Stroke — an overview 1994

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In most Western Societies, and I believe here in Sri Lanka, Stroke is the 3rd leading cause of death, after Myocardial Infarction and Cancer, in the 60+ age group. About 100,000 people suffer a first Stroke each year in England and Wales. Each year nearly 60,000 people are reported to die of Stroke and this represents 12% of all deaths. About 5% of the NHS Budget Costs go towards the Hospital Management of Stroke. Survivors are often left with severe disabilities, leading to untold misery and suffering.

The Framingham Study has looked at the probability of Stroke in a normal population, aged between 55 and 84 years of age, over a period of ten years. 472 Strokes occurred in a Cohort of 2372 men and 3362 women. The ten year probability of Stroke was 9.6% in men and 6.5% in women. Stroke probability increased steadily with age and to the presence of risk factors.

Investigation of stroke

Major advances have occurred in the investigation of Stroke. CT and MR scanning have enabled us to locate ischaemic lesions in the brain in symptomatic as well as asymptomatic patients. In general, the main use of these two investigations are in differentiating Stroke from Subdural Haematomas, Neoplasms, and other CNS lesions causing focal Neurological disturbances. They are also very valuable in differentiating Primary intracerebral haemorrhage, subarachnoid bleeding and haemorrhagic transformation in Infarcts.

SPECT scanning using Technetium 99 m labelled HMPAO (Hexamethyl propylene amine oxime) is a valuable method of determining the reduction of blood flow in the area of the Stroke in the acute setting. These scans can be repeated to determine whether reperfusion has been achieved following the use of Thrombolytic therapy or following Angioplasty which is now being done increasingly in the treatment of acute Strokes. It is a relatively simple test to do compared to PET scanning which can also be done for a similar purpose.

Ultrasound imaging, as you know, is a well established procedure used very widely in determining the Anatomy of the origin of the Internal Carotid (ICA) in the neck. Trans Cranial Doppler studies are capable of imaging the more distal portions of the internal carotid and the major intracranial branches. The Vertebro-Basilar system including the Posterior Cerebrals can be visualised.

Magnetic Resonance Angiography is a totally non-invasive method of examining both the Carotid and Vertebrobasilar systems in the neck as well as their intracranial branches. The technical quality of these examinations is being improved all the time as better software is developed, and it is more than likely that it will replace conventional invasive contrast angiography in the near future. The great advantage of this technique is that several views from many different angles can be superimposed on brain images enabling abnormalities to be studied in great detail.

Conventional Contrast Enhanced Angiography which has been further improved by digital subtraction techniques remains the Gold standard. Cannulation of the Arch of the Aorta via the Femoral or the Brachial artery with selective injection of the Carotids or the Vertebral systems is unsurpassed in terms of image quality. Unfortunately the morbidity and mortality with this procedure is significant (1.4%).

In the case of the origin of the ICA in the neck, a very important measurement is the degree of Stenosis. As you know, at present, Carotid Endartectomy is the recommended method of treatment for stenotic lesions at this site of between 70% and 90%. This percentage is a ratio which is calculated by expressing the narrowest diameter of the vessel divided by the normal diameter of the distal ICA beyond the Carotid Bulb. This method has some drawbacks although it is the one that has been used in all major trials so far. There is significant inter observer variation. The distal Carotid will narrow if the blood flow is reduced beyond the Stenosis because the artery will be less distended and hence the degree of Stenosis will be underestimated. Distal carotid diameter varies in atheromatous arteries. This percentage does not measure the blood flow which of course is the most important parameter in determining brain injury. Ackerman and Candia have recently proposed that measurement of the smallest lumen diameter using Angiography and Duples ultrasonic scanning may be more accurate and useful than the percentage stenosis. They suggest that reduction of blood flow only occurs if the minimum internal diameter is 1.5 mm or less.

In a recent paper MITTL compared MR Angiography Duplex ultrasound scanning and Conventional Arteriography for the detection of 70 — 99% stenosis. MRA demonstrated a sensitivity of 92%, a specificity of 75% and a negative predictive value of 96%. Duplex US had a sensitivity of 81%, a specificity of 82% and a negative predictive value of 90%. There was no significant difference between MRA and DUS and both were comparable screening examinations in determining this degree of

stenosis. Neither can at present replace conventional angiograpy.

Recently the proximal parts of the Aorta have been implicated as a source of emboli. Protruding mobile or wafting atheroma is associated with a high incidence of Cerebral and systemic emboli.

