REVIEW ARTICLE

AN UPDATE ON STROKE PREVENTION

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ABSTRACT

Stroke is a heterogeneous disorder and is the leading cause of physical disability. A comprehensive approach in identifying the pathomechanism and managing the vascular risk factors both in primary and secondary stroke prevention settings can lower the risk of first and recurrent stroke. Recent studies highlight the benefits of blood pressure treatment in the elderly and the use of statins in healthy subjects with normal LDL.

Key Words: *Stroke, Management, Risk Factors, Prevention, Hypertension, Diabetes Mellitus.*

This article may be cited as: Khan K, Shuaib A. An update on stroke prevention. KUST Med J 2010; 2(2): 69-72.

INTRODUCTION

Stroke is the second most common cause of death worldwide and the leading cause of disability resulting in a huge financial impact on the care giver and health care systems. The lifetime direct and indirect cost of major types of strokes was estimated to be in excess of 40 billion dollars in USA in an incidence based model assessed by Taylor and colleagues for the year 1990.[1] In the western countries the incidence of stroke was steadily decreasing from the early 1950's to the mid 1980's. It plateaued for a decade and is on the rise again. There is general consensus that the significant decrease in stroke incidence was a result of better control of risk factors. The recent increase in the incidence is felt to be the result of the rising percentage of the elderly. Stroke affects all ages but the incidence substantially increases with age so as the prevalence of modifiable risk factors – hypertension, atrial fibrillation, dyslipidemia, diabetes and metabolic syndrome. Other important risk factors include obesity, sedentary life style, obstructive sleep apnea and smoking. Among these hypertension is the most prevalent with the highest relative risk. In young patients without the conventional risk factors- arterial dissection, vasculitis, congenital heart disease or recreational drug use should be considered. Up to 40% stroke may be preceded by transient ischemic attack (TIA) or non-disabling stroke.[2]

There are several studies reporting the high risk of stroke following TIA's: 10-20% within 90 days and 50% of these were within the first 2 days. Early preventive strategies can make a difference.[3-6]

This brief review will focus discussion relating to primary prevention in the management of hypertension and hyperlipidemia. Secondly, we will review recent development in the use of appropriate antithrombotic therapy in patients with TIAs and acute stroke.

Primary prevention and cerebrovascular disease:

Primary preventive intervention is influenced by the patient's vascular risk factor profile. A healthy lifestyle is one of the most important interventions.

Hypertension often remains undiagnosed in many patients. The risk of stroke in diabetic patients with hypertension is increased. Blood pressure and blood glucose levels should be optimally controlled. The incidence of cerebrovascular events can be reduced if these modifiable risk factors are identified and managed early.

Hypertension is the most common and important risk factor for all types of strokes. Across WHO regions, research indicates that about 62 per cent of strokes and 49 per cent of heart attacks are caused by high blood pressure.[7]

There is evidence that even high normal blood pressure (Systolic 130-139 and diastolic 85-89 mmHg) is a marker of an elevated risk of cardiovascular disease irrespective of gender and age (age range 35 – 90 years).[8,9] About two-thirds of the cerebrovascular disease burden is attributable to non-optimum blood pressure control.[7]

Multiple studies have shown 30% to 40% reduction of recurrent stroke with treatment of hypertension.[10] Benefits are seen irrespective of the class of antihypertensive agents and the severity of hypertension.[11]

Several categories of antihypertensive agents, including thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), adrenergic receptor blockers, and calcium channel blockers, reduce cardiovascular risk, including the risk of stroke, in patients with hypertension. The benefits of

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Date Submitted: 30 June 2010
Date Revised: 06 December 2010
Date Accepted: 08 December 2010

optimum blood pressure therapy have been shown even in the elderly. In a recent prospective randomized placebo controlled study of elderly individuals ≥ 80 years with sustained systolic BP of ≥ 160 showed good outcome with antihypertensive treatment. In this study, more than 3800 individuals were enrolled with only 11.8% with cardiovascular history, and treated with Indapamide (1.5 mg) with or without Perindopril (2-4 mg). A mean blood pressure reduction of 15/1 mmHg was achieved in the active arm compared to placebo. A significant 39% (P= 0.05) reduction in stroke related death rate was noted at 2 years. A 30% (P=0.06) reduction in fatal and non-fatal strokes and 64% (P 0.001) reduction in heart failure was achieved.[12] These findings show efficacy and safety in treating hypertension in the very elderly.

