. Level of Evidence and Grade of Recommendation

The level of evidence and the grade of recommendation are assigned to each recommendation through the systematic search and interpretation of evidences. The level of evidence refers to the quality and strength of the scientific evidence of a statement, and the grade of recommendation implies how strongly a statement is recommended. The current CPG employs the method of the US Agency for Health Care Policy and Research listed below.

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials.
Ib	Evidence obtained from at least one randomized controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomization.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grade	Recommendation
A (evidence Levels Ia, Ib)	Required - at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation.
B (evidence Levels IIa, IIb, III)	Required - availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation.
C (evidence level IV)	Required - evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP Good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

6. Funding

The current CPG was developed by the support of the Korea Health R&D project (HI10C2020), the Ministry of Health and Welfare, Republic of Korea. This is a part of the project of the Ministry of Health and Welfare to facilitate clinical research of major diseases in Korea.

The Clinical Research Center for Stroke, under the leadership of the principal investigator, Professor Byung-Woo Yoon at Seoul National University Hospital, was launched in May 2006 with 6 subprojects to be undertaken over

9 years. The goal of this project is to lay the foundation for the development of Korean clinical practice guidelines for stroke and to implement the guidelines into clinical practice. The Steering Committee and the Writing Committees did not receive any other financial support for the CPG development. Accordingly, we declare that the current CPG is free from influences of the Government, pharmaceutical companies, hospitals, or other interested organizations.

February 2013
The Clinical Research Center for Stroke

※ Endorsed by the following academic societies (Feb 2013)

- The Korean Stroke Society
- The Korean Neurological Association
- The Korean Society of Geriatric Neurology
- The Korean Society of Cerebrovascular Surgeons
- The Korean Society of Interventional Neuroradiology
- The Korean Society of Intravascular Neurosurgery

※ The CPGs is accessible online (http://www.stroke-crc.or.kr).

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Primary prevention of stroke

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1.1 Non-modifiable risk factors

1.1.1 Age

Introduction

The risk of stroke rises with increasing age because of the progression of risk factors for stroke and aging of cerebrocardiovascular systems. The stroke risk doubles every 10 years beyond the age of 55.[1,2]

Korean recommendations

None

1.1.2 Sex

Introduction

The incidence of stroke is higher in men than in women, which is attributable not only to biological factors but to difference in lifestyles related to stroke risk factors.

Korean recommendations

None

1.1.3. Low birth weight

Introduction

In a prior study, low birth weight was associated with an increased risk of stroke incidence and mortality.[1] It has been suggested that maternal nutrition during pregnancy might affect off-springs' stroke risk and stroke mortality in their adulthood. It might partly explain a regional disparity in stroke incidence and mortality within a country.

Korean recommendations

None

1.1.4. Genetic factors

Introduction

Genetic factors play a role in development of stroke risk factors such as hypertension and diabetes, and also influence on the susceptibility to the effect of stroke risk factors. Several rare genetic disorders vulnerable to stroke have been identified. At present, genetic factors are considered non-modifiable. However, research is under way to treat malfunctioning genes or directly correct deficiencies due to gene abnormalities.

Korean recommendations

1. Evidence is insufficient to recommend a genetic screening for primary stroke prevention (GOR: GPP).

1.2. Well-documented and modifiable risk factors

1.2.1 Hypertension

Introduction

Hypertension is the most prevalent modifiable and the highest population-attributable risk factor for stroke. Hypertension is more strongly associated with stroke than with coronary arterial disease (CAD). Compelling evidences have shown that blood pressure (BP) control reduces the stroke risk.

Korean recommendations

1. Regular BP monitoring is recommended in adults, particularly in the elderly or those with other cerebrocardiovascular risk factors (GOR: GPP).
2. Lifestyle modification is recommended for prevention and treatment of hypertension (weight loss if overweighed, low-fat/low-salt diet, exercise, moderate drinking, and no smoking). If necessary, drug therapy should be initiated to lower BP (LOE: Ia, GOR: A).
3. The target BP is $<$ 140/90 mmHg for primary prevention of stroke (LOE: Ia, GOR: A).
4. In patients with diabetes and/or renal disease, the target BP is $<$ 130/80 mmHg (LOE: Ia, GOR: A).
5. Systolic hypertension in the elderly should be treated with the same principles and methods as other hypertension (LOE: Ia, GOR: A).
6. For primary stroke prevention, an adequate BP control is the most important rather than choosing a specific class of antihypertensive agent. However, given no compelling indications, calcium channel blockers or renin-angiotension system inhibitors are recommended over beta-blockers, (LOE: Ia, GOR: A).

1.2.2 Smoking

Introduction

The epidemiologic studies have indicated that smoking is a potent risk factor for stroke. Smoking exerts both acute effect o thrombogenesis and chronic effect of accelerating atherosclerosis.

Korean recommendations

1. Smoking should be ceased, and smokers should be strongly advised to quit (LOE: III, GOR: B).
2. Secondary smoking should be avoided (LOE: III, GOR B).
3. Counseling, nicotine replacement therapy, and oral smoking cessation aids should be considered in smokers (LOE: Ia, GOR: A).

1.2.3 Diabetes

Introduction

Diabetes is one of the modifiable risk factors for stroke. Large-scale, case-control studies have demonstrated that diabetes is an independent risk factor for ischemic stroke. While strict blood pressure control and lipid lowering with a statin reduce the stroke risk, the evidence that a tight blood glucose control could reduce stroke risk is lacking. However, as it is widely recognized that blood glucose control prevents microvascular complications, a strict blood glucose control is recommended. If patients with diabetes have hypertension or hyperlipidemia, more rigorous control of BP or blood lipid is required.

Korean recommendations

1. In diabetes patients, comprehensive and aggressive evaluations and treatments are needed to manage not only blood glucose but other risk factors such as hypertension, hyperlipidemia, and smoking together (LOE: Ib, GOR: A).
2. In diabetes patients, a more aggressive and rigorous blood glucose control is recommended for prevention of cerebrocardiovascular events (LOE: Ia, GOR: A). The recommended target BP and LDL cholesterol level are $<$130/80mmHg (LOE: Ib, GOR: A) and $<$100mg/dL (LOE: Ia, GOR: A), respectively. For type 2 diabetes patients who have additional risk factors, aggressive lipid lowering with a statin is recommended for primary prevention of stroke (LOE: Ib, GOR: A).

1.2.4 Atrial fibrillation

Introduction

Revised: Dec 2012

Atrial fibrillation (AF) is a major risk factor of stroke. The prevalence of AF increases substantially with age, and the estimated prevalence is about 10% in people aged 80 years or older. As AF-related strokes usually develop a large cerebral infarction and result in severe neurologic deficits, they are more disabling and more fatal than non-AF-related strokes. However, AF-related strokes can be effectively prevented with an appropriate antithrombotic therapy, the primary prevention of stroke is of great importance in patients with AF. After the publication of the first edition of 2009 guidelines, several large randomized clinical trials were published regarding the new antithrombotic therapies for preventing stroke and systemic embolism in patients with non-valvular AF. Accordingly, the current updated guidelines revised the recommendations for primary prevention of stroke in patients with AF, reflecting the new evidences.

Revised Korean Recommendations

1. In AF patients with valvular heart diseases (particularly those with mechanical valves), warfarin is recommended (Level of Evidence Ia, Grade of Recommendation A).
2. In patients with non-valvular AF, antithrombotic treatment (warfarin, dabigatran,

rivaroxaban, apixaban or aspirin) is recommended for primary stroke prevention. The selection of antithrombotic treatment should be individualized based on thromboembolic risk, bleeding risk, patient's preference, and feasibility of anticoagulation monitoring (Level of Evidence Ia, Grade of Recommendation A).

3. In patients with AF who are at high risk for stroke (annual stroke risk > 4%), warfarin (INR 2.0-3.0) is recommended, unless contraindicated (Level of Evidence Ia, Grade of Recommendation A). Dabigatran, rivaroxaban, and apixaban are useful alternatives to warfarin (Level of Evidence Ib, Grade of Recommendation A).
4. For dabigatran, a dose of 150 mg twice daily is recommended. In patients who are at high risk of bleeding, a lower dose of 110 mg twice daily is recommended (Level of Evidence Ib, Grade of Recommendation A).
5. For rivaroxaban, a dose of 20 mg once daily is recommended. In patients with moderate renal impairment (Creatinine Clearance, CrCl 30-49 mL/min), 15 mg once daily is recommended (Level of Evidence Ib, Grade of Recommendation A).
6. For apixaban, a dose of 5 mg twice daily is recommended. A dose of 2.5 mg twice daily is recommended for patients with two or more of the following characteristics: serum creatinine $\geq$ 1.5 mg/dl, age $\geq$ 80 years, or weight $\leq$ 60 kg (Level of Evidence Ib, Grade of Recommendation A).
7. In patients with non-valvular AF and severe renal impairment (CrCl $\leq$ 30 mL/min), dabigatran, rivaroxaban, and apixaban are not recommended (Level of Evidence IIa, Grade of Recommendation B).
8. In patients with AF who are at high risk for stroke (annual risk of stroke $\rightarrow$ 4%), but unsuitable for warfarin, aspirin (Level of Evidence Ia, Grade of Recommendation A), combination therapy with aspirin plus clopidogrel (Level of Evidence IIa, Grade of Recommendation B), or apixaban (Level of Evidence Ib, Grade of Recommendation A) is recommended. Apixaban is preferred to aspirin and combination therapy with aspirin plus clopidogrel. In patients at low risk of bleeding, combination therapy with aspirin plus clopidogrel can be considered in preference to aspirin alone.

Table. Nonvalvular Atrial Fibrillation Risk Stratification and Treatment Recommendations: Risk Stratification by $CHADS_2$ Scheme

$CHADS_2$ Score	Risk level	Rate of stroke	**Treatment Recommendations** Based on Risk Stratification
0	Low	1.0%/year	Aspirin (75-325 mg daily)
1	Low-moderate	1.5%/year	Warfarin INR 2-3 or aspirin (75-325 mg daily) †
2*	Moderate	2.5%/year	Warfarin INR 2-3 †
3	high	5.0%/year	Warfarin INR 2-3
≥4	Very high	>7%/year	Warfarin INR 2-3

Congestive heart failure, hypertension, age >75 y, or diabetes = 1 point. Stroke or TIA* = 2 points.

*All nonvalvular atrial fibrillation patients with prior stroke or transient ischemic attack should be considered high risk and treated with anticoagulants; the $CHADS_2$ scheme should be applied for primary prevention.

† Consider patient preferences, bleeding risk, and access to good INR monitoring. For those with a $CHADS_2$ Score=1, the number needed to treat to prevent 1 stroke over 1 y with warfarin is $\approx$ 100; excellent anticoagulation control is essential to achieve this benefit.

1.2.5 Other cardiac conditions

Introduction

Other cardiac conditions that increase the risk of cardioembolic stroke include dilated cardiomyopathy, valvular heart disease (mitral valve prolapse, endocarditis, and prosthetic valves), and congenital heart disease (patent foramen ovale, atrial septal defect, and atrial septal aneurysm).[1] Acute myocardial infarction (MI) increases the risk of cardioembolic stroke by formation of ventricular wall thrombi or developing AF.[1] Open heart surgery has a higher risk of stroke than other types of surgery.[2,3]

Korean recommendations

1. For patients with ST-elevated MI who have a cardiac condition of increased cardioembolic risk (AF, mural thrombus, akinetic regions, for example), combination therapy with antiplatelet (aspirin etc.) and anticoagulant is reasonable. Duration of the anticoagulant therapy should be determined based on the cardiac conditions: long-term anticoagulation for those with persistent AF, and at least 3 months anticoagulation for those with mural thrombi or akinetic left ventricular segments (LOE: Ib, GOR: A).
2. Warfarin may be considered in severe left ventricular dysfunction, whether or not heart failure is present (LOE: IV, GOR: C).
3. Treatment of cardiac conditions associated with an elevated risk of stroke, such as valvular heart disease, angina pectoris, and acute MI, should follow the general practice guidelines for heart disease (GOR: GPP).
4. For patients undergoing coronary bypass surgery who have a high risk (advanced age of °√65, left main coronary artery stenosis, peripheral vascular disease, history of TIA or stroke, or carotid bruits upon auscultation), evaluating stroke risk such as carotid stenosis should be considered (GOR: GPP).

1.2.6 Dyslipidemia

Introduction

Inconsistent findings for the association between cholesterol level and stroke observed in earlier epidemiological studies were likely attributable to indiscriminating hemorrhagic and ischemic stroke.[1,2] Recent studies showed that increased total cholesterol and/or LDL cholesterol is associated with an increased ischemic stroke risk in both men and women. Lower level of HDL-cholesterol is associated with ischemic stroke only in men. Clinical trials and meta-analyses during the last decade demonstrated that lowering cholesterol with statins is effective in primary and secondary prevention of cerebrocardiovascular diseases.[3] For ischemic stroke, statins were also effective in primary and secondary prevention.[4,5]

Korean recommendations

1. Determination of the target LDL cholesterol follows the general guidelines;

1) For patients with coronary artery disease or equivalent risk (such as carotid artery disease, peripheral vascular disease, abdominal aneurysm, and diabetes), <100 mg/dL.