The prevention of stroke

The major work here in recent times has been done in relation to the origin of the Internal Carotid and also in the management of Cardiogenic emboli. Carotid Endarterectomy has now a well established role in the treatment of symptomatic patients with an ipsilateral stenosis of 70% to 99%. This was well established in both the North American Symtomatic Carotid Endarterectomy Trial (NASCET) and in the European Carotid Surgery Trial (ECST).

A very important fact here that the Surgical Teams doing these must have a low mortality and morbidity and it certainly is not a job for occasionals. In the case of NASCET the average operative mortality was 1.4% and most centres these days have mortalities less than 2%. Both trials are continuing at present to evaluate the role of Endarterectomy in the symptomatic 50 — 70% stenotic group and these results should be available in 1995 or 1996.

Three trials attempted to evaluate the role of Endarterectomy in asymptomatic group. The European based CASANOVA (Carotid artery stenosis with asymptomatic narrowing, Operation vs Aspirin) in 410 patients with 50 — 90% stenosis. The Mayo Clinic trial 71 patients was done on similar lines. Neither of these showed any benefit. The Veterans Affairs Trial 197 patients claimed a benefit but when their figures were carefully analysed it became clear that the only benefit was that subsequent TIAs were reduced but not the end points of death, Stroke or death from Stroke. Ulcerating atheromatous plaques in the Internal Carotid have been claimed to be a strong predictor of Stroke. Careful Duplex scanning and a new technique called Spiral CT scanning can demonstrate these lesions quite well. Whether Endarterectomy would benefit this group has not been answeres but is currently under study.

Platelet Inhibition

In 1956 Dr L L Craven of Glendale, California, published an observation relating to 8000 men in his practice. Two tablets of Aspirin a day were given to this group for a period of 7 years. He wrote:

> "Not a single case of detectable Coronary or Cerebral Thrombosis occurred among the patients who have faithfully adhered to this regimen."

This study was then totally unacceptable to the Scientific Community and was thrown out as a heap of rubbish. Since then almost every study has established the beneficial effects of Aspirin in the Secondary prevention of Stroke.

In the recently published Antiplatelet Triallists Collaboration Study a Meta Analysis of 145 randomised trials was done involving 70,000 High Risk and 30,000 Low Risk patients. The High Risk group had evidence of some vascular disease or other condition implying an increased risk of occlusive vascular disease whereas the low risk group had none of these factors. Taking a group of 10,000 patients with a past history of TIA the incidence of vascular events over a period of 3 years was 18% in the Aspirin treated group compared to 22% in the control group. (A 3 year benefit of 40/1000). The incidence of stroke in the Low Risk or Primary prevention group was slightly increased although the figures were not statistically significant.

Aspirin and ticlopidine

The dose of Aspirin has varied from 38 mg in the Dutch trial to 1300 mg in the UK trial which also compared 325 mg vs 1300 mg. All doses of Aspirin were effective although the larger doses seemed to have a better therapeutic effect up to 325 mg. The best trade off between side effects and therapeutic effect appears to be 325 mg. In Australia the commonest dose used is 150 mg.

Ticlopidine is an antiplatelet aggregant which is more effective than Aspirin in Stroke prevention. In both the Ticlopidine Aspirin Stroke Study (TASS) and the Canadian American Ticlopidine study this fact was established.

The most serious side effect of Ticlopidine is Neutropenia which occurs in 2.4% with severe Neutropenia in 0.8%. All cases of severe Neutropenia occurred within 62 days of starting therapy and hence the WBC should be monitored every 2 weeks during therapy for the first 4 months. The dose is 250 mg BD with meals. No cases of GI bleeding were noted and so far the Neutropenia has been reversible with no fatal consequences. 20% of patients gave up Ticlopidine because of one or another side effect mainly diarrhoea, nausea, skin rash or lassitude. It appears that the best candidates for treatment with this drug are those who cannot tolerate Aspirin, Aspirin failures, patients with extensive intracranial arterial disease, females and perhaps diabetics. A later derivate of this drug which is curiously called Clopidogrel is now under trial and could be better. In the US, therapy with Ticlopidine costs between $ 75 and $ 100 per month compared with Aspirin at 325 mg per day which costs about $ 2 per month.