In summary, there is compelling evidence that treatment of hypertension is associated with significant reduction of first ever stroke and stroke related death. The corner stone to successful outcome is instituting sustained lifestyle changes and early pharmacotherapy to achieve target goals as recommended by the Canadian Hypertension Education Program (CHEP) (< 140/90 mmHg in all: < 130/80 mmHg in diabetes and renal failure). Unless there are specific indications, initial therapy may include thiazide diuretics, angiotensin- converting enzyme (ACE) inhibitors, long-acting calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) or beta-blockers (in those younger than 60 years of age). In individuals whose systolic blood pressure is 20 mmHg and diastolic blood pressure is 10 mmHg above target – dual antihypertensive regime may be considered at the start. There is no evidence for combination of ACE inhibitors and ARBs unless compelling indications are present to suggest consideration of such combination. For isolated systolic hypertension, thiazide diuretics, long-acting dihydropyridine CCBs or ARBs are considered appropriate. In patients with cerebrovascular disease, an ACE inhibitor/diuretic combination is preferred. According to CHEP recommendations in selected high-risk patients in whom combination therapy is being considered, an ACE inhibitor plus a long-acting dihydropyridine CCB is preferable to an ACE inhibitor plus a thiazide diuretic.[13]

Dyslipidemia A clear cut causal relationship between rising levels of serum cholesterol and the risk of stroke is lacking but there is evidence from randomized trials that statins can reduce the risk of stroke. In the Heart Protection Study the incidence of first ever stroke was reduced by 29% as compared to placebo.[14] This effect was seen independent of a history of previous vascular disease and the level of serum cholesterol levels. Other studies have shown similar results.[15]

In JUPITER (17,802 patients) trial the effect of Rosuvastatin was compared to placebo in healthy subjects with normal LDL (<3.4 mmol/L) and elevated high sensitivity C-reactive protein (≥ 2mg). It showed significant reduction in major cardiovascular events (stroke 16% P=0.002, myocardial infarction (MI) 20% P=0.002 and composite endpoint of MI, stroke, revascularization and death 40% P=0.00001). The median LDL was 2.8 mmol/L and HDL 1.3 mmol/L in both active and placebo arms. Rosuvastatin reduced LDL by 50% and C-reactive protein by 37%. There was no difference in intracranial hemorrhage between the two groups (6 in Rosuvastatin and 9 in placebo).[16]

In a single large trial (SPARCL) on the use of statins; patients with cerebrovascular disease without cardiac history were studied. The SPARCL (stroke prevention by aggressive reduction in cholesterol level) trial randomized 4731 with LDL level of 2.6 – 4.9 mmol/L to receive Atorvastatin 80 mg or placebo. The five year absolute risk reduction for fatal and non fatal stroke was 2.2% (unadjusted hazard ratio P=0.05) and the risk of major cardiovascular events was 3.5 percent (P=0.002). This overall reduction in the incidence of stroke and other cardiovascular events was noted despite a small increase in hemorrhagic strokes.[17]

Diabetes Mellitus

Type 2 diabetes increases the susceptibility to atherosclerosis and hypertension. Optimum glycemic control must be emphasized. Aggressive blood pressure control in diabetics reduces the incidence of stroke.[18]

Secondary Prevention and cerebrovascular disease

The risk of a completed stroke in patients with a TIA is approximately 10.5% at 90 days. This is especially high in patients with a history of hypertension or diabetes, in whom the neurological symptoms last for over 10 minutes and consist of focal weakness or aphasia. The two-day risk of stroke in such patients may be as high as 8%.[19] Recent evidence from two independent studies has shown that the 90 day risk can be reduced by as much as 80% if the patients are evaluated and their treatment initiated within 24 hours of the onset of symptoms.[20,21] It is imperative that we improve our ability to rapidly asses and manage such patients. In addition to the liberal use of anti-hypertensive and statin therapy, as outlined above, such patients also require immediate antithrombotic therapy.