2) For patients with 2 or more risk factors, <130 mg/dL.

3) For patients with 1 or fewer risk factors, <160 mg/dL.
(Risk factors: smoking, hypertension, HDL cholesterol <40mg/dL, history of coronary artery disease in the first degree family members (male aged <55 and female <65), and age (men ≥45 and women 55≥)) (LOE: Ia, GOR: A).

2. For hypertensive patients with or at high risk of CAD, statin treatment along with lifestyle modification is recommended even at a normal LDL cholesterol level (LOE: Ia, GOR: A).
3. In diabetic adults, the target LDL cholesterol of < 100 mg/dL is recommended (LOE: Ia, GOR: A).
4. For type 2 diabetes patients who also have other risk factors, lipid-lowering with statins is recommended for primary prevention of stroke (LOE: Ib, GOR: A).
5. For patients with CAD and a low HDL cholesterol level, niacin or gemfibrozil may be recommended along with weight loss, physical activity, and smoking cessation (LOE: Ib, GOR: A).

1.2.7 Asymptomatic carotid stenosis

Introduction

Revised: Oct 2011

The definition of asymptomatic carotid stenosis slightly differs across studies. In recent clinical trials, asymptomatic carotid stenosis is usually defined as the carotid stenosis that has not caused ischemic symptom in the stenotic carotid territory within six months. With the advances in diagnostic tests, the detection of asymptomatic carotid stenosis is increasing. It has been reported that 5-10% of people aged ≥65 years have ≥50% carotid stenosis, and about 1% have ≥80% stenosis. The estimated annual stroke risk in patients with asymptomatic carotid stenosis of 50-99% is 1-3.4%. In the 1990s and the early 2000s, several clinical trials demonstrated the benefit of carotid endarterectomy (CEA) over the best medical treatment in patients with severe asymptomatic carotid stenosis. Since then, medical treatment and carotid angioplasty and stenting (CAS) have evolved, and CEA technique has improved as well. The more treatment options are available for patients and physicians, the more careful consideration should be given to the choice of an optimal treatment.

Revised Korean Recommendations

1. In patients with asymptomatic carotid stenosis, well-documented and modifiable risk factors should be thoroughly investigated and aggressively controlled.
   1) In patients with hypertension, antihypertensive treatment is recommended to lower the blood pressure below 140/90mmHg (Level of Evidence Ia, Grade of Recommendation A).
   2) Smokers should be highly recommended to receive smoking cessation interventions and to quit smoking (GPP).
   3) Statin treatment is recommended to lower LDL cholesterol level below 100 mg/dL (Level of Evidence Ia, Grade of Recommendation A).
   4) In patients with diabetes, strict blood glucose control with lifestyle modification (diet and exercise) and glucose-lowering medications can be useful to prevent cardiovascular diseases (Level of Evidence Ia, Grade of Recommendation A).

2. In patients with ≥50% asymptomatic carotid stenosis, antiplatelet therapy is recommended unless contraindicated (Level of Evidence IIa, Grade of Recommendation

B). In patients with <50% asymptomatic carotid stenosis, the use of antiplatelet therapy should be determined after taking into account of risks of both cardiovascular disease and bleeding complications (GPP).

3. In patients with 60-99% asymptomatic carotid stenosis, prophylactic CEA or CAS may be considered if the procedural complications rates are under 3% (CEA: Level of Evidence Ia, Grade of Recommendation A; carotid angioplasty/stenting: Level of Evidence IIb, Grade of Recommendation B). Patient selection should consider comorbidity, life expectancy, patient preference, and other individual factors. The benefit and risk of treatment should be thoroughly discussed with patients. Because of the advances in medical treatment, the current benefits of CEA might be lowered. Therefore, lowering the 3% threshold of surgical complication rate can be considered for treatment decision. In contrast to CEA, CAS has not been directly compared to the best medical treatment.

4. In patients with 60-99% asymptomatic carotid stenosis who are at high risk for CEA, CAS may be considered as an alternative (Level of Evidence IIa, Grade of Recommendation B). However, no trial has yet compared CAS and the best medical treatment in patients at high risk for CEA.

1.2.8 Postmenopausal hormone therapy

Introduction

In women, stroke risk dramatically increases after menopause. Experimental or observational studies suggested that postmenopausal hormone therapy might prevent cerebrocardiovascular events and decrease the stroke severity. However, on the contrary, clinical trials have demonstrated that the postmenopausal hormonal therapy increases stroke risk.

Korean recommendations

1. Postmenopausal hormone therapy is not recommended for primary prevention of stroke (LOE: Ia, GOR: A).
2. If postmenopausal hormone therapy is needed for other indications, adequate explanation and counseling about the elevated cerebrocardiovascular risk should be provided (GOR: GPP).

1.2.9 Diet and nutrition

Introduction

Adequate intake of fruits and vegetables helps to prevent stroke. Restricting sodium intake and taking potassium-enriched diet also have an effect of stroke prevention which seems to be exerted via BP reduction.

Korean recommendations

1. A low-sodium / high-potassium diet is recommended for BP reduction and stroke prevention (LOE: Ia, GOR: A). The recommended daily intake is ≤2.3g (100mmol) for sodium or ≤6g for salt and ≥4.7g (120 mmol) for potassium.

2. It is recommended to increase dietary intake of fruits, vegetables, and low-fat dairy products (low-fat milk, cheese, yogurt, etc.) and to decrease saturated and total fat intake (LOE: Ib, GOR: A).
3. A diet rich in fruits and vegetables (at least 5 servings daily) is recommended (LOE: III, GOR: B).
4. A weight loss diet is recommended for those with a high body mass index (BMI) (LOE: Ib, GOR: A).

1.2.10 Physical activity

Introduction

Regular physical activity reduces premature death and cerebrocardiovascular mortality and morbidity. Physical activity also helps to prevent stroke. The effects seem to be attributable to blood pressure reduction, glucose control, and weight loss.

Korean recommendations

1. Increasing physical activity is recommended for primary prevention of stroke (LOE: III, GOR: B).
2. Regular daily exercise of moderate intensity for 30 minutes or longer is recommended to prevent stroke (LOE: III, GOR: B).

1.2.11 Obesity

Introduction

For Korean, obesity is defined as a BMI (Body Mass Index; body weight (kg) / height (meter)[2] ≥25. Abdominal obesity is defined as a waist circumference ≥90cm (men) or ≥85cm (women). In the 2005 Korean National Health and Nutrition Examination Survey, the prevalence of obesity in adults 20 and older was 31.7% (35.1% in men and 28.0% in women), a significant increase from the 26.3% (25.0% in men and 27.0% in women) in the 1998 survey.[1] The risk of stroke is known to increase in proportion to the severity of obesity.

Korean recommendations

1. Weight reduction lowers BP (LOE: Ia, GOR: A), which leads to reducing stroke risk (LOE: III, GOR: B).

1.3 Less well-documented or potentially modifiable risk factors

1.3.1 Metabolic syndrome

Introduction

Metabolic syndrome refers to a constellation of multiple conditions comprising abdominal obesity, dyslipidemia, impaired glucose tolerance, and hypertension along with insulin resistance. With the recent surge in its prevalence, metabolic syndrome is associated with an increased risk of not only diabetes but cerebrocardiovascular diseases such as stroke. Among diverse diagnostic criteria for metabolic syndrome, the one for Asians devised by the International Diabetes Federation is widely employed (Table in below).[1]

Korean recommendations

1. Metabolic syndrome is a risk factor for stroke. Lifestyle modification and drug therapy are recommended for each of its components (LOE: III, GOR: B).

Table. Metabolic syndrome as defined by the International Diabetes Federation[1]

Abdominal obesity
Waist circumference*: Men ≥ 90cm, Women ≥ 80cm (in Asians)
Abdominal obesity plus at least 2 of the following conditions
Serum triglyceride: > 150mg/dL (1.7mmol/L) or drug-controlled
HDL cholesterol: Men < 40mg/dL (1.03mmol/L), Women < 50mg/dL (1.29mmol/L), or drug-controlled
Blood pressure: SBP ≥ 130mmHg or DBP ≥ 80mmHg or drug-controlled
Fasting blood glucose: ≥ 100mg/dL (5.6mmol/L) or diagnosis with type 2 diabetes
(For ≥ 100mg/dL, an additional oral glucose tolerance test is not needed for the diagnosis purpose, but is recommended for the treatment purpose.)

* A BMI ≥30kg/m^2 is regarded abdominal obesity, irrespective of the waist circumference.

1.3.2 Alcohol

Introduction

A number of retrospective cohort studies have reported that mild or moderate drinking, particularly of grape wine, may reduce stroke risk. Heavy drinking, however, is known to increase stroke risk.

Korean recommendations

1. Heavy drinking should be avoided for various health purposes. With regard to stroke prevention, no more than 2 drinks per day for men or 1 drink per day for non-pregnant women may be protective against stroke (LOE: III, GOR: B).

1.3.3. Drug abuse

Introduction

Drug abuse is a chronic disease with a high recurrence rate. In addition to causing numerous health problems, it has a serious social implication. Use of cocaine, amphetamine, or heroin is associated with stroke.[1]

Korean recommendations

1. Sympathomimetics such as cocaine, amphetamine, or heroin increase risk of stroke and should not be used (LOE: III, GOR: B).
2. Medical counseling to drug abusers can be useful (LOE: IV, GOR: C).

1.3.4. Oral contraceptives

Introduction

The evidence that oral contraceptives might be associated with ischemic stroke came from earlier studies investigating the 1st generation agents containing high doses of estrogen. Newer formulations with lower estrogen content appear safe in terms of the risk of stroke.

Korean recommendations

1. In women with no risk factor for stroke, low estrogen containing oral contraceptives are less likely to increase the risk of stroke (LOE: III, GOR: B).
2. In women with risk factors for stroke such as smoking and thromboembolism, avoiding oral contraceptives is reasonable (LOE: III, GOR: B).
3. If use of oral contraceptives is needed despite presence of stroke risk factors, a rigorous treatment of the risk factors would be helpful (LOE: IV, GOR: C).

1.3.5. Sleep disordered breathing

Introduction

Sleep disordered breathing (SDB) is closely associated with major risk factors for stroke such as hypertension and abdominal obesity. Some investigators have insisted that SDB is an independent risk factor for stroke[1]. SDB is a main cause of refractory hypertension hardly controlled with drug therapy, and successful treatment of SDB led to a significant BP reduction.[1] The complicated interaction between SDB and stroke risk factors, however, makes it difficult to determine whether SDB is a direct cause of stroke or an instigator of other risk factors. Data on whether treating SDB reduces stroke is lacking.

Korean recommendations

1. In patients with a history of cerebrocardiovascular diseases or with stroke risk factors such as obesity and hypertension, the screening for SDB symptoms including habitual snoring and daytime sleepiness is reasonable. For patients with refractory hypertension in particular, referral to sleep specialists may be considered for a proper assessment (LOE: III, GOR: B).
2. Evidence is insufficient to recommend a routine SDB screening and treatment for primary prevention of stroke (LOE: III, GOR: B).

1.3.6 Migraine

Introduction

Migraine begins mostly before age of 40 and persists through the remaining lifetime. The prevalence of migraine is about 12%, and it is three times higher in women than in men.[1] The association of migraine with stroke has been reported in young women.

Korean recommendations

1. There are insufficient data to recommend a migraine prophylaxis for primary prevention of stroke in migraine women (including the ones with aura) (LOE: IV, GOR: C).

1.3.7 Hyperhomocysteinemia

Introduction

Homocysteine is an amino acid produced in the methionine metabolism. Its blood level was shown to be positively correlated with the risk of cerebrocardiovascular diseases such as coronary artery disease and stroke in numerous prospective observational studies, case-control studies, and meta-analyses. Some vitamins such as folic acid, cobalamin (vitamin B12), and pyridoxine (vitamin B6) can effectively reduce blood homocysteine levels. Nonetheless, the causal relationship between an elevated blood homocysteine level and cerebrocardiovascular events including stroke remains obscure.

Korean recommendations

1. For population with inadequate dietary folic acid intake, folic acid supplementation aimed at reduction in the blood homocysteine level may be considered for primary prevention of stroke (GPP).
2. For patients with a high risk for cerebrocardiovascular events (diabetes or coronary artery disease, for example), use of vitamin B6 aimed at reduction in the blood homocysteine level might increase the risk of ischemic heart disease and thus requires a caution (LOE: IIa, GOR: B).

1.3.8 Hypercoagulability

Introduction

Hypercoagulability can be suspected if stroke occurs in young patients without risk factors. Antiphospholipid antibodies are found frequently in young female patients with cerebral infarction.[1] However, while acquired or hereditary hypercoagulability is associated with venous thrombosis, its association with ischemic stroke has not been demonstrated. In patients with patent foramen ovale (PFO), whether the hypercoagulability contributes to developing ischemic stroke needs further research.

Korean recommendations

1. There are insufficient data to provide a specific recommendation for primary prevention of stroke in patients with inherited or acquired hypercoagulability (LOE: III, GOR: B).
2. Hypercoagulability might be present in patients with antiphospholipid antibody syndrome or cancer. However, evidence is lacking with regard to the use of antiplatelets or anticoagulants for primary prevention of stroke in these patients (LOE: III, GOR: B).

