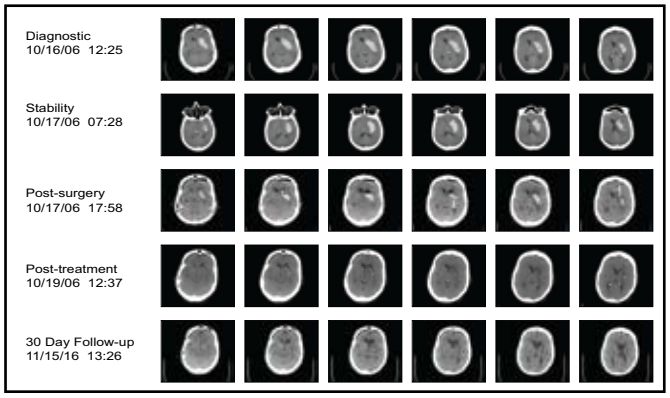
Update on the MISTIE Trial

Intracerebral hemorrhage (ICH) mortality estimates range from 37% (STICH trial) to 56% (SCHIPA trial). The Minimally Invasive Surgery plus t-PA for Intracerebral Hemorrhage Evacuation (MISTIE) trial was a phase 2 study sponsored by the National Institute of Neurological Disease and Stroke. The objective of the study was to determine whether reduction of clot size in ICH leads to lower mortality and better outcomes for patients. Daniel F. Hanley, MD, Johns Hopkins University, Baltimore, MD, presented recent findings from this study on behalf of Mario Zuccarello, MD, University of Cincinnati, Cincinnati, OH, and the MISTIE Investigators.

The hypothesis of this ongoing trial is that clot reduction that uses minimally invasive surgery (MIS) combined with recombinant tissue plasminogen activator (rt-PA) is safe and that clot size reduction would be better than in medically treated patients. In order to enter the trial, patients had to have met the following criteria: be between the ages of 18-80 years, have a Glasgow Coma Scale score ≤14 or an NIH Stroke Scale ≥6, an ICH ≥25 cc, a stable clot at a second CT scan 6 hours later, systolic blood pressure of <200 mm Hg or MAP <130 mm Hg over 6 hours, and historical Rankin of 0 or 1. Patients with brain tumors, infratentorial ICH, intraventricular hemorrhage with external ventricular drainage management, irreversibly impaired brain stