STROKE REHABILITATION UPDATE

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- American Heart Association/American Stroke Association (AHA/ASA) publish new stroke rehabilitation guidelines in 2016
- Selective serotonin uptake inhibitors may improve stroke recovery – an update
- Neurological recovery of the arm from stroke may be all too predictable
- Stem cell trials for treatment of stroke are advancing

AHA/ASA Stroke Rehabilitation Guidelines

Stroke remains the 5th leading cause of death and leading cause of disability in the US. There are an estimated 795,000 new strokes yearly, with 610,000 being first time strokes. Someone in the US has a stroke every 40 seconds and stroke has a worldwide prevalence of 25.7 million. The most common neurological deficit is motor impairment, which is present in approximately 80% of strokes. Rehabilitation is needed by 50% to 65% of stroke survivors with the majority doing reasonably well at 6 months, but with a substantial minority significantly disabled. A large meta-analysis of 28 trials of more than 5000 patients receiving multi-disciplinary team rehabilitation vs. general medical shows a 1 year reduction in mortality, institutionalized care, and dependency in those individuals receiving team stroke rehabilitation. One study has suggested that for every 100 patients receiving stroke rehabilitation, an extra 5 return home independent.

Newly published guidelines for stroke rehabilitation from the AHA/ASA analyze various components of the rehabilitation process. Interventions related to all phases of stroke rehabilitation are categorized by risk versus benefit, which is modified by the amount and quality evidence to support the recommendation. Some highlights from this report include an emphasis on provision of coordinated, inter-professional care in an enriched environment. There are a host strongly recommended interventions aimed at preventing secondary medical complications, including recognition and treatment of post-stroke depression. The rehabilitation process should include careful assessment of mobility, activities of daily living, and instrumental activities of daily living followed by graded, task-specific training. There should also be careful attention to safety issues such as fall prevention. Finally, the acute stroke rehab process should be followed by maintenance of fitness and exercises when patients return to the community. Among the post-stroke interventions that may be of particular interest to neurologists is the Class 1, Level A evidence for the use of botulinum toxin to treat spasticity and improve a variety of functions in both upper and lower extremities.

Certain “do nots” are also noted. Prophylactic anti-epileptic medications should not be prescribed. Frequently used measures such as use of elastic compression hose and splints or taping to prevent wrist/finger spasticity are to be avoided. Although prompt initiation of rehabilitation measures after stroke is advisable, the AVERT trial demonstrated that intensive, early mobilization within 24 hours of stroke onset should not occur. There have been many novel neuromodulation and pharmacological interventions for enhancing stroke recovery that have been introduced over the past decade. While some of these have been promising, the guidelines find none with sufficiently strong evidence to support widespread use at this time.

Selective serotonin uptake inhibitors may improve stroke recovery – an update

Publication of the FLAME trial in 2011 provided the strongest evidence to date of a role for pharmacotherapy in enhancing treatment of stroke related hemiparesis. The FLAME trial was a double-blind, placebo-controlled trial (N=118) of fluoxetine 20 mg administered within 5-10 days of an ischemic hemiparesis. The primary outcome for the study was the Fugl-Meyer Motor Score (FM) score at 90 days post-stroke. The FM score is a well-tested, reliable and valid measure of neurological motor function. The exam apportions 66 points for the arm and 34 points for the leg, with 100 points being normal. The modified Rankin Scale (mRS) was designated as a secondary outcome.

The results were very encouraging. Subjects in the fluoxetine group had mean FM scores 18.6 points higher than the control group. The gain in upper limb function was particularly impressive with a difference of 13.5 points. Estimated minimal clinically important differences on the FM are 9-10 points for the arm and 6 points for the leg. On the mRS, there were 3 fluoxetine-treated subject v. 1 control subjects that were left with no significant disability; 12 fluoxetine treated subject v. 4 controls were left with slight disability.

A larger (N=374), single blind trial with longer follow-up (180 days) was reported from China in 2016. The co-primary outcomes were the NIH stroke scale and the Barthel Index. Outcomes were statistically better in the fluoxetine treated group, although the differences were small and unlikely to be of clinical significance. Another study, which was an exploratory analysis of outcomes after stroke in patients who had been pretreated with SSRIs prior to stroke onset suggested that SSRI were associated with improved early recovery, a shorter duration of hospitalization and better outcomes after discharge.