1.3.9 Inflammation

Introduction

Risk factors or medical conditions that lead to damage and inflammation in cerebrovascular endothelial cells increase the risk of intravascular thrombosis and stroke. Atherosclerosis, a major cause of stroke, is a chronic inflammatory disease following vascular endothelial damages.[1] However, inflammatory surrogate markers for stroke have not been well-defined.

Korean recommendations

1. Evidence is insufficient to recommend a routine hs-CRP screening for the evaluation of cerebrocardiovascular risk (LOE: IV, GOR: C).
2. In patients with a high risk for stroke, an aggressive control of the risk factors is recommended, regardless of hs-CRP level (LOE: Ia, GOR: A).
3. In patients with a moderate risk for stroke, hs-CRP level may be considered to determine the intensity of risk factor control (LOE: III, GOR: B).

1.3.10 Infection

Introduction

Recent infection within 1 week might promote a thrombosis that could potentially lead to stroke. Microorganisms such as Chlamydia pneumoniae, Cytomegalovirus, Helicobacter pylori, and gram negative germs responsible for periodontal disease have been reported to be associated with atherosclerosis. Various pathogens encountered through lifetime might be involved in diverse stages of stroke development.

Korean recommendations

1. Even with seropositivity for pathogens potentially associated with stroke, evidence is insufficient to recommend antibiotics aimed at these pathogens for primary prevention of stroke (LOE: IV, GOR: C).

1.3.11 Asymptomatic lacunes and white matter change

Introduction

Brain MRI of healthy people commonly reveals asymptomatic lacunes or white matter changes. Asymptomatic lacunes are observed in about 20% of elderly population aged 60 to 90. Asymptomatic lesions are 5 times higher in number than symptomatic lesions. Asymptomatic and symptomatic lacunes share the same risk factors.

White matter change is common in the elderly, with almost 100% prevalence in those aged 85. On the T2-weighted MRI or proton density weighted image, the change is detected by the high intensity signal seemingly produced by a focal increase in the water content following white matter loss. The risk factors for white matter change include hypertension, atherosclerosis, and history of smoking.

Korean recommendations

1. If asymptomatic lacunes or white matter changes are detected on brain MRI in the absence of stroke history, the treatment strategy for primary prevention of stroke should be made by taking concomitant risk factors into account (LOE: IV, GOR: C).

1.4 Aspirin for primary prevention of stroke

Introduction

Revised: Oct 2011

Multiple clinical trials have proved the efficacy of aspirin, a prototype antiplatelet, for the secondary prevention of cardiovascular disease. For the primary prevention of cardiovascular disease, aspirin reduced the risk of ischemic heart disease in men and the risk of ischemic stroke in women at risk. Recently, several randomized clinical trials and meta-analyses have demonstrated that aspirin failed to reduce the risk of cardiovascular disease including stroke in patients with diabetes and no established cardiovascular disease and those with asymptomatic peripheral arterial disease. Accordingly, we updated our recommendations of aspirin for primary stroke prevention, reflecting these new evidences.

Revised Korean Recommendations

1. Low dose aspirin (75 - 325 mg, once daily) for the primary prevention of cardiovascular disease is recommended for persons in whom the risk of cardiovascular disease is high enough (a 10-year risk of 6 - 10% or higher) to outweigh the risk of bleeding. (Level of Evidence Ia, Grade of Recommendation A).
2. Aspirin is not useful for the primary prevention of overall cardiovascular disease, ischemic heart disease, or stroke in persons having only diabetes without established cardiovascular disease or asymptomatic peripheral arterial disease. (Level of Evidence Ia, Grade of Recommendation A).
3. In men, aspirin can be recommended for the primary prevention of ischemic heart disease, but not for the primary prevention of ischemic stroke. (Level of Evidence Ia, Grade of Recommendation A).
4. In women, aspirin can be recommended for the primary prevention of ischemic stroke, but not for the primary prevention of ischemic heart disease. (Level of Evidence Ia, Grade of Recommendation A).
5. A long-term use of aspirin significantly increases the risk of bleeding including intracranial hemorrhage. Therefore, the benefit of preventing cardiovascular disease should be carefully weighed against the risk of bleeding (Level of Evidence Ia, Grade of Recommendation A). It needs to be considered that the incidence of intracerebral hemorrhage is higher in Koreans than in Caucasians (GPP).

1.5. Public Awareness and Education of Stroke

Introduction

New: May 2012

Stroke is a medical emergency that should be treated as soon as possible after the symptom onset. However, the public awareness of stroke warning signs and act on stroke still remains low. The chain of survival and achieving better outcome after stroke consists of 3 steps: 1) immediate recognition of stroke warning signs and act on stroke of seeking emergency medical care by patients, family members, or witnesses; 2) pre-hospital emergency medical system (EMS) that ensures immediate dispatch of EMS personnel and rapid transportation of patients to the closest appropriate hospital; and 3) in-hospital acute stroke care system that provides immediate evaluation and treatment. The most important obstacle to emergency treatment is the first step: recognition of stroke warning signs and act on stroke. Accordingly, public education about the stroke warning sign and importance of emergency treatment of stroke must allow more patients to receive appropriate and timely treatment and reduce the social and economic burden of stroke.

Korean Recommendations

1. In order to reduce the pre-hospital delay and to increase the treatment rate of intravenous thrombolysis, educational programs are necessary to enhance the public awareness of stroke (Level of Evidence IIb, Grade of Recommendation B).
2. Conducting stroke education on the general public via the mass media is recommended (Level of Evidence III, Grade of Recommendation B).
3. Educational programs for EMS personnel are recommended to enhance their knowledge of pre-hospital management of stroke (Level of Evidence IIb, Grade of Recommendation B).

1.6 Unruptured intracranial aneurysm

1.6.1 Screening of Unruptured Intracranial Aneurysm

Introduction

New: Jan 2013

Subarachnoid hemorrhage due to the rupture of an intracranial aneurysm usually has a poor prognosis despite the recent advances in the management. Prevention of rupture would be of great importance to reduce the mortality and morbidity caused by intracranial aneurysm, and screening tests for high-risk populations are being considered.

Korean Recommendations

1. Screening for unruptured intracranial aneurysms may be considered for individuals who have 2 or more first degree relatives with intracranial aneurysm (Level of Evidence III, Grade of Recommendation B).
2. Screening for unruptured intracranial aneurysms may be considered for patient with autosomal dominant polycystic kidney disease (Level of Evidence III, Grade of Recommendation B).
3. In patients with previous subarachnoid hemorrhage due to aneurysmal rupture, regular screening for detecting new aneurysms should be considered (Level of Evidence III, Grade of Recommendation B).

1.6.2 Treatment of Unruptured Intracranial Aneurysm

Introduction

New: Jan 2013

The management of an unruptured intracranial aneurysm should be determined based on the natural history of the lesion, but data about the natural history of unruptured intracranial aneurysms are limited. All aspects of patient-specific factors of age, co-morbidity, and health condition and aneurysm-specific factors of size, location, and morphology should be taken into account for the treatment decision. Aneurysmal clipping has been the standard method for treatment. However, with the technological advances in devices, endovascular treatment has been used with increasing frequency. The selection of treatment method for an unruptured intracranial aneurysm should be individualized based on patient' s factors, aneurysmal factors, and facility and performance of centers.

Korean Recommendations

1. For patients with an unruptured intracranial aneurysm who are managed conservatively without treatment, treatment of high blood pressure, cessation of smoking, and regular angiographic follow-up, even without symptoms, are recommended (Level of Evidence III, Grade of Recommendation B).

2. Symptomatic unruptured intracranial aneurysms should be treated in principle. For patients at high risk of treatment because of co-morbid medical conditions, old age, or location and morphology of the aneurysm, the risks and benefits of treatment should be weighed for treatment decision.
3. Treatment is not generally recommended for asymptomatic epidural intracranial aneurysm (Level of Evidence III, Grade of Recommendation B).
4. Taking into account of the risks associated with treatment of asymptomatic unruptured intracranial aneurysm, treatment might be considered for patients who have a life expectancy of more than 10 years and have one or more of the following conditions:
   1) Aneurysm at high risk of rupture
   (1) Size of 5 mm or more (Level of Evidence III, Grade of Recommendation B).
   (2) Aneurysm located in the posterior circulation, anterior communicating artery, or posterior communicating artery (Level of Evidence IIB, Grade of Recommendation B).
   (3) History of previous subarachnoid hemorrhage (Level of Evidence IIb, Grade of Recommendation B).
   (4) Family history of aneurysm (Level of Evidence III, Grade of Recommendation B).
   (5) Aneurysm undergoing increase in size or change in morphology during follow-up (Level of Evidence IV, Grade of Recommendation C).
   (6) Patients with age less than 50 years, hypertension, and multiple aneurysms (Level of Evidence III, Grade of Recommendation B).
   (7) Aneurysm with high aspect ratio (the ratio of aneurysm height to neck width) or high size ratio (the ratio of aneurysm size to the parent artery size), or aneurysm with multilobule or bled (Level of Evidence III, Grade of Recommendation B).
   2) Patients who have anxiety or depression because of the diagnosis of aneurysm (Level of Evidence IV, Grade of Recommendation C).
5. It is recommended that the treatment decision for unruptured intracranial aneurysm should be determined after taking into account of patient-specific factors of age, co-morbidity, and health condition and aneurysm-specific factors of size, location, and morphology. The facility and performance of centers also should be considered for the selection of treatment method. In the decision-making process, the informed consent should be obtained after providing sufficient explanation to the patient or the patient' s family (Level of Evidence IV, Grade of Recommendation C).
6. Surgical aneurysm clipping and endovascular treatment yield comparable results. And the selection of treatment should be determined upon consideration of the risks of treatment and recurrence rate (Level of Evidence Ib, Grade of Recommendation A).
7. Long-term follow-up is recommended after treating unruptured intracranial aneurysm. In particular, for patients managed with endovascular treatment, angiographic follow-up is recommended to detect incomplete occlusion or recurrence (Level of Evidence IIb, Grade of Recommendation B).

CLINICAL RESEARCH CENTER FOR STROKE

Acute Stroke Management

뇌졸중임상연구센터
Clinical Research Center For Stroke

2.1 Stroke care system

2.1.1 Prehospital management and field treatment: EMS/119

Introduction

Stroke is a medical - or sometimes surgical- emergency. In a number of studies, use of the national emergency medical service (EMS/119) as an initial response to stroke was associated with a shorter time to hospital and a higher thrombolysis treatment rate compared with other responses. Training of the emergency medical service professionals and systemic patient management are critical to successful stroke care.

Korean recommendations

1. Use of the EMS/119 is recommended for transfer of a stroke patient to hospital (LOE: III, GOR: B).
2. The EMS team takes a stroke patient in the shortest time possible to a hospital that provides proper stroke care (GOR: GPP).

2.1.2 Stroke units and stroke centers

Introduction

A stroke unit or center is an independent treatment unit made up of multidisciplinary teams, facilities, and guidelines exclusively dedicated to stroke care. They have become increasingly significant for successful stroke care.

Korean recommendations

1. It is recommended that stroke patients be treated at a stroke unit or a stroke center (primary or comprehensive) (LOE: Ia, GOR: A).

2.2 Acute evaluation

2.2.1 History taking, physical / neurological exams, and lab tests

Introduction

Acute ischemic stroke is treatable only within a short period of time after onset. A prompt diagnosis and evaluation of the ischemic infarction is critical. Systemic protocols and teams dedicated for stroke care enable a fast decision making along the course of clinical diagnosis, diagnostic tests, and early treatment determination. History taking, physical examinations, and neurological examination represent core evaluations needed for clinical diagnosis. They are ultimately aimed at providing definite diagnosis and checking the patient against indications / contraindications of acute treatments such as recombinant tissue plasminogen activator (rt-PA). Since time is a critical variable in the emergency care, it is recommended that the number of tests for the diagnostic purpose should be limited.

Korean recommendations

1. Hospitals providing stroke care prepare the clinical guidelines for a prompt diagnosis and evaluation of stroke (LOE: IV, GOR: C).
2. The early tests for acute stroke include respiratory rate, pulse, blood pressure, and body temperature as well as neurological examinations (LOE: IV, GOR: C).
3. Use of NIHSS (the NIH Stroke Scale) is recommended for early evaluation of the stroke severity (LOE: III, GOR: B).
4. The basic diagnostic tests for stroke include complete blood counts, blood glucose, electrolytes, renal function, PT-INR, and aPTT (LOE: IV, GOR: C).
5. Clinical heart examinations and 12-lead ECG are performed in all stroke patients (LOE: III, GOR: B)
6. Simple chest X-ray may be selectively used in patients with acute ischemic stroke (LOE: IV, GOR: C)
7. The cerebrospinal fluid (CSF) test may be performed in patients suspected of having subarachnoid hemorrhage that is not detected on CT or MRI (LOE: IV, GOR: C).
8. Electroencephalography (EEG) is recommended in patients having symptoms suggestive of seizures as an early sign or a complication of stroke (LOE: III, GOR: B).

2.2.2 Emergency neuroimaging

Introduction

The brain imaging tests have become increasingly significant with the advance in acute stroke treatment. Findings on the size / location of the lesion, vessel status, and presence of hemorrhage influence the decision of short-term and long-term treatment strategy. They help to assess the salvageable area of ischemic brain tissue, vessels, and cerebral hemodynamics, and determine the target patients for reperfusion by enabling the risk evaluation for hemorrhage or by viewing of the vascular occlusion. CT and MRI may be selected as an early imaging tool.

