The following papers presented at the 2007 International Stroke Conference were of special interest.

**MANAGEMENT OF ACUTE ISCHEMIC STROKE**

**Hemicraniectomy for Malignant MCA Infarction**

The case fatality from malignant middle cerebral artery (MCA) infarction is as high as 80%. Non-randomized studies have suggested that decompressive surgery reduces mortality, but uncertainty has remained owing to fear of allowing survival in an unacceptably poor clinical state.

Combined data from three ongoing European randomized, controlled trials (DECIMAL, DESTINY, and HAMLET) were presented by Werner Hacke, MD, PhD, of Ruprecht-Karls-Universität, Heidelberg, Germany, with the final manuscript published shortly after the conference (Lancet Neurology 2007;6:215-22). This pooled analysis was undertaken because of slow recruitment and ethical concerns about continuation of randomization despite differences in mortality. Although the individual study entry criteria and design differed slightly, the authors predefined inclusion criteria and an analysis plan for the combined group before data analysis. Patients aged 18-60 years with an MCA stroke and a National Institutes of Health Stroke Scale (NIHSS) score >15 were included. In addition, there had to be CT evidence of infarct greater than 50% of the MCA territory or MRI diffusion imaging volume of >145 cm$^3$. The primary outcome measure was a dichotomized modified Rankin Scale (mRS) score at 1 year. An mRS score of 0-4 was considered favorable and a score of 5 (severe disability) or 6 (death) was considered unfavorable. Secondary outcome measures were dichotomized as an mRS score of 0-3 versus 4-6 and 1-year case fatality. Primary outcomes were significantly better in patients with decompressive surgery [75% versus 24%; absolute risk reduction (ARR) 51%, $P = 0.0001$], as were secondary outcomes of mRS score $\leq$3 (43% versus 21%; ARR 23%, $P = 0.014$) and survival (78% versus 29%; ARR 50%, $P = 0.0001$).

This study proved that survival is improved with early surgical decompression in malignant MCA infarction. In addition, as the study used a point of dichotomization of 4 (moderately severe disability) on the mRS for the primary outcome measure, it could be argued that many of the surviving patients are left with some disability. However, significant results were also seen using 3 (moderate disability but ambulating without assistance) as the cut point. The conclusion of the investigators was that early (within 48 hours) decompressive surgery reduces mortality and improves functional outcome in survivors, but individual patient factors should be taken into account in the decision to perform surgery.

**Laser Therapy**

Björn Dahlöf, MD, PhD, of Göteborg University in Sweden presented the results of the NeuroThera Effectiveness and Safety Trial (NEST), a phase 2 trial using transcranial infrared laser technology for acute ischemic stroke. Laser-generated infrared radiation (photon energy) can penetrate various tissues, including the brain, and has been shown to induce angiogenesis, modify transforming growth factor-β signaling pathways, and enhance protein synthesis in animal models. This novel modality has previously shown significant and sustained benefit in functional outcomes in animal models of ischemic stroke. Funding for the trial was provided by ProThera, Inc. (Reno, NV), the device manufacturer.

This was a prospective, randomized, multicenter trial of patients with acute ischemic stroke of moderate-to-severe severity (initial NIHSS score of 7-22); patients receiving t-PA were excluded. Patients were enrolled up to 24 hours after onset of symptoms; the mean time to treatment was about 18 hours. The total enrollment was 120 patients (79 treatment and 41 sham control). There were no significant differences in age, time to treatment, or NIHSS score between the treatment and control groups. The treatment group received infrared laser therapy administered over various sites of the symptomatic hemisphere over a 1-hour period. The primary outcome measure was a binary NIHSS score, defined as the presence or absence of a good outcome: either complete recovery (defined as a score of 0-1) or a decrease in total score of 9 points or more. The treatment group had significant improvement in outcomes at 90 days (70% versus 51%, $P = 0.048$) as
measured by binary NIHSS score. Improvement in the dichotomized mRS score was seen as well (59% versus 44%, \( P = 0.034 \)) and remained statistically significant when stratified by severity and time to treatment. No significant differences were seen in mortality or serious adverse events between the groups. However, the study was not powered to detect differences for these measures. There was a trend toward increased infection (19.5% versus 6.3%) and increased central nervous system serious adverse events (19.5% versus 7.6%) in the sham group which could explain some of the improved outcomes in the treatment arm. Potential advantages of this treatment include the extended time window and favorable safety profile. Additional data from the ongoing NEST-2 trial will provide more information about this novel treatment.

IN-HOSPITAL CARE

Aggressive Glucose Lowering

Up to half of acute ischemic stroke (AIS) patients have hyperglycemia on presentation. Initial hyperglycemia is associated with poor outcomes, irrespective of the presence of diabetes mellitus, including increased rates of hemorrhagic conversion and poorer long-term recovery. Intensive lowering of glucose levels to 80–110 mg/dL has been shown in medical intensive care patients to significantly reduce morbidity but not mortality (N Engl J Med 2006;354:449–61). However, whether similar benefits occur in stroke is as yet unknown.

The final results of the United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) were presented by Christopher Gray, MD, of Newcastle School of Clinical Medical Sciences, UK. GIST-UK was a multi-center, randomized, controlled trial that enrolled acute ischemic and hemorrhagic stroke patients with an admission glucose level of 110–306 mg/dL within 24 hours of symptom onset. Patients were randomly assigned to a treatment group in which variable glucose, potassium, and insulin (GKI) infusion was given to maintain a target blood glucose level of 72–126 mg/dL and a control group in which a saline (GKI) infusion was given to maintain a target blood glucose level of 110–306 mg/dL within 24 hours of symptom onset. The primary outcome measure was all-cause mortality; a secondary outcome was severe disability (mRS score of 4–6) at 90 days.