Cardiogenic emboli

Cardiogenic emboli are a significant cause of Stroke accounting for 20% of all Strokes both in the Carotid and Vertebrobasilar territories. 80% of emboli from the heart pass into the Carotid territory and 20% are in the Vertebrobasilar territory. This corresponds to the distribution of the blood flow to the brain. A fact that is not appreciated

is that occlusion of the proximal internal carotid can be due to cardiac emboli. Jorgensen and Torvik, Castaigne, and Blackwood have all shown in postmortem studies that nearly 20% of occlusions of the ICA are due to cardiac emboli.

Whilst many esoteric conditions causing cardiac emboli are interesting, the commonest cause of Cardiac emboli is Atrial Fibrillation. AF is a very common dysrhythmia in the elderly and Stroke is the most devastating associated complication. The risk of Stroke appears to be unrelated to whether AF is paroxysmal or persistent and is not related to the duration of the AF.

Three Categories of patients can be recognised with regard to Stroke risk.

1. Patients having "Lone AF" i.e., AF unassociated with Hypertension or any known Cardiac disease after careful investigation and under the age of 60 years. These patients have a risk of Cerebral embolism which is the same as the normal population of about 0.5% per year rising to 2.7% by the age of 70.
2. AF associated with Rheumatic mitral valve disease has a very high risk of Stroke which is about 17 times that of normals. The risk is very similar in patients with prosthetic mitral valves. This group requires lifelong high dose Warfarin therapy to prevent a Stroke and the aim here is to maintain the INR between 3.5% and 4.5%.
3. Most recent attention has been devoted to Non Valvular AF where 6 randomised trials have been completed. The patients can be stratified into a High and Low risk categories.

It is very clear that these patients with Non Valvular AF require appropriate therapy to prevent Stroke, especially if they are in the high risk group. Several trials have established the benefits of Anticoagulation in these patients.

The Stroke prevention in AF (SPAF trial) show very similar results.

The dose of Warfarin used in these trials was low and the aim was to get INRs between 1.9 to 2.7. Aspirin is also superior to Placebo in treating this group.

Aspirin may be the treatment preferred in patients who have a contraindication to the use of Warfarin, who refuse Warfarin, and those in whom monitoring therapy may be difficult. This was very much the case here in Sri Lanka when I worked here many years ago and it may be that Asprin is more useful from a practical point of view.

The treatment of established stroke

At present there are at least 6 large studies which are using early Thrombolytic therapy either TPA or Streptokinase (STK). In the Australian Streptokinase Trial 1.5×10^6 units of STK in 100 ml of saline is administered over a period of one hour to one group with placebo to the other in a randomised double blind trial. Strict criteria are used.

1. Patients must be between 18 and 85 years of age.
2. The Neurological deficit must be consistent with an acute Ischaemic Stroke which has been present for less than 4 hours. The degree of the deficit is assessed using a modified Canadian Neurological score which should be less than 9 points. i.e. indicate a moderate or severe deficit.
3. They must all have a CT Brain scan to exclude intracranial haemorrhage and Tumour.
4. Consent must be obtained from the patient or relations after careful explanation.
5. All patients were given Cardiprin which is buffered Aspirin in a dose of 100 mg.
6. All results are finally assessed in 3 months.
7. There should be no Contraindication to the administration of STK.

The results cannot be assessed yet, but the early fears that disasters by converting Infarcts into haemorrhagic areas causing severe deficits or death have not occurred. A recent meta analysis of several small Japanese trials have shown a benefit in those patients receiving STK. It is very important to realise that at present there is no clear evidence as to the results of this form of therapy.

Reduction in infarct size

Competitive N-Methyl-D-Aspartate Antagonists (NMDA) exert a Neuro protective effect in Ischaemic brain damage. Administered as a bolus injection shortly after MCA ligation in Sprague-Dawley rats followed by a 24 hour infusion reduces Infarct size significantly. Limited human studies have confirmed this benefit. The theory behind this approach is that NMDA receptors are activated in acute ischaemia which leads to the substantial entry of ionic Calcium into the cell through an ion channel linked to these receptors. The calcium activates intracellular enzymes which cause the cell damage. NMDA antagonists block this influx of Calcium and hence their protective effect.

You will note that I have not discussed the role of the coagulopathies such as anti-thrombim[3] DEF, protein C & S DEF, anti cardiolipin AR's, lupus AC's the OC pill.

Finally, Mr. Chairman, perhaps the greatest encouragement that we have in a combined approach to the prevention and treatment of Stroke is that we have successfully reduced both the mortality and the morbidity from this devastating condition. In the past 20 years the incidence of stroke has declined by 25% in the UK and USA and perhaps with all the present methods one would hope that there would be a further decline.