Korean recommendations

1. A prompt brain imaging test should be performed in patients suspected of having acute stroke (GOR: GPP).
2. In most cases, non-enhanced CT provides critical information for treatment decision in the ER (GOR: GPP).
3. Use of the multi-modality CT or MRI is recommended since they help improve the diagnosis and treatment of acute ischemic cerebral infarction (LOE: Ib, GOR: A).
4. For the intra-arterial drug administration or intervention, the vascular imaging tests (CT angiography, MRA, conventional angiography, and vascular ultrasound) that provide cranio-cervical vascular information are needed (LOE: IIb, GOR: B).

2.3 Acute treatment

2.3.1 General supportive care

2.3.1.1. Airway, ventilator, and oxygen supply

Introduction

Adequate oxygen supply and respiration may be important to maintain the metabolic function of the ischemic penumbra. Infarctions involving large area of brain or brainstem might present with respiratory dysfunction, which could further lead to aspiration pneumonia, heart failure, pulmonary embolism, or aggravation of chronic lung disease. Early intubation for artificial ventilation may be needed in patients with severe respiratory distress, severe hypoxemia / hypercapnea, or impaired consciousness. The evidence is insufficient, however, to recommend a uniform oxygen supply in all patients with cerebral infarction.

Korean recommendations

1. Intubation or, if necessary, mechanical ventilation is recommended in patients with decreased consciousness and/or impaired respiration. Intubation may also be helpful in patients at risk of respiratory failure from bulbar palsy (LOE: IV, GOR: C).
2. A supplemental oxygen supply is not recommended in cerebral infarction without hypoxia (LOE: III, GOR: B).

2.3.1.2. Fever

Introduction

An elevated body temperature increases the metabolic rates, further aggravating the brain tissue damage in acute cerebral infarction. If fever arises in those patients, a thorough test for infection is essential. Adequate use of antibiotics and antipyretics is needed.

Korean recommendations

1. The body temperature of a patient with acute cerebral infarction should be maintained normal as far as possible (LOE: II, GOR: B).
2. If fever exists, the infection site and causative pathogens should be investigated to ensure a proper antibiotic treatment (LOE: IV, GOR: C).
3. If fever exists, reducing body temperature may be helpful (LOE: IV, GOR: C), and antipyretics may be used (LOE: IIa, GOR: B).

2.3.1.3. Cardiac rhythm

Introduction

Cardiac rhythm abnormality is found in up to 15 to 30% of the post-cerebral infarction patients. In most cases, however, it has been there as a risk factor, and the detection is

rather coincidental with the diagnosis of the infarction. There are reports, however, that if a certain area of brain is affected, a secondary cardiac abnormality such as arrhythmia follows. Heart failure, acute MI, and sudden death may be included in the clinical course of cerebral infarction. Maintaining a proper cardiac output, heart rate, and normal blood pressure is essential in the management of stroke.

Korean recommendations

1. Cardiac rhythm monitoring is considered during the acute phase of cerebral infarction (LOE: IV, GOR: C).

2.3.1.4. Blood pressure

Introduction

BP elevation is commonly observed during the acute phase of ischemic cerebral infarction. Proper BP monitoring and control is important. In the ischemic lesions, the autoregulation of cerebral blood flow is disturbed, letting the mean arterial pressure (MAP) have a direct impact on the cerebral blood flow. An abrupt reduction in BP should be avoided, therefore, to ensure an adequate cerebral perfusion. An excessive drop in BP during the acute phase of stroke, though rare, may be treated with fluid supply or inotropic agents.

Korean recommendations

1. For SBP ≤220 mmHg or DBP ≤120 mmHg in acute ischemic stroke, a deferral of aggressive BP lowering is recommended (LOE: IV, GOR: C).
2. If the thrombolytic therapy is under way, BP lowering agents can be used to lower SBP < 185 mmHg and DBP <110 mmHg (LOE: IV, GOR: C).
3. Though a uniform BP lowering is not recommended in acute ischemic stroke, an adequate BP reduction is needed in the following conditions that increase the risk for hypertensive complications: hypertensive encephalopathy, aortic aneurysm with renal artery invasion (LOE: Ia, GOR: A), heart dysfunction, aortic dissection, acute MI, acute renal failure, and intravenous heparin use (LOE: IV, GOR: C).
4. For hypotension occurring in acute stroke patients, the causal analysis is recommended. Hypovolemia, if present, may be corrected with saline supplementation. Correction is also recommended for arrhythmia that reduces cardiac output (LOE: IV, GOR: C).

2.3.1.5. Blood glucose

Introduction

In acute stroke patients, hyperglycemia may be induced by stress or acute illness even without history of diabetes. It might also represent new diagnosis of diabetes or aggravation of existing diabetes by acute illness. Hyperglycemia adversely affects the prognosis of cerebral infarction, whether the patient is diabetic or not, and might require a temporary insulin treatment. Hypoglycemia, on the other hand, might present symptoms similar to cerebral infarction. The differential diagnosis and treatment is needed.

2.3.1.6. Volume expansion, hemorheologic therapy

Introduction

Maintaining cerebral infusion is important to prevent a further infarction progression and to minimize damage to the ischemic penumbra. Some argue that hemodilution may reduce the infarction size by improving cerebral flow to the damaged brain tissue.

Korean recommendations

1. Evidence is insufficient for a uniform recommendation of hemodilution and volume expansion in all acute cerebral infarction patients to improve symptoms or prognosis. Their use may be considered in certain patients, however (LOE: IV, GOR: C).

2.3.2 Prevention and management of medical complications

2.3.2.1. Prophylaxis of deep vein thrombosis

Introduction

While the risk of deep vein thrombosis (DVT) increases with neurological impairment, its clinical expression (as pulmonary embolism, for example) is only in about 1%. Prevention is important since DVT represents an obstacle to recovery from stroke and rehabilitation, and might lead to severe respiratory symptoms.

Korean recommendations

1. Early rehabilitation may be useful for DVT prevention in acute stroke (LOE: III, GOR C).
2. In the high risk groups for DVT, subcutaneous heparin injection may be used, but the increased risk of bleeding should be considered (LOE: Ia, GOR: A). Low molecular weight heparin (LMWH) may be used in place of heparin (LOE: Ib, GOR: A).
3. Antiplatelets are also moderately effective in prevention of DVT, and they should be used in patients with acute cerebral infarction (LOE: Ia, GOR: A).
4. Though the effects of monotherapy with compressive stockings or pneumatic compression machines on DVT prevention are not clear, their use may be considered as an adjunctive to other treatments if hypercoagulability is suspected or in upper/lower limb paralysis (LOE: IIb, GOR: B).

2.3.2.2. Nutrition

Introduction

In many acute stroke patients, an adequate nutrition intake is hard to achieve because of dysphagia. Dietary nutrition is further limited in unconscious patients due to the risk of aspiration pneumonia. The resulting nutrition imbalance or malnutrition adversely affects the recovery of stroke patients.

Korean recommendations

1. In acute stroke patients, the screening for dysphasia and nutritional status should be performed as early as possible after admission (LOE: IIb, GOR: B).

2. For patients with an inadequate oral nutrition intake, a nasogastric tube should be used for supply of nutrients and medications. While treating dysphagia, periodic reevaluations is required to review the necessity for maintaining the tube (LOE: IIb, GOR: B).
3. Though efforts should be made to restore the nutritional balance in patients with malnutrition, a uniform use of dietary supplements in all stroke patients is not necessary (LOE: Ib, GOR: A).
4. Percutaneous endoscopic gastrostomy may be considered if the nasogastric tube is required for a long time or its maintenance is difficult for other reasons (LOE: IV, GOR: C).

2.3.2.3. Pressure sore

Introduction

Pressure sore is a complication of long-term hospitalization. Once developed, it is hard to treat and likely to prolong the hospitalization. Prevention is very important.

Korean recommendations

1. Frequent examinations for pressure sore are recommended in stroke patients(GOR: GPP).
2. Early mobilization may be helpful in prevention of pressure sore (GOR: C, LOE: IV).
3. If early mobilization is not possible, frequent position changes in bed or use of an air mattress may be considered (GOR: B, LOE: IIb).

2.3.2.4. Aspiration pneumonia

Introduction

Dysphagia in acute stroke often leads to aspiration pneumonia, which is a significant cause of death during the acute phase of stroke.

Korean recommendations

1. If fever arises in stroke patients, the evaluation for aspiration pneumonia is needed before treatment determination (GOR: GPP).
2. Before starting oral feeding, proper screenings (for dysphagia, for example) are needed to identify those at high risk of aspiration pneumonia (GOR: B, LOE: III).
3. If the risk is determined high, the nasogastric tube is recommended over oral feeding (GOR: C, LOE: IV).

2.3.2.5. Urinary tract infection

Introduction

Urinary tract infection or UTI is an important complication of acute stroke, which might adversely affect the neurological prognosis unless detected and treated early.

Korean recommendations

1. If UTI is confirmed, a proper antibiotic treatment is needed (GOR: GPP).
2. Prophylactic use of antibiotics for prevention of UTI is not recommended (GOR: GPP).
3. Bladder catheterization is recommended only if necessary for the shortest possible time (GOR: C, LOE: IV).

2.3.3 Thrombolysis

2.3.3.1. Intravenous thrombolysis

Introduction Revised DEC.2012

In ischemic stroke, ischemic brain damage progresses with time after thrombosis or embolism blocks the blood flow in the brain. Thrombolysis aims to reopen the blood vessel by dissolving the clot before the ischemic brain damage advances. In 1995, NINDS study confirmed that administering intravenous (IV) thrombolysis with tissue plasminogen activator (tPA) within three hours after the stroke onset improves the prognosis of patients with ischemic stroke. Since then, it has been the only approved treatment for acute ischemic stroke. However, as the 3-hour time window is too narrow, efforts have been made to extend the time window. In a pooled individual patient-level analysis of 4 major clinical trials, the benefit of IV tPA in the 3- to 4.5-hour window was suggested although the benefit decreased as time from onset to treatment initiation increased. The ECASS III trial to test the efficacy and safety of IV tPA in the 3- to 4.5-hour window confirmed the benefit of IV tPA treatment in the 3- to 4.5-hour window. Accordingly, the current updated guidelines revised the recommendations to extend the time window for IV tPA treatment up to 4.5 hours, reflecting the new evidences. However, the faster it is administered, the greater the effect, so efforts should be taken to treat patients as early as possible. Moreover, the eligibility criteria for IV tPA treatment in the 3- to 4.5 hour window slightly differs from those for treatment within 3 hours, so the differences should be noted.

Revised Korean recommendations

1. IV tPA is recommended for ischemic stroke patients within three hours after the symptom onset (the last known normal time; the last time the patient was seen normal) unless contraindicated. (Level of Evidence Ia, Grade of Recommendation A). Cerebral hemorrhage should be excluded on brain imaging, and other eligibility criteria are outlined in Table 1. -Revised from the previous guideline.
2. IV tPA within 3-hour window is also recommended for eligible patients aged 81 years or more (Level of Evidence Ib, Grade of Recommendation A). - New recommendation.
3. IV tPA is recommended for eligible patients presenting in the 3- to 4.5-hour window after the symptom onset (the last known normal time; the last time the patient was seen normal). (Level of Evidence Ia, Grade of Recommendation A). - New recommendation.
   * The benefit of IV tPA within 3- to 4.5-hour window is not well established for the following patients: 1) patients >80 years old, 2) those presenting extremely severe neurologic deficit (NIHSS score >25), 3) those having a history of both previous stroke and diabetes mellitus, and 4) those taking oral anticoagulant.
4. The increased risk of intracerebral hemorrhage associated with IV tPA should be noted (Level of Evidence Ia, Grade of Recommendation A).
5. Intravenous streptokinase is not recommended because of the high risk of bleeding (Level of Evidence Ia, Grade of Recommendation A).
6. The effects of intravenous thrombolytic drugs other than tPA (urokinase, tenecteplase, desmoteplase) in ischemic strokes is not established (Level of Evidence IV, Grade of Recommendation C).
7. The earlier the IV tPA is administered, the better the patient prognosis, so treatment should be initiated as quickly as possible after reviewing the eligibility criteria listed in Table 1 (Level of Evidence Ia, Grade of Recommendation A).
8. The method for administering IV tPA is outlined in Table 2 (Level of Evidence Ia, Grade of Recommendation A) - New recommendation.