Nevertheless, the unequivocal benefits of SSRI for stroke recovery remain uncertain. The answer may be forthcoming with the results of an ongoing European, multi-center, collaborative study. This large study will enroll 6000 subjects and will examine the effect of fluoxetine on stroke outcomes at 6 months using the mRS as the primary outcome. There are currently over 3000 patients enrolled, with the results likely to be available in 2-3 years.

Neurological recovery of the arm from stroke may be all too predictable

The ability to predict neurological recovery soon after stroke would be extremely useful for setting appropriate rehabilitation goals, efficient deployment of rehabilitation resources, and facilitating design of clinical research studies. In 2008, Krakauer and colleagues made an interesting observation regarding arm recovery post stroke. They obtained FM scores at 24-72 hours post ischemic stroke and again at 3 months. What they noted was that the outcomes were highly predictable for the vast majority of patients by taking the initial FM score and adding 70% of the difference from the maximum score of 66. Some patients, essentially those with extremely low initial FM scores did not hold to the rule. In similar work, Stinear and colleagues developed an algorithm for predicting arm recovery – the **P**redicting **Re**covery **P**otential for Upper Limb after Stroke (PREP) – using a simple 72 hour clinical exam, and, at 2 weeks, assessing for the presence or absence of motor evoked potentials using transcranial magnetic stimulation (TMS) and the integrity of the posterior limb of the lesioned internal capsule. In 39 of 40 subjects, functional recovery occurred as predicted. There was 88% positive and 83% negative predictive power for complete arm recovery. All patients in these studies received rehabilitation therapy, however, it appeared that most recovery might be somewhat independent of rehabilitation. More recently this same group extended their observations and compared it with the “70% rule”. Patients with within 2 weeks of ischemic stroke were given FM scores, tested for motor evoked potentials with TMS, along with brain MRI for DTI for assessment of posterior limb of the internal capsule integrity. FM scores were reassessed at various intervals up to 24 weeks post-stroke. Remarkably, at 24 weeks, virtually all patients that had some degree of internal capsule integrity showed recovery in keeping with the “70% rule”. It was also noted that outcomes were independent of the amount of upper limb therapy that was received. This latter observation is consistent with somewhat sobering findings from a number of carefully designed studies, such as the ICARE study, that have found that enhanced arm therapy during the subacute stroke period does not improve functional outcomes. As for chronic stroke, a recently published trial by Lang et al. found no evidence of a dose-response effect of therapy on functional capacity in the arms of patients who were ≥ 6 months post-stroke. While rehabilitation therapy may be important for global stroke recovery, the timing, type, and/or intensity of therapy that will significantly enhance neurological arm function beyond intrinsic biological recovery, is yet to be determined.

Stem cell trials for treatment of stroke are advancing

There has been considerable interest using stem cells for facilitating stroke recovery. Several types and routes of delivery for stem cells have been tried in small studies and it has been generally concluded that stem cells are not likely to improve post-stroke function by tissue replacement of lost neurons. However, current thinking proposes that stem cells secrete a variety of substances, e.g. growth factors, cytokines, or chemokines, that may attenuate immune responses and reduce inflammation, promote neurogenesis, or promote angiogenesis. In 2016, Steinberg et al, published their experience with bone-marrow-derived mesenchymal cells in an phase 1/2A study. Cells were implanted stereotactically at 3 doses via 3 cannula tracks in the peri-stroke region of chronic stroke patients. This study demonstrated reasonable safety – in the 18 implanted patients there was 1 seizure and 1 subdural hygroma. At 12 months, the pooled data analysis suggested efficacy with a mean reduction in NIHSS of 2 points and a mean FM motor score increase of 11.4 points. Among the interesting observations was an

association of functional improvement with the development of new, transient FLAIR signal change on brain MRI, post-implant. In addition, there were 2 subjects that showed remarkable improvement at just 24 hours after implantation. The reasons for these rapid dramatic response are unknown. Plausible explanations include the rapid facilitation of synaptic transmission by some secretory product from the stem cells or possibly serendipitous lesioning of neural pathways that were inhibiting neuronal function. This series of industry-sponsored trials remains in progress.

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