Critical Care and Emergency Medicine Neurology in Stroke

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Intracerebral Hemorrhage

Dramatic changes have occurred in the area of critical care and emergency stroke treatments of intracerebral hemorrhage (ICH). New data from three sponsored clinical trials: STICH (British National Health System-Medical Research Council), NOVO Seven (Novonordisk), and intraventricular hemorrhage (IVH) clot lysis (FDA Orphan Drug Program) were presented at the 29th International Stroke Meeting and the World Stroke Congress. Several avenues of approach to the problem of ICH are opening. Although the data from these trials are now under peer review, the initial presentations have demonstrated several principles that seem clear. First, craniotomy (though not better than initial medical management) is safe and not worse than initial medical management. Second, deterioration occurs frequently (~25% of the time) in the initial days after ICH. Deterioration was treated with surgery. Third, a strategy of emergent clot stabilization is safe and shows trends toward efficacy in the NOVO Seven dose finding study. Finally, catheter-assisted removal of blood clot from the obstructed ventricular system in IVH can be accomplished safely with low dose recombinant tissue plasminogen activator (rtPA). These trial results suggest that the basic elements of aneurysm care are now being applied to ICH care: emergent stabilization of the bleeding site, followed by removal of blood and management of cranial vault mechanics. Data are now beginning to support that applying these principles leads to improvement in mortality and morbidity.

We hope that the robustness of the peer-reviewed data continues to point to the value of emergent intervention for the ICH patient. New sponsored trials have already started: CLEAR IVH, a phase Ib dose optimization trial directed at finding the best dose of rtPA to rapidly remove blood from the ventricles (FDA Orphan drug program); MISTIE, an NIH sponsored phase II safety study of minimally invasive surgery plus rtPA for parenchymal ICH removal; CHANT, a neuroprotectant, NXY-059, safety study (Cerovive, Astra Zeneca) directed at testing the early use of this “spin trap” drug as a neuroprotectant in ICH; and most probably a phase three trial of activated factor seven based on the best dose found in the NOVO Seven dose finding study. The targets for investigation include hemorrhage extension, clot removal, and free radical damage to brain tissue, particularly white matter.

Animal models of hemorrhage extension have not been developed, but translation of animal models of clot removal and amelioration of tissue injury seem plausible from the preliminary human data that exist. Animal models of inflammation, microvascular injury, and perihematoma edema are all under development and may provide additional targets for treatment or mechanistic observations for the analysis of current human data. Additional positive surrogate outcomes would be welcome as a validation of the clinical benefits associated with clot removal in the ICH patient. In the last year, progress has occurred in our understanding of the process by which injuries occur in human ICH. Several studies have pointed to a role for MMP-9 as a measure of the extent of vessel wall and perihematoma injury. Chronic blood pressure elevation is well known as a risk factor for ICH, and now it seems that acute phase blood pressure elevation may be associated with hematoma extension/enlargement. The role of blood pressure management will become even more important as we attempt to eliminate hematoma expansion and minimize the hemorrhagic conversion of damaged tissue into parenchymal hematomas.

Understanding the risks for primary and secondary hemorrhage may assist clinicians in this task of decreasing hemorrhage. Blood pressure elevation, alcohol exposure, smoking, hypercholesterolemia, low circulating von Willebrand factor, and cerebral amyloid are all factors associated with primary ICH. Amyloid can now be identified via the presence of abnormal T2* signals on MRI; whether this funding allows for the selection of high risk patients whose future hemorrages can be controlled with risk factor amelioration remains to be proved. An NIH sponsored trial directly testing the safety of the idea that a glycosaminoglycan-mimetic “Cerebrill TM” can decrease amyloid-related bleeding is now underway (Neurochem, Inc). Whether other factors such as ETOH intake and BP reduction can be helpful in reducing bleeding in the cerebral amyloid patient should also be evaluated.