Table 1. Eligibility criteria of IV tPA treatment

1. Ischemic stroke causing measurable neurological deficit
2. Ischemic stroke without spontaneously and rapidly improving symptoms
3. Caution needed for extremely severe neurologic deficit
4. Symptoms not caused by subarachnoid hemorrhage
5. No history of serious head trauma or stroke within previous 3 months
6. No history of acute myocardial infarction within previous 3 months
7. No history of gastrointestinal or urinary tract hemorrhage within previous 21 days
8. No history of major surgery within previous 14 days
9. No history of arterial puncture at noncompressible site within previous 7 days
10. No history of intracranial bleeding
11. Systolic blood pressure ≤185 mm Hg and diastolic blood pressure ≤110 mm Hg)
12. No evidence of serious hemorrhage or trauma (including fracture) onphysical examination
13. INR ≤1.7 for patients currently taking oral anticoagulant
14. Normal range of aPTT for patients receiving heparin within 48 hours
15. Platelet count ≥100,000 /mm3
16. Blood glucose ≥50 mg/dL (2.7 mmol/L)
17. No neurologic deficit due to seizure (Todd' s paralysis)
18. No multilobar infarction (hypodensity > 1/3 cerebral hemisphere) on CT
19. Understanding of patients or legally authorized representatives about the risk and benefit of treatment

Table 2. Administering Method for IV tPA

1. Infusion of 0.9 mg/kg over 60 minutes with 10% of the total dose as a bolus for 1 minute (maximum dose, 90 mg).
2. Admission to stroke unit or intensive care unit for monitoring.
3. Neurological assessments every 15 minutes during IV tPA infusion, every 30 minutes for the next 6 hours, and every hour for the next 16 hours.
4. If the patient develops severe headache, abrupt increase in blood pressure, nausea, or vomiting, stop the administration of IV tPA and conduct emergency CT.
5. Blood pressure measurement every 15 minutes during and after IV tPA infusion for the first 2 hours, every 30 minutes for the next 6 hours, and every hour for the next 16 hours.
6. Blood pressure control

1) If the systolic pressure is over 180 mm Hg or the diastolic pressure is over 105 mm Hg
- Administer 10 mg of labetalol intravenously over 1-2 minutes. If the blood pressure is not controlled, repeatedly administer 10 mg of labetalol in 10-20-minute intervals (maximum dose, 300mg).
- Alternatively, administer 10 mg of intravenous labetalol followed by continuous infusion 2-8 mg/min.

2) If the systolic pressure is over 230 mm Hg or the diastolic pressure is over 140 mm Hg
- Administer 10 mg of labetalol intravenously over 1-2 minutes. If the blood pressure is not controlled, repeatedly administer 10 mg of labetalol in 10-20-minute intervals (maximum dose, 300mg).
- Alternatively, administer 10 mg of intravenous labetalol followed by continuous infusion 2-8 mg/min.
- Alternatively, administer continuous infusion of intravenous nicardipine, starting with 5 mg/h. To titrate, increase the infusion rate by 2.5 mg/h every 5 minutes maximum rate, 15 mg/h).

2.3.3.2. Intra-arterial thrombolysis

Introduction

Revised: Dec 2012

Intra-arterial (IA) thrombolysis is a catheter-based reperfusion therapy by directly delivering fibrinolytics into or mechanically disrupting or removing the clot. Although IA thrombolysis has disadvantages of the accessibility at experienced centers and a longer time for treatment initiation, it has advantages of higher recanalization rates and a lower risk of systematic bleeding (in particular, mechanical thrombectomy that could avoid the use of pharmacological fibrinolytic agents). Accordingly, IA thrombolysis can be useful for patients who have failed to respond to or have contraindications to intravenous thrombolysis. Because of the difficulty conducting large-scale clinical trials, the evidence of IA thrombolysis has not been well established. However, a recently published meta-analysis analyzing earlier trials corroborates the benefit of IA thrombolysis. As IA thrombolysis is now being accepted as a treatment of significant evidences, we revised the recommendations for IA thrombolysis in acute ischemic stroke. Various mechanical devices such as MERCI device, Penumbra system, and EKOS microcatheter have been used in clinical practice. Recently stent retrievers such as Solitaire or TREVO have shown better results over MERCI device, and therefore the stent-assisted embolectomy is expected to be a mainstream technique of IA thrombolysis.

Revised Korean Recommendations

1. IA thrombolysis can be considered for patients who have occlusions in the middle cerebral artery or the internal carotid artery of $\leq$6 hours, or those who are contraindicated for intravenous thrombolysis (for example, recent surgery) (Level of Evidence Ia, Grade of Recommendation A). - Revisions made in the Level of Evidence and Grade of Recommendation.
2. The institution conducting IA thrombolysis should accommodate a rapid access to cerebral angiography and experienced interventionalists. Each institution is encouraged to define criteria of interventionalists who can perform IA thrombolysis (GPP). ? Revisions made in the Level of Evidence and Grade of Recommendation.
3. IA thrombolysis can be considered for patients who have occlusions in the posterior circulation such as the basilar artery, depending on the criteria of each institution (Level of Evidence III, Grade of Recommendation B). - Revisions made in the Level of Evidence and Grade of Recommendation.
4. In patients indicated for IV tPA, IV tPA should be administered first. For patients who have not responded to IV tPA, additional IA thrombolysis can be considered (Level of Evidence III, Grade of Recommendation B). - New recommendation.
5. Mechanical thrombectomy can be considered for patients presenting $<$ 8 hours with major ischemic strokes caused by large artery occlusions. Stent retrievers are preferred to other devices, but the selection of treatment method should be made by responsible interventionalists, taking into account of the patient' s conditions (Level of Evidence Ib, Grade of Recommendation A). -New recommendation.

2.3.4 Antiplatelet agents

Introduction

Ischemic stroke is mostly due to cerebral vascular occlusion by thrombus or embolus. Use of aspirin during the acute phase is expected to decrease death, disability, recurrence, and other cardiovascular events associated with ischemic stroke.

Korean recommendations

1. In the hemorrhage-excluded, acute ischemic stroke patients, the oral administration of aspirin should start within 24 to 48 hours of onset (the loading dose 160-300mg) (LOE: Ia, GOR: A).
2. Aspirin can not replace acute interventions including IVT (LOE: Ia, GOR: A).
3. Aspirin should not be taken within 24 hours of thrombolysis (LOE: Ia, GOR: A).
4. Intravenous injection of the glycoprotein IIb/IIIa receptor antagonists, including abciximab, is not recommended in patients with acute ischemic stroke (LOE: Ib, GOR: A).

2.3.5 Anticoagulants

Introduction

Though anticoagulants are widely used for the prophylactic treatment of ischemic stroke, their usefulness in acute patients is still controversial. No consensus has been made on what to choose, when and how to administer, how much to give, or how long. Evidence from the large-scale, controlled studies so far has been insufficient to support use of anticoagulants as a treatment of acute ischemic stroke.

Korean recommendations

1. There is no scientific evidence on the usefulness of heparin used within 48 hours of ischemic cerebral infarction. It might increase the risk of bleeding, compared with aspirin (LOE: Ia, GOR: A).
2. LMWH or heparinoids is not recommended as an early treatment of cerebral infarction (LOE: Ia, GOR: A).
3. Use of anticoagulants within 24 hours of rt-PA administration is not recommended (LOE: IIa, GOR: B).

2.3.6 Neuroprotectants

Introduction

A number of different neuroprotectants whose effects were shown in animal experiments have failed to demonstrate efficacy in clinical trials. The large-scale randomized controlled trials (RTCs) of NMDA receoptor antagonists, calcium channel blockers, magnesium, free radical scavengers, cell membrane stabilizers, and therapeutic hypothermia all have failed to prove efficacy. While the causal anlaysis is needed, clinical trials are under way to investigate the possibility of a shortened treatment duration or improved efficacy of combinations.

Korean recommendations

1. Treatment with neuroprotectants during the acute phase of ischemic cerebral infarction is not recommended in general (LOE: Ia, GOR: A).

2.3.7 Treatment of neurologic complications

2.3.7.1. ICP elevation, brain edema and hemorrhagic transformation

Introduction

Brain edema is usually seen within 24 to 48 hours of cerebral infarction. Edema in a gross infarction invading the cerebral hemisphere or cerebellum causes ICP elevation and herniation, leading to loss of consciousness and even death in severe cases.

Korean recommendations

1. A gross cerebral infarction invading the cerebral hemisphere or cerebellum is highly likely to cause brain edema and ICP elevation. A close, intensive monitoring is reasonable to reduce the edema and prevent a neurological aggravation (LOE: III, GOR: B).
2. If hydrocephalus is caused by the cerebellar infarction or for other reasons, the extraventricular drainage is needed to reduce ICP (LOE: III, GOR: B).
3. Surgical decompression is needed if the signs of brainstem compression arise in a large cerebellar infarction (LOE: III, GOR: B).
4. Different medical decompressions, including osmotherapy, may be used to treat the malignant edema following cerebral infarction. The effects of hyperventilation are short-lasting, and the prognosis is unclear. Medical decompressions may delay the need for surgery (LOE: III, GOR: B).
5. Surgical decompression for malignant edema caused by the hemispheric infarction might save lives as well as achieving neurological improvement. Determinants of the surgery include age and location of the lesion (the non-dominant or dominant hemisphere). Surgery may be recommended in severe patients, but a thorough discussion with the patient is needed about the risk of unfavorable outcomes such as lifetime disability (LOE: IIa, GOR: B).
6. No particular treatment exists for asymptomatic hemorrhagic transformation following cerebral infarction. Symptomatic hemorrhagic transformation is treated according to the treatment guidelines for cerebral hemorrhage. BP control may be considered to reduce the risk of hemorrhagic transformation following thrombolysis or carotid stent placement (LOE: IV, GOR: C).
7. Use of the routine-dose or high-dose corticosteroids aimed at ICP reduction is not recommended in cerebral infarction because of uncertain effects and the increased risk of infection (LOE: Ib, GOR: A).

2.3.7.2. Seizures

Introduction

Seizures in acute stroke are mostly focal and develop within 24 hours of the onset. Secondary generalized seizures are not unusual. While intermittent seizures are believed unassociated with the stroke prognosis, status epilepticus, though rare, might threaten lives.

Korean recommendations

1. A uniform anticonvulsant prophylaxis is not considered in patients with no post-stroke seizures (LOE: IV, GOR: C).
2. Early seizures in acute stroke may be treated in the same way as the seizures occurring in the acute phase of other neurological disorders (LOE: IV, GOR: C).
3. The anticonvulsant treatment may be considered if early seizures are likely to worsen the stroke or progress into status epilepticus (LOE: IV, GOR: C).
4. For a lobar hemorrhage, a prophylactic use of anticonvulsants for about 1 month and a gradual discontinuation thereafter may be considered if no seizure is observed (LOE: IV, GOR: C).

2.4 Treatment of intracerebral hemorrhage

2.4.1 Medical treatment of intracerebral hemorrhage

2.4.1.1. ICP control

Introduction

According to the Western reports, cerebral hemorrhage accounts for 10-15% of total stroke, with 30-day mortality of 35-52% and half the deaths occurring within the first 2 days. ICP elevation and brain edema following cerebral hemorrhage are associated with high mortality. The brain tissue damage and shifts following hemorrhage induces ICP elevation. Further clinical aggravation is caused by hemorrhage expansion, edema or ischemia in the surroundings, hydrocephalus, or secondary intracranial hemorrhage. In some patients with an elevated ICP and decreased consciousness, close ICP monitoring is needed. Medical decompression needs to take precedence over surgery.

Korean recommendations

1. Treatment and monitoring at the intensive care unit (ICU) is recommended in acute hemorrhage patients because of the need for ICP elevation monitoring, BP control, intubation, and mechanical ventilation (LOE: III, GOR: B).
2. For control of an elevated ICP, a gradual treatment is considered. The patient head should be elevated by about 30° for a start. Limited use of analgesics and/or sedatives may be considered in patients with pain and/or unstable conditions (LOE: IV, GOR: C).
3. A more aggressive ICP control includes use of mannitol and hypertonic saline solution, CSF drainage via the ventricular catheter, neuromuscular blockade, and hyperventilation. In general, maintaining CPP at ≥70 mmHg is recommended along with a close monitoring of ICP and blood pressure (LOE: IV, GOR: C).

2.4.1.2. Medical treatment of the anticoagulant-associated intracerebral hemorrhage

Introduction

If intracerebral hemorrhage occurs in patients on anticoagulants such as warfarin or heparin, the increase in PT-INR (prothrombin time-international normalized ratio) or aPTT (activated partial thromboplastin time) is correlated with the hematoma enlargement and prognosis. A prompt correction is imperative.

Korean recommendations

1. In the heparin-induced intracerebral hemorrhage, heparin should be discontinued immediately. Protamine sulfate may be considered to reverse the effects of heparin (LOE: IV, GOR: C).
2. In the warfarin-induced intracerebral hemorrhage, warfarin should be discontinued immediately. Intravenous vitamin K may be considered to reverse the effects of warfarin,

together with the coagulation factor replacement (LOE: IV, GOR: C).
3. Prothrombin complex concentrates, factor IX complex concentrates, and recombinant factor VIIa normalize the INR more rapidly with a smaller volume, compared with fresh frozen plasma. They may be used to correct the clotting abnormalities in intracerebral hemorrhage, but also present the risk of thromboembolism. Fresh frozen plasma may be recommended as an alternative, but it requires a slow, large-volume infusion (LOE: IV, GOR: C).

2.4.1.3. Blood pressure management after intracerebral hemorrhage

Introduction

BP control in acute cerebral hemorrhage should be individualized to presence / absence of chronic hypertension, ICP elevation, age, cause of hemorrhage, and the time of onset in each patient. Despite some disagreement, treating hypertension is generally recommended in acute cerebral hemorrhage in order to prevent re-bleeding from the ruptured small arteries.