The planned sample size was 2,355 patients, but the trial was stopped early in March 2006 due to slow enrollment (total of 933 patients: 469 saline and 464 GKI). The mean post-stroke hyperglycemia was moderate, at 152 mg/dL. Median time from stroke onset to treatment initiation was nearly 14 hours. The intervention was resource intensive, as 16% of patients required intravenous dextrose rescue and 74% required at least one change in their GKI infusion rates. Blood pressure declined in both groups, but it was significantly lower by 9 mm Hg in the GKI group at 18–24 hours. There was no difference in mortality between the two groups (30% GKI, 27% saline; \( P = 0.37 \)) or any beneficial effect on residual disability at 90 days.

This negative result is disappointing. However, the damage cascade initiated by hyperglycemia probably begins at stroke onset, and so it may be that initiation of glucose-lowering therapy at 14 hours after stroke onset is too late. In addition, it is possible that any benefit of GKI therapy was confounded by the significantly lower blood pressure seen in the GKI group, as there is some evidence that lowering blood pressure in the acute stroke period is associated with worse outcomes. Perhaps further light will be shed on this important topic upon completion of two additional trials of acute GKI therapy, “Treatment of Hyperglycemia in Ischemic Stroke” and “Glucose Regulation in Acute Stroke Patients.”

Venous Thromboembolism Prophylaxis

Deep venous thrombosis (DVT) remains a major cause of morbidity after stroke, affecting up to 20% of patients. Pulmonary embolism (PE) occurs in approximately 12% of AIS patients without prophylactic treatment with a nearly 50% case fatality rate. Although there is strong consensus that DVT/PE prophylaxis is valuable in AIS patients with restricted mobility, the most effective method of anticoagulation is unknown.

The Prevention of Venous Thromboembolism after Acute Ischemic Stroke with Enoxaparin (PREVAIL) trial was a prospective, open-label, multinational study of AIS patients randomized within 48 hours of symptom onset to 40 mg enoxaparin subcutaneously daily versus 5,000 IU unfractionated heparin (UFH) subcutaneously twice daily for 10 ± 4 days. Patients were included if they had AIS and leg motor impairment and excluded if they had evidence of venous thromboembolism (VTE) at screening or a contraindication to anticoagulation therapy. Primary outcome measures were confirmed VTE, classified as asymptomatic or symptomatic DVT or PE. Secondary outcomes were intracerebral hemorrhage (ICH), major extracranial hemorrhage, and minor bleeding during the treatment phase.

In 1,762 patients randomized (UFH 878 and enoxaparin 884), the average treatment duration was 10.5 days. In patients treated with enoxaparin, there was a relative risk reduction of 43% of total VTE (UFH 18.1% versus enoxaparin 10.2%, \( P = 0.0001 \)) as well as significant benefit for symptomatic VTE (UFH 1.0% versus enoxaparin 0.3%, \( P = 0.01 \)). This benefit was present for both patients with mild and severe strokes and for patients treated before or 24 hours after stroke onset. The risk reduction did not come at the expense of increased total bleeding (UFH 8.1% versus enoxaparin 7.9%, \( P = 0.83 \)) or total clinically important bleeding (UFH 1.3% versus enoxaparin 0.7%, \( P = 0.52 \))
despite a significant increase in major extracranial hemorrhage (UFH 0.0% versus enoxaparin 0.8%, \( P = 0.01 \)). In addition, there was no effect on incidence of ICH (UFH 0.7% versus enoxaparin 0.5%, \( P = 0.52 \)).

This study is a first step in establishing the best method to prevent a major complication of stroke. However, it remains to be seen whether the study will lead to widespread changes in clinical practice, particularly because most of the risk reduction was seen in asymptomatic rather than symptomatic VTE.

GENDER EFFECTS IN STROKE TREATMENT

Julia Warner Gargano, MS, from Michigan State University presented an analysis from a statewide stroke registry that sought to answer the question of whether men and women receive similar acute stroke care. Detailed chart information was collected for subjects admitted with stroke or transient ischemic attack (TIA) to 16 Michigan hospitals \(( n = 2,566 )\) in 2002. Women with atrial fibrillation were less likely to be treated with anticoagulation agents (32% versus 47%) at stroke onset, after adjustment for age and co-morbidities. During acute care, women were less likely to receive thrombolytic therapy [odds ratio (OR) 0.56], have serum lipid panels checked (OR 0.75), or have echocardiography performed (OR 0.84). Although Christian Foerch, MD, from the Johann Wolfgang Goethe-Universität, Frankfurt found similarly in a German stroke registry that women were significantly less likely to be treated with thrombolytic agents than were men (OR 0.867, \( P = 0.006 \)), this effect was largely driven by the decreased likelihood that women arrived within 3 hours of stroke onset (OR 0.902, \( P < 0.001 \)). However, in the Michigan registry, the lower rate of thrombolytic therapy in women persisted even after adjustment for time to presentation. Among patients arriving in less than 2 hours, 28.3% of men and only 18.5% of women received thrombolytic agents (adjusted OR 0.54, 95% confidence interval 0.34–0.86). Women were less likely to be discharged to home as well (OR 0.79). The large differences in women receiving thrombolytic agents acutely and women with atrial fibrillation who are receiving anticoagulation agents is very concerning, and further study is needed to define the scope of this problem and design potential interventions to attempt to reduce this disparity.

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