Antithrombotic treatment options are limited to Aspirin (ASA), Clopidogrel and a combination of ASA and extended release dipyridamole (ASA+ERDP). The recently published guidelines of the Antithrombotic Collaboration would suggest that any one of the three agents is indicated as the first-line therapy for stroke prevention in patients with transient ischemic attack (TIA) or ischemic stroke of non-cardiac origin. Clopidogrel and ASA+ERDP are however significantly more expensive than ASA and may have relatively more side-effects. Studies have compared the relative efficacy of ASA to clopidogrel or ASA to ASA+ERDP. In such studies, these agents have shown better results when compared to ASA. The effect has been marginal with clopidogrel (absolute difference 0.5% and relative risk reduction 11%).[22] With ASA+ERDP, this effect was more robust (relative risk reduction of 37%).[23] There were however, until recently, no studies that compared Clopidogrel to ASA+ERDP in stroke prevention.

The PRoFESS trial published recently was the first large study that compared the efficacy of Clopidogrel to ASA+ERDP in patients with ischemic stroke.[24] Over 20,000 patients were followed for 4 years and the primary outcome was the occurrence of recurrent ischemic stroke. Secondary outcomes included the incidence of serious complications, including development of systemic or intracerebral hemorrhage (ICH). There was no significant difference in the development of recurrent stroke in the two treatment groups. There were however more complications, including an increased risk of ICH, in the ASA+ERDP treated group. Despite the excess in hemorrhagic strokes, the number of patients with fatal or disabling strokes was similar in two groups.[24] In antiplatelet naïve patients, it is our preference to start patients on ASA as the first line therapy. Patients who are unable to tolerate ASA may be treated with Clopidogrel.

At present there is no evidence that the combination of ASA with Clopidogrel is superior to the use of single agent treatment. Such combination is routinely used in patients with acute coronary syndromes or in patients who require arterial stenting. The MATCH study showed that the combination was no better than Clopidogrel alone, but did increase the risk of symptomatic ICH in patients with stable TIAs or ischemic stroke.[25] The combination is therefore not recommended in stroke prophylaxis. A recent preliminary study, FASTER, however showed that in the very acute phase after onset of a TIA, the combination might be superior to ASA alone.[26] FASTER was however, a feasibility study. A larger FASTER II study is in the planning stages and may answer this important question on the very early use of combination antithrombotic therapy for a short time in patients presenting with a TIA.

Atrial fibrillation

Atrial fibrillation increases the risk of stroke and death. Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly. Stroke is a major yet highly preventable complication of AF, and the strokes related to AF often are disabling. Warfarin is the treatment of choice in high-risk patients with AF. Oral anticoagulation with warfarin reduces the risk of stroke by 70%.[27] The target INR should be between 2 and 3. In non cardioembolic stroke, anticoagulation (warfarin) has no advantage over aspirin.

Recently Dabigatran (110 mg) has been shown to have similar efficacy compared to warfarin with lower rates of hemorrhagic complications. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.[28] Anticoagulation is recommended for atrial fibrillation in patients > 60 years with history of hypertension, prior TIA or stroke, diabetes, cardiac disease and for all ≥ 75 years with atrial fibrillation.[29]

Carotid disease

Carotid endarterectomy in symptomatic carotid stenosis of more than 50% leads to significant stroke risk reduction as compared to medical treatment. This benefit is substantial with stenosis ≥ 70% and if performed within 2 weeks of the initial cerebral event.[30]

SUMMARY

Multiple studies show significant reduction in the incidence of stroke with hypertension treatment. Even in the very elderly treatment of hypertension does not impact negatively. Therefore judicial use of antihypertensives should be considered for optimum blood pressure control.

There is evidence from several trials in high risk patients without cerebrovascular disease that treatment with statins will significantly reduce the risk of stroke. SPARCL showed that this effect was also evident in patients with established cerebrovascular disease. Canadian, USA and European guidelines recommend that in high risk patients with cerebrovascular disease, LDL should be targeted to less than 2 mmol/L. This requires the use of high dose statins in most patients.

Early intervention should be instituted in high risk TIAs. There is no strong evidence for dual antiplatelet therapy in stroke prevention. We consider Aspirin as first antiplatelet choice in Aspirin naïve patients unless there is intolerance to Aspirin. There is some evidence that short term combination of ASA and clopidogrel may be more efficacious in acute phase. However the later warrants further evidence. Optimum antithrombotic prophylaxis, blood pressure and cholesterol management to currently recommended targets must be implemented to reduce recurrence of TIA or stroke. Importance of healthy life style must be emphasized.

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CONFLICT OF INTEREST
Authors declared no conflict of interest