Korean recommendations

1. The following guidelines are recommended for BP control in acute intracerebral hemorrhage (LOE: III, GOR: B).

Table 1. Treatment guidelines for hypertension in spontaneous intracerebral hemorrhage

1. For SBP > 200mmHg or MAP > 150mmHg, measure BP every 5 minutes, and lower BP aggressively with intravenous antihypertensives.
2. For SBP > 180mmHg or MAP > 130mmHg with (suspected) ICP elevation, maintain CPP at > 60-80mmHg, and lower BP with intravenous antihypertensives (bolus or infusion).
3. For SBP > 180mmHg or MAP > 130mmHg without evidence of ICP elevation, clinically evaluate the patient every 15 minutes, and control BP with intravenous antihypertensives (bolus or infusion) to maintain MAP 110mmHg or SBP/DBP 160/90mmHg.

Table 2. Drugs that can be used for BP control in spontaneous intracerebral hemorrhage

Drug name	Bolus dose	Infusion rate
Labetalol	5-20mg, every 15 minutes	2mg/min (up to 300mg/day)
Nicardipine	No indication	5-15mg/hour
Esmolol	250㎍/Kg, loading dose	25 - 300 ㎍/Kg per minute
Enalapril	1.25 - 5 mg, every 6 hours	No indication
Hydralazine	5 - 20mg, every 30 minutes	1.5 - 5 ㎍/Kg per minute
Nipride	No indication	0.1 - 10 ㎍/Kg per minute
Nitroglycerine	No indication	20 - 400 ㎍/min

For enalapril, the first test dose of 0.625mg is recommended to avoid excessive drop in BP.

2.4.1.4. Seizure prevention and treatment

Introduction

In general, the rate of epilepsy is higher following intracerebral hemorrhage than ischemic stroke. Epilepsy requires a proper treatment since it might worsen the neurological conditions or increase the midline shifting.

Korean recommendations

1. Post-cerebral hemorrhage seizures should warrant use of proper anticonvulsants (LOE: Ib, GOR: A).
2. A short-term use of anticonvulsants immediately following a lobar hemorrhage may decrease the risk of early seizures and is recommended (LOE: IIa, GOR: B).
3. Anticonvulsants used in cerebral hemorrhage should be gradually discontinued if no recurrence is observed. In case of recurrence, a chronic therapy may be considered (LOE: IV, GOR: C).

2.4.2 Surgical treatment of intracerebral hemorrhage

Introduction

The ideal surgical treatment of intracerebral hemorrhage involves minimization of the brain damage associated with the surgery itself and a fast removal of the largest hematoma possible. Many different surgery methods, either tried or being developed, are available. In some cases, conservative treatment might have priority over surgery, depending on the location and size of the hemorrhage. Clear guidelines are needed in this regard. Though guidelines are also needed on an intracerebral hemorrhage secondary to cerebral aneurysm or cerebral arteriovenous malformation that requires surgical removal too, only primary intracerebral hemorrhage is focused in the present CPG.

Korean recommendations

1. If cerebral herniation is suspected or if loss of consciousness is rapid, early craniotomy may be considered (LOE: IV, GOR: C).
2. Craniotomy is considered for a lobar hemorrhage located within 1 cm from the surface with the consciousness level of GCS 9-12 (LOE: IIb, GOR: B).
3. Craniotomy is recommended for a cerebellar hemorrhage of $\geq$ 3cm in diameter or for symptoms suggestive of the brainstem compression or hydrocephalus (LOE: IIb, GOR: B).
4. For hemorrhages located deep inside the brain, a non-craniotomy surgery may be considered (LOE: IV, GOR: C).
5. For intraventricular hemorrhages, thrombolysis via the ventricular puncture may be considered (LOE: IV, GOR: C).

2.5 Rehabilitation in acute stroke

2.5.1 Timing of rehabilitation

Introduction

Early rehabilitation in stroke is known to prevent complications such as DVT, joint contracture, and pressures sore. It also improves functional recovery in the transfer activity or activity of daily living. Rehabilitation should begin, therefore, once the patients regain medical and neurological stabilization. The exact timing might be influenced by the severity of stroke and neurological status in each patient. Therapy intensity should be individualized, too.

Korean recommendations

1. Rehabilitation therapy in an acute stroke patient should begin as early as possible once the patient is medically stabilized (LOE: Ia, GOR: A).

2.5.2 Intensity of rehabilitation

Introduction

Intensity of the post-stroke rehabilitation might be affected by variables such as patient compliance, degree of the brain damage, medical stabilization, and cognitive / motor impairment. While determining the intensity is important, it is difficult to standardize the intensity or to quantify different components of the rehabilitation therapy.

Korean recommendations

1. In stroke patients, an adequate rehabilitation therapy within the patient adaptability is recommended for functional recovery (LOE: Ia, GOR: A).
2. A continuous and repetitive use of the skills learned from rehabilitation is recommended (LOE: Ia, GOR: A).

2.5.3 Underlying approach to rehabilitation

Introduction

Many different rehabilitation techniques have been tried to reduce the impairment with and improve the functions for daily activities. They can be classified by the type of stimulations, specificity of trainings, or difference in the learning principles applied. It is very significant that all members of the rehabilitation team recognize the importance of a consistent approach to rehabilitation and to provide it in a way to maximize the functional recovery. Motor re-learning and many other techniques are currently available, but comparative analysis is difficult due to the wide variability in the makeup or outcomes of different rehabilitation techniques.

Korean recommendations

1. An individualized combination and application of the rehabilitation techniques including motor re-learning, neurophysiological approach, and biomechanics is recommended for motor function improvement (LOE: Ia, GOR: A).
2. Involvement of patients and caregivers in the rehabilitation goal setting is recommended (LOE: IIb, GOR: B).
3. Rehabilitation goals should be set both in the short and long terms. Achievement evaluation and goal resetting are considered (LOE: IV, GOR: C).

2.5.4 Prevention of complications

Introduction

Common post-stroke complications include pressure sore, aspiration pneumonia, joint contracture, falls and fractures, and pain. Once developing, they undermine rehabilitation, adversely affecting the prognosis. An effective prevention of potential complications will contribute to a great degree to improving the outcomes of rehabilitation.

Korean recommendations

1. The post-stroke pressure sore compromises functional recovery. Preventive measures are reasonable (LOE: III, GOR: B).
2. Periodic skin evaluations, right postures, and frequent position changes are considered for prevention of pressure sore (LOE: IV, GOR: C).
3. Maintaining the right postures is recommended for prevention of the post-stroke joint contracture (LOE: Ib, GOR: A).
4. Early mobilization is recommended for prevention of the post-stroke complications including joint contracture, aspiration pneumonia, central pain, and DVT (LOE: III, GOR: B).
5. Risk evaluation for falls and fractures is recommended in stroke patients (GOR: GPP).
6. Evaluation of the pain arising in stroke patients is needed (GOR: GPP).

CLINICAL RESEARCH CENTER FOR STROKE

Secondary prevention of stroke

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3.1. Risk factor management

3.1.1 Hypertension

Introduction

Primary prevention of stroke by hypertension treatment was shown to be 30 to 40% risk reduction of stroke in randomized controlled trials (RCTs).[1] Nonetheless, evidence is relatively insufficient for hypertension treatment aimed at secondary prevention of stroke.[1,2] A large-scale meta-analysis of the RCTs showed that hypertension treatment in stroke patients significantly lowered the mortality and recurrence of stroke and other cardiovascular events.[2]

Korean recommendations

1. In patients with stroke or TIA, antihypertensive treatment beyond the hyperacute phase reduces recurrent stroke and other cardiovascular events (LOE: Ia, GOR: A). The benefit of antihypertensive treatment is independent of prior history of hypertension. Adequate BP control is therefore recommended in all patients with stroke (LOE: Ib, GOR: A).
2. Determination of the antihypertensives and target BP should be individualized after taking into account of characteristics of patient such as steno-occlusion in intra- and extracranial vessels, diabetes, and renal disease (LOE: IV, GOR: C).
3. Although selection of the antihypertensives after stroke or TIA is still controversial because of insufficient evidence,,combination therapy of ACE inhibitors with diuretics may be considered (LOE Ib, GOR: A).
4. For an adequate BP control, drug therapy should be accompanied by lifestyle modifications (LOE: IV, GOR: C).

3.1.2 Diabetes

Introduction

The prevalence of diabetes is 15 to 33% of patients with ischemic stroke.[1,2] Diabetes is an important predictor of stroke recurrence,[3] and is also known to be highly associated with the multiple lacunar infarction.[4]

Several clinical trials have shown that blood glucose control reduced the risk of microvascular complications.[5,6] Accordingly, most of practice guidelines for secondary prevention of stroke and cardiovascular events are recommending blood glucose control. Evidence is limited, however, on the effect of blood glucose control on macrovascular complications.

Korean recommendations

1. For prevention of microvascular (LOE: Ia, GOR: A) and macrovascular (LOE: IIa, GOR: B) complications in stroke patients with diabetes, rigorous glucose control to near normal level is recommended.
2. A target HbA1c level of 7% or less would be reasonable (LOE: IIb, GOR: B).

3.1.3 Hyperlipidemia

Introduction

Hyperlipidemia is an important risk factor of coronary arterial disease (CAD), but its association with stroke has not been clear.[1] The diverse stroke mechanisms in addition to the similar one to CAD mechanism might attribute to this unclear association. For hemorrhagic stroke, a number of cohort studies have suggested that low cholesterol levels were associated with an increased incidence and mortality of hemorrhagic stroke.[2,3] The suggestion is particularly notable for Korea that has more hemorrhagic stroke patients compared with western countries. On the other hand, hyperlipidemia is considered an important risk factor of ischemic stroke, particularly for atherosclerotic stroke, as demonstrated by many statin clinical trials.[4,5] In addition to reducing cholesterol levels, statins might have pleiotropic effects.

Korean recommendations

1. Hyperlipidemia in patients with TIA or ischemic stroke should be treated. For patients with atherosclerotic ischemic stroke or in ischemic stroke with CAD co-morbidity, treatment should follow the NCEP-ATP III guidelines. Lifestyle modification, diet control, and drug therapy should be combined. For drug therapy, use of statins is recommended (LOE: Ia, GOR: A).
2. In symptomatic atherosclerotic ischemic stroke or ischemic stroke coexisting with CAD, the target LDL cholesterol is $<$ 100mg/dL (LOE: Ia, GOR: A).
3. For high risk patients with multiple risk factors, a more aggressive treatment might be considered (LOE: Ia, GOR: A).

3.1.4 Smoking

Introduction

Smoking is a major independent risk factor for ischemic stroke[1,3] in all ages, genders, and races.[1,2] Compared with non-smokers, the risk of stroke almost doubles in smokers.[1] The mechanism for the increased risk of stroke includes hemodynamic changes[4] and atherosclerotic vascular stenosis.[5,6]

Korean recommendations

1. Smoking cessation should be strongly recommended in stroke patients who smoke (LOE: IV, GOR: C).
2. Avoidance of secondary smoking should also be recommended in stroke patients (LOE: IIb, GOR: B).

3.1.5 Alcohol

Introduction

Alcohol drinking is one of the independent risk factors for stroke. Hypertension, hypercoagulability, drop in cerebral blood flow, and atrial fibrillation might be related to the increased risk.

Korean recommendations

1. Stroke patients with heavy alcohol consumption should be recommended to stop or to reduce their drinking to less than 1 (for non-pregnant women) or 2 (for men) drinks per day (LOE: IV, GOR: C).

3.1.6 Obesity

Introduction

Obesity and overweight are considered to be associated with stroke. The increase of stroke risk is proportional to the increase of obesity.

Korean recommendations

1. Weight gain is associated with the increased risk of stroke in a dose-response relationship. An aggressive weight reduction is recommended in the overweight or obese patients (LOE: IV, GOR: C).

3.1.7 Physical activity and exercise

Introduction

Studies have suggested that physical activity might be inversely related to the risk of stroke, but data from well-designed controlled trials are lacking. Physical activity and exercise are known to curb the risk of stroke by reducing the risk factors.

Korean recommendations

1. Physical activity and exercise might reduce the risk of stroke through blood pressure reduction, weight loss, and changes in blood cholesterol levels. Therefore, regular exercise is recommended (LOE: IV, GOR: C).

3.1.8 Diet

Introduction

Numerous studies have shown that dietary habits are associated with the risk of stroke. A sufficient intake of fruits and vegetables is known to reduce the risk of stroke. Minerals intake such as high sodium and low potassium intake are also associated with the increased stroke risk.

Korean recommendations

1. Reducing daily sodium intake and increasing potassium intake is recommended for stroke prevention (GOR: GPP).
2. A sufficient intake of fruits and vegetables may be beneficial for stroke prevention (GOR: GPP).

3.1.9 Hyperhomocysteinemia

Introduction

Hyperhomocysteinemia might contribute to the development of atherosclerosis that leads to stroke and CAD. It is not clear, however, whether vitamins such as folic acid that reduce blood homocysteine levels decrease the risk of stroke.

Korean recommendations

1. For ischemic stroke or TIA patients with hyperhomocysteinemia, homocysteine-lowering vitamins might be considered, given their low cost and treatment-associated risk as compared to those of other risk factors control. (LOE: IV, GOR: C).