Emergency Treatment of Stroke

This year has again been one of synthesis of prior findings and consolidation of the elements of care central to successful...
acute ischemic stroke treatment. The most important event was the publication of the meta-analysis of the recent large stroke trials, including NINDS, ECASS, and ATLANTIS.20 This meta-analysis demonstrates that onset to treatment time is critically associated with improved functional outcome (Rankin 0,1 at 90 days). As opposed to the post hoc analysis of the NINDS trial, where an effect of time was not found in the prespecified analysis of the 90 and 180 minute groups, this larger meta-analysis sample nicely demonstrates a greater likelihood of good outcome, OR 2.8, for treatment in the 0- to 90-minute time frame versus OR of 1.6 and 1.4 for the 90- to 180- and 180- to 270-minute time frame. Interestingly, time from symptom onset did not influence the likelihood for hemorrhage conversion. These findings of time dependence of tPA effectiveness parallel the well-known effect of time on the severity of infarcts in animals. The meta-analysis solidifies the rationale for the investment of significant public health effort in the development of EMS and hospital based teams to treat stroke rapidly. The recent findings of the CLOTBUST investigators demonstrate more rapid vessel opening and improved functional outcomes with the coadministration of IV rtPA and focused ultrasound directed at intracerebralvascular clot disruption.21 Although a larger trial is needed to demonstrate reproducibility and define the actual benefit, the lesson is the same as that from the meta-analysis: early vessel opening is good.

Two analyses of the early treatment of stroke patients demonstrate the need for ongoing public education and multimodality interventions to improve stroke symptom recognition and early diagnosis. A population based study of the greater Cincinnati region demonstrated that only 22% of stroke patients arrive in under 3 hours from onset of symptoms and only 50% of these are eligible for tPA using the NINDS criteria.22 An analytic review of the Genetech Stroke Presentation Survey study population demonstrated that the mean time from symptom onset to CT was 4 hours.23 Both make the case for system-wide changes to promote more rapid access to IV tPA. An overview of ten distinct programs that have produced more rapid treatment times and increased numbers of treated patients suggests that multimodal changes in stroke care delivery are needed.24 The ability of EMS to respond to 911 stroke calls is among the most critical of steps leading to improvement in many cities. We now know that EMS personnel can identify the cardinal signs of stroke rapidly and reliably when compared with physicians using the Face Arm Speech Test (FAST).25 Similarly, we now know that putative neuroprotectant treatments such as intravenous Mg can be delivered safely and reliably during the transport of stroke, decreasing the time to treatment with neuroprotectant to within 100 minutes of symptom onset.26 Finally, efforts to increase the time window for patients with brain tissue at risk for further ischemic injury continues. The most notable of these efforts is the Phase II study of desmoteplase. This study uses perfusion diffusion mismatch as the entrance criteria for iv thrombolytic treatment after 3 hours of symptoms. Data from the dose finding study suggest that significant improved outcomes associated with drug-mediated revascularization occur in desmoteplase-treated stroke patients despite the more prolonged period to treatment.27 A phase III study will start early in 2005 to definitively explore this important idea regarding patient selection outside the current 3-hour time window.

**Intensive Care of Stroke**

Additional demonstrations of the ability of stroke units/ intensive care to identify events such as hypotension, hypertension, and hypoxia28,29 more rapidly have been reported in the last year. Additionally, the ability of neuro ICU’s to produce efficient fever reduction with appropriate cooling devices represents a significant therapeutic addition to the interventions now available for the critically ill stroke patient.30

Unfortunately, a major gap continues in the area of stroke care: the use of stroke units with dedicated stroke teams. This intervention has been demonstrated clinically effective in reducing mortality31,32 and is cost-effective in multiple environments.28,33 Little doubt exists that stroke units, particularly multimodality units combining acute care and rehabilitation, are among the most cost-effective treatments today,34 yet their widespread adoption is proceeding slowly. Some would undervalue life preservation and continue to argue that care at home by untrained family members is equivalent to care provided by specialists in specialty environments.35 This argument continues to excite those interested in cost reduction. This argument would be very unattractive if the care in question were cancer care or heart disease care, where even small increments of care technology continue to be adopted at high cost but with substantially less benefit. Hopefully governments and other social units will support the widespread adoption of simple stroke unit measures that preserve life (18% absolute improvement) and function (10% absolute improvement) in a robust manner.34,36

We can hope that the year 2005 will bring tangible signs of progress toward nationwide adoption and implementation of stroke units.37

**References**