3.2. Antithrombotic therapy for noncardioembolic stroke or TIA

3.2.1 Antiplatelet therapy

3.2.1.1. Aspirin

Introduction

Use of the low-dose aspirin is known effective in prevention of the thrombotic and embolic cerebral infarction. The acetyl group of aspirin binds to platelet membranes, irreversibly inhibiting cyclooxygenase and thromboxane A2 synthesis. Aspirin exerts effects, via these mechanisms, to prevent the recurrence of occlusive arterial diseases such as MI, cerebral infarction, and peripheral vascular disease.

Korean recommendations

1. Aspirin (50-300mg daily) can be recommended for prevention of recurrent ischemic symptoms in patients with noncardioembolic ischemic stroke and TIA (LOE: Ia, GOR: A).

3.2.1.2. Thienopyridines

Introduction

Revised: Mar 2010

Ticlopidine and clopidogrel are thienopyridine antiplatelets used for secondary prevention of stroke in patients with non-cardioembolic ischemic stroke. They can be used as an initial therapy for secondary prevention along with aspirin monotherapy. Since ticlopidine is potentially associated with serious complication of neutropenia, clopidogrel has a better safety profile.

Korean recommendations

1. Clopidogrel monotherapy may be an initial therapy in noncardioembolic ischemic stroke, along with aspirin monotherapy and the aspirin plus extended-release dipyridamole combination (LOE: Ib, GOR: A).
2. Clopidogrel and other alternatives are recommended in patients with aspirin hypersensitivity (LOE: Ib, GOR: A).
3. Although ticlopidine might be superior to aspirin for secondary stroke prevention (LOE: 1b, GOR: A), caution is required, however, for the risks of neutropenia (LOE: Ib, GOR: A).

3.2.1.3. Other antiplatelet agents: triflusal, dipyridamole, and cilostazol

Introduction

Revised: Apr 2012

For the secondary prevention of non-cardioembolic ischemic stroke, use of antiplatelet agent is

strongly recommended. In addition to aspirin and clopidogrel, triflusal and cilostazol have approved and are being widely used in clinical practice in Korea. Triflusal and cilostazol differ from aspirin or clopidogrel in their mechanisms of action and binding sites, and they have been reported to have lower risks of bleeding. Another antiplatelet agent, dipyridamole combined with aspirin has shown a greater efficacy than aspirin alone for the secondary stroke prevention.
After the publication of the first edition of the Korean clinical guidelines for stroke, a large randomized clinical trial and a meta-analysis comparing cilostazol and aspirin for the secondary stroke prevention were reported in 2010 and 2011. The results of these studies, being published recently, have not been yet reflected in foreign guidelines. However, given that the ethnicity of the studied population was similar to Korean population and that cilostazol are being widely used in Korea, the writing committee decided to revise the recommendations of cilostazol use for the secondary stroke prevention.

Revised Korean Recommendation

1. Cilostazol monotherapy can be used for the secondary stroke prevention in patients with non-cardioembolic stroke - particularly in patients with lacunar infarction (Level of Evidence Ia, Grade of Recommendation A). - New recommendation.
2. Extended-release dipyridamole combined with low-dose aspirin is an acceptable option for initial therapy for the secondary stroke prevention (Level of Evidence Ib, Grade of Recommendation A).
3. Triflusal can be considered for the secondary stroke prevention in patients who are not suitable for aspirin or clopidogrel (Level of Evidence Ib, Grade of Recommendation A) - Revised from the previous guideline.
4. Cilostazol or triflusal may be recommended for the secondary stroke prevention in patients at high risk of bleeding, including cerebral hemorrhage. (Level of Evidence Ib, Grade of Recommendation A). - Revised from the previous guideline.

3.2.1.4. Antiplatelet combination therapy

Introduction

Antiplatelets with different mechanisms of action have been combined to prevent more effectively the recurrence of noncardioembolic ischemic stroke or TIA. While the aspirin plus dipyridamole combination significantly decreased the recurrence of ischemic stroke and TIA, the clopidogrel plus aspirin combination has shown rather disappointing results of increased bleeding complications except for in patients who have both ischemic stroke and ischemic heart disease. Research is still ongoing to identify a better antiplatelet combination that could provide a more effective prevention of the recurrence and that can be used for patients who had stroke during antiplatelet monotherapy.

Korean recommendations

1. Compared with the aspirin monotherapy, the aspirin plus extended release dipyridamole combination may be more effective in preventing the recurrence of noncardioembolic ischemic stroke or TIA (LOE: Ia, GOR: A).
2. The clopidogrel + aspirin combination may be effective in secondary prevention of stroke in some stroke patients with CAD (unstable angina or non Q-wave MI). The risk of intracranial hemorrhage should be considered, however (LOE: Ia, GOR: A).
3. Cilostazol may be considered in patients with symptomatic intracranial arterial stenosis (LOE: III, GOR: B).

3.2.2 Anticoagulation

Introduction

Previous studies have investigated whether anticoagulants have an equal or greater efficacy in preventing secondary stroke when compared to antiplatelets in patients with noncardioembolic ischemic stroke or TIA. However, so far, clinical trials of oral anticoagulants have failed to demonstrate a superior efficacy to the antiplatelets in secondary stroke prevention while showing higher rates of serious bleeding complications.

Korean recommendations

1. For prevention of the recurrent noncardioembolic ischemic stroke or TIA, antiplatelets are recommended over oral anticoagulants (LOE: Ia, GOR: A).

3.2.3 Use of antiplatelets in specific conditions

3.2.3.1. Recurrent ischemic stroke during antiplatelets use

Introduction

If ischemic stroke recurs in patients already taking antiplatelets, the acceptable treatment options include a switch to other antiplatelets with different modes of action or add-on of a new antiplatelet. The decision requires a comprehensive review of data of efficacy and side effects which were reported by recent clinical trials of combination antiplatelet therapies Selection of antiplatelets should be individualized based on risk factors, clinical characteristics, and drug tolerability of each patient.

Korean recommendations

1. Evidence is lacking for increasing aspirin dose in patients with recurrent ischemic stroke who have been already taking aspirin. Also, data are lacking for switching to an another antiplatelet or combination therapy in these patients. Therefore, selection of antiplatelet(s) should be individualized based on patients' clinical characteristics and drug-specific risks (LOE: IV, GOR: C).

2. Based on physician's discretion and individual patients' profiles, the fixed-dose combination of aspirin and extended release dipyridamole may be used following stroke recurrence in patients with non-cardioembolic stroke who are already taking aspirin for secondary prevention. If the extended release dipyridamole can not be used, clopidogrel monotherapy may be used as an alternative. Data for use of other antiplatelets in this clinical setting are insufficient (LOE: IV, GOR: C).
3. For patients with non-cardioembolic ischemic stroke who have been already taking non-aspirin antiplatelets, data from clinical trials are lacking to recommend a specific antiplatelet therapy for secondary stroke prevention (LOE: IV, GOR: C).

3.2.3.2. Ischemic stroke with cerebral hemorrhage

Introduction

There is no clear evidence on the efficacy and safety of the antithrombotics in patients with ischemic stroke coexisting with hemorrhage. Cerebral infarction can develop in patients with a previous cerebral hemorrhage, and the post-thrombolysis cerebral hemorrhage may develop in relation to the previous hemorrhage. The uncertainty of clinical evidence spells the need for further clinical studies. In patients with AF coexisting with a lobar hemorrhage or a deep hemorrhage, use of anticoagulants should weigh between the recurrence of hemorrhage and the risk of ischemia, with the greatest concern given to the patient quality of life. Use of antiplatelets following cerebral hemorrhage should be considered only in those at low risk of re-bleeding.

With the advance in the brain imaging technology, cerebral microbleeds are increasingly detected by the low signal intensity lesions on the gradient-echo MRI. In most cases, they are suggestive of clinically asymptomatic microvascular bleedings.[1] Cerebral microbleedings show a widely varying prevalence between the Asians and non-Asians, with the incidence increasing in the advanced ages or hypertension.[2,3] The association of the antithrombotic treatment with cerebral microbleeds is still controversial, and further prospective research is needed.

Korean recommendations

1. Determining whether to resume the antithrombotic treatment or not following cerebral hemorrhage should be based on the risk of thrombosis, recurret hemorrhage, and the over all risk profile in each patient (LOE: IV, GOR: C).
2. In patients with the anticoagulation-associated cerebral hemorrhage, the angicoagulants might be switched into antiplateltes in patients with low risk of recurrent thromboembolism or high risk of bleeding tendency. The antocoagulation therapy should resume, however, if the

risk of cerebral emolism is clearly high. Timing of the re-administration may be 7 to 10 days later from the cerebral hemorrhage (LOE: III, GOR: B).

3. Reliable studies about the relation between microbleeds and antithrombotics have not been reported. Therefore, the restrictions for using antithrombotics in patients with microbleeds on MR imaging should not be necessary (LOE: IV, GOR: C).

3.3. Antithrombotic therapy for cardioembolic stroke or TIA

3.3.1 Anticoagulants

Introduction

While cardioembolic stroke is shown to represent about 20% of ischemic stroke in western countries,[1] the prevalence of cardioembolic stroke from hospital-based stroke registry in Korea is reportedly lower.[2] Though the exact pathologic mechanism in each patient is hard to identify, cardioembolic stroke is generally suspected in ischemic stroke patients with a heart abnormality associated with a high risk of embolism. A list of such conditions is provided in the Table below. The patients with these cardiac conditions have been predicted to show the annual rate of ischemic stroke $\geq$2%[3].

Table. Cardiac conditions to increase the risk of ischemic stroke [3]

- Left atrial thrombus
- Left ventricular thrombus
- Atrial fibrillation
- Paroxysmal atrial fibrillation
- Sick sinus syndrome
- Sustained atrial flutter
- Recent myocardial infarction, within 1 month
- Rheumatoid mitral or aortic valve disease
- Bioprosthetic and mechanical heart valves
- Chronic myocardial infarction with a low ejection fraction of less than 28%
- Symptomatic congestive heart failure with an ejection fraction of less than 30%
- Dilated cardiomyopathy
- Nonbacterial thrombotic endocarditis

Korean recommendations

1. Because patients with stroke or TIA coexists with potential sources of cardioembolism might have higherpossibility of recurrent cardioembolic stroke or TIA, unless contraindicated, warfarin treatment (INR 2.0-3.0) should be recommended (LOE: III, GOR: C, GPP).

3.3.2 Antiplatelet therapy or combination therapy

Introduction

Warfarin is known as the first-line preventive treatment for cardioembolic stroke, especially in patients with AF. If the patients are contraindicated to anticoagulation or if ischemic stroke recurs despite an adequate anticoagulation therapy, the following options may be considered; increasing the anticoagulation strength, switching to antiplatelets, or combining with antiplatelets.

Korean recommendations

1. In patients with cardioembolic ischemic stroke or TIA in whom the anticoagulation therapy can not be used, aspirin can be considered for secondary prevention (GOR: GPP).

3.3.3 Treatments for stroke patients with other specific conditions

3.3.3.1. Atrial fibrillation

Introduction

About 16% (11% to 29%) of cerebral infarction is reported attributable to nonvalvular AF in western countries.[1-4] The prevalence rate is relatively low in Korea at 8.4%, according to the hospital-based epidemiological data published in 1993 in Korea.[5] Nonetheless, stroke occurrence in AF patients is reported at an annual rate of ≈4.5%,[6] and the rate of recurrence is particularly high at 12% in those with previous stroke due to AF.[7] Risk factors such as advanced age, congestive heart failure, hypertension, diabetes, and previous thromboembolism further increases the risk. AF now has a greater implication than ever before in rapidly aging society including Korea since its prevalence markedly increases with age.[8]

Korean recommendations

1. Warfarin treatment (INR 2.0 - 3.0) is recommended, unless contraindicated, in patients with ischemic stroke or TIA coexisting with sustained or paroxysmal AF (LOE: Ia, GOR: A).
2. If anticoagulants can not be used, aspirin can be used instead (LOE: Ia, GOR: A). A recommended daily dose of aspirin is 325mg. In Korea, a prescribable dose of 300mg may be considered (LOE: IV, GOR: GPP).
3. For the recurrence of ischemic stroke or TIA in the AF patients already receiving adequate anticoagulation therapy, increasing the therapeutic target to INR 2.5-3.5 or initiating a combination with antiplatelets may be considered (LOE: IV, GOR: C).

3.3.3.2. Congestive heart failure

Introduction

Cardiomyopathy with a low left ventricular ejection fraction (LVEF) is known as a cause for cardiogenic ischemic stroke. Cardiomyopathy is classified into ischemic cardiomyopathy resulting from CAD and non-ischemic dilated cardiomyoapthy. The lower the LVEF, the higher the risk of stroke. Therefore, aggressive secondary prevention of stroke is required in congestive heart failure with a low LVEF.

Korean recommendations

1. Warfarin or antiplatelets may be considered for secondary prevention of stroke in cardiomyopathy with a low LVEF (GOR: GPP).

3.3.3.3. Acute myocardial infarction

Introduction

Acute myocardial infarction (MI) with the left ventricular thrombus is one of the major risk factors of cardioembolic ischemic stroke. Ischemic stroke is more frequently developed during the acute phase of anterior wall MI.

Korean recommendations

1. In patients with ischemic stroke or TIA following acute MI with left ventricular thrombus, warfarin treatment (INR 2.0 - 3.0) of 3 to 12 months is reasonable, unless contraindicated (LOE: IIa, GOR: B).
2. Aspirin should continue throughout anticoagulation treatment (LOE: Ia, GOR: A).

3.3.3.4. Valvular heart disease

Introduction

Embolism recurs in 30-65% of the patients with rheumatic mitral valve disease with previous embolism.[1-4] Mitral valve repair alone has known not to be reduced the risk of systemic embolism.[5,6] Aggressive antithrombotic therapy should be considered for the prevention of embolism.

As for prosthetic valves, the risk of embolism varies depending on the site and type of the valve, presence/absence of anticoagulant or antiplatelet treatment and its intensity, and history of embolism. For example, mitral valve replacement with "St. Jude Medical bileaflet valves" is known to be associated with an annual thromboembolism rate of 22% without medical therapy,[7] therefore adequate anti-thrombotic therapy should be considered.

Korean recommendations

1. Warfarin treatment (INR 2.0-3.0) is recommended, unless contraindicated, in ischemic stroke or TIA coexisting with rheumatic mitral valve disease, regardless of the presence of AF (LOE: III, GOR: B).
2. Patients with recurrent embolism despite of anticoagulants in ischemic stroke or TIA coexisting with rheumatic mitral valve disease, a combination of warfarin with the low-dose aspirin (100mg daily) can be considered (LOE: IV, GOR: C).
3. Warfarin treatment (INR 2.5-3.5) is recommended, unless contraindicated, in ischemic stroke or TIA that occurs after mechanical heart valve replacement (LOE: IIb, GOR: B).
4. Patients with recurrent embolism following mechanical heart valve replacement despite ofanticoagulants, a combination of warfarin with the low-dose aspirin (100mg daily) is recommended (LOE: IIa, GOR: B).
5. Warfarin treatment (INR 2.0-3.0) may be considered in ischemic stroke or TIA that onsets after bioprosthetic valve replacement without other cause for the thromboembolism (LOE: IV, GOR: C).

3.4. Surgical or interventional treatment of large artery steno-occlusive disease

3.4.1 Extracranial carotid artery stenosis

Introduction

Revised: Nov 2011

Pivotal large randomized clinical trials that influence on the current clinical practice for symptomatic extracranial carotid artery stenosis have been published. The benefit of carotid endarterectomy in patients with severe symptomatic carotid artery stenosis has already been proved. In recent years, there have been studies of clinical trials, meta-analyses, and subgroup analyses comparing short-term and long-term efficacy and safety of carotid endarterectomy and angioplasty/stenting. Based on these results, several foreign guidelines have revised their recommendations, and there has been an ongoing debate among Korean experts. Accordingly, the writing committee decided to revise the recommendations for the management of symptomatic extracranial carotid artery stenosis, reflecting and summarizing the new evidences regarding carotid endarterectomy, angioplasty/stenting, and medical treatment.

Revised Korean Recommendations

1. In patients with severe (70-99% degree of stenosis) symptomatic extracranial carotid artery stenosis (experiencing transient ischemic attack or ischemic stroke in the carotid territory within the past 6 months), carotid endarterectomy is recommended. Carotid endarterectomy is best performed by a surgeon whose perioperative rate of stroke and death is less than 6% (Level of Evidence Ib, Grade of Recommendation A).
2. In patients with moderate (50-69% degree of stenosis) symptomatic extracranial carotid artery stenosis, carotid endarterectomy can be considered depending on the patient's age, gender, co-morbidities, and the manifestation of the initial symptoms (Level of Evidence Ib, Grade of Recommendation A).
3. In patients with mild (below 50% degree of stenosis) symptomatic extracranial carotid artery stenosis, medical treatment alone is recommended (Level of Evidence Ib, Grade of Recommendation A).
4. When carotid endarterectomy is indicated and there is no contraindication for early revascularization, carotid endarterectomy within 2 weeks of the occurrence of ischemic symptoms is preferred to delayed surgery (Level of Evidence IIb, Grade of Recommendation B). Data of the appropriate time for angioplasty/stenting are not available yet.
5. In patients with moderate to severe (degree of stenosis of 50% or greater) symptomatic extracranial carotid artery stenosis, angioplasty/stenting is a reasonable alternative to carotid endarterectomy if the peri-procedural rate of stroke and mortality is expected to be less than 6% (Level of Evidence Ib, Grade of Recommendation A). The selection of carotid revascularization should be individualized based on the patient's age, gender, and the center's experience (GPP).
6. In patients treated with angioplasty/stenting, the combination of clopidogrel plus aspirin is recommended immediately before and for at least 1 month after the procedure (Level of Evidence IIb, Grade of Recommendation B).

7. Best medical therapy including antiplatelet therapy, statin therapy, and aggressive risk factor control is recommended for all patients with symptomatic extracranial carotid artery stenosis (Level of Evidence IIb, Grade of Recommendation B).

3.4.2 Vertebrobasilar artery stenosis

Introduction

Studies on the treatment of occlusive vertebrobasilar artery disease are mostly case series, with very few large-scale RCTs. Atherosclerotic stenosis is common at the origin of the vertebral artery and over the intracranial part of it. The areas are also prone to arterial dissection. To determine which treatment is superior, medical or surgical, more randomized trials are needed.

Korean recommendations

1. For repetitive ischemic symptoms in patients with vertebrobasilar artery stenosis despite an adequate medical treatments, stent placement may be considered for intravascular intervention (LOE: IV, GOR: C).

3.4.3 Intracranial artery stenosis

Introduction

Atherosclerotic stenosis of intracranial arteries is one of the most significant causes of ischemic stroke. Though the risk of stroke recurrence is relatively high despite drug therapy, no effective prevention - including surgery - has been known yet. With the recent development in the interventional devices and techniques, angioplasty has gained a new significance as a method for stroke prevention. Angioplasty can improve blood flow by dilating the narrowed vessels, but its use for stroke prevention has only been introductory. The safety and usefulness should be determined in more reliable studies.

Korean recommendations

1. If drug therapy fails in atherosclerotic stenosis of intracranial arteries (50% and greater), angioplasty or self-expandable stent placement may be considered for stroke prevention (LOE: IV, GOR: C).
2. There is insufficient evidence that stenting is superior to angioplasty as a prevention of atherosclerotic stenosis of intracranial arteries (LOE: IV, GOR: C).

3.4.4 Extracranial-intracranial artery bypass surgery

Introduction

If cerebrovascular blockage occurs, collateral circulation restores blood flow to the affected part of the brain. Disturbance in the compensation leads to TIA or cerebral infarction. The extracranial-intracranial (EC/IC) bypass surgery may be considered in the events to improve blood flow and prevent the recurrence of cerebral infarction. There is no clear conclusion, however, that the EC/IC bypass surgery is superior to drug therapy.

Korean recommendations

1. The EC/IC bypass surgery is not routinely recommended in symptomatic carotid occlusion (LOE: Ib, GOR: A)
2. The EC/IC bypass surgery may be performed in some carotid occlusion patients who have recently had cerebral infarction or TIA, if a treatment effect is expected after the cerebral blood flow evaluation (LOE: IV, GOR: C).
3. The EC/IC bypass surgery is not recommended during the acute phase (LOE: III, GOR: B).

3.5. Management of other specific conditions

3.5.1 Secondary prevention of intracerebral hemorrhage

Introduction

To identify and manage the risk factors for cerebral hemorrhage presents high morbidity and mortality is important in preventing its recurrence. Hypertension is considered as one of the most critical risk factor, and adequate blood pressure control could reduce the risk of hemorrhage recurrence in half. This is equally important for those without history of hypertension.

Korean recommendations

1. A thorough hypertension treatment is needed for prevention of recurrent cerebral hemorrhage (LOE: Ia, GOR: A).
2. Avoiding smoking or heavy drinking is reasonable for secondary prevention of cerebral hemorrhage (LOE: III, GOR: B).

3.5.2 Secondary prevention of ischemic stroke mixed with cerebral hemorrhage

Introduction

There is no clear consensus on the safety and efficacy of the antithrombotic treatment in ischemic stroke coexisting with cerebral hemorrhage. Cerebral infarction might develop in patients with a previous hemorrhage, and on the contrary, cerebral hemorrhage might not be unusual in the post-thrombolytic stagel. In patients with AF coexisting with a lobar hemorrhage or a deep hemorrhage, use of anticoagulants should weigh between the recurrence of hemorrhage and the risk of ischemia, with the greatest concern given to the patient quality of life. Use of antiplatelets following cerebral hemorrhage should be considered only in those at low risk of re-bleeding.

Korean recommendations

1. Determining whether to resume the antithrombotic treatment or not following cerebral hemorrhage should be based on the risk of thrombosis, recurrent hemorrhage, and the over all risk profile in each patient (LOE: IV, GOR: C).
2. In patients with the anticoagulation-associated cerebral hemorrhage, the angicoagulants might be switched into antiplateltes in patients with low risk of recurrent thromboembolism or high risk of bleeding tendency. The antocoagulation therapy should resume, however, if the risk of cerebral emolism is clearly high. Timing of re-administration may be 7 to 10 days later from the cerebral hemorrhage (LOE: III, GOR: B).

3.5.3 Arterial dissection

Introduction

Extracranial carotid or vertebral artery dissection is a main cause of stroke in young adults. It may lead to ischemic stroke by causing arterial embolism or steno-occlusion of the proximal

arteries. And also, thrombosis occurs following formation of pseudo-aneurysm. Extensive dissection involving the intracranial vertebrobasilar artery may cause subarachnoid hemorrhage due to the arterial rupture. Management of ischemic stroke with arterial dissection is aimed for prevention of stroke recurrence and healing of the dissected vessels. Management should include anticoagulants (intravenous heparin or oral anticoagulants), antiplatelets, stent placement for endovascular treatment, and surgery.

Korean recommendations

1. Use of anticoagulants or antiplatelets for 3-6 months is recommended in ischemic stroke or TIA with extracranial artery dissection (LOE: IIa, GOR: B). Long-term antiplatelet therapy may be considered beyond 3-6 months (LOE: IV, GOR: C).
2. Stenting is recommended if ischemic events recur despite of best medical management (LOE: III, GOR: B). Surgery could be considered in patients who are not candidates for stenting (LOE: IV, GOR: C).

3.5.4 Patent foramen ovale and atrial septal aneurysm

Introduction

Patent foramen ovale (PFO) is a relatively common congenital heart disease. It is a major underlying cause in cryptogenic ischemic stroke or TIA in the young. The risk of stroke is known to rise particularly high if atrial septal aneurysm (ASA) coexsts.

Korean recommendations

1. The screening for PFO or ASA is reasonable in young patients with cryptogenic ischemic stroke (LOE: III, GOR: B).
2. Use of antiplatelets is reasonable in patients with cryptogenic ischemic stroke with PFO (LOE: IIb, GOR: B).
3. Warfarin treatment may be considered in patients with cryptogenic ischemic stroke withPFO and other conditions, such as hypercoagulable disease or deep vein thrombosis (LOE: IV, GOR: C).
4. There is insufficient evidence regarding the usefulness of PFO closure in patients with first-ever ischemic stroke with PFO. However, tt may be considered in cryptogenic ischemic stroke recurs despite of adequate medical therapy (LOE: III, GOR: B).

3.5.5 Antiphospholipid antibody syndrome

Introduction

Antiphospholipid antibodies are found in about 1-6.5% of the general population, with higher rates in the elderly or in the lupus patients.[1] Of stroke patients, they are observed in 8.2-9.7%,[2] and the association with stroke is particularly high in younger stroke patients aged 50 and below.[3] Antiphospholipid antibody syndrome (APS) is a rare clinical condition that may cause venous and arterial occlusion of multiple organs, miscarriage, and/or livedo reticularis.[4] The widely varying clinical presentations and the difficulty in diagnosis act as barriers to the well-designed clinical trials on APS treatment. Currently available practice guidelines for APS provide only limited information.

Korean recommendations

1. antiplatelets should be recommended in patients with cryptogenic ischemic stroke or TIA and positive antiphospholipid antibodies (LOE: III, GOR: B).
2. In patients with ischemic stroke or TIA who fullfillthe diagnostic criteria of APS, including venous and arterial thrombosis of multiple organs, miscarriage, and livedo reticularis, use of oral anticoagulants (INR 2-3) should be recommended (LOE: III, GOR: B).

3.5.6 Venous Infarction

Introduction

Venous infarction presents widely varying symptoms including headache, focal neurological deficit, seizures, impaired consciousness, and papilledema. Diagnosis is elusive with only minute changes detected on CT and MRI. Though invasive angiography was used for definite diagnosis in the past, the MR venogram is of the widest use now. Venous infarction in many cases coexists with hemorrhage and vasogenic edema. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been in use for medical therapy, despite lack of evidence from the large-scale RCTs.

Korean recommendations

1. UFH or LMWH may be used in venous infarction even in cerebral hemorrhage coexist (LOE: IIa, GOR: B).
2. Use of oral anticoagulants is reasonable for the first 3-6 months followed by antiplatelet therapy in patients with venous infarction (LOE: IV, GOR: C).

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ISBN 978-89-94181-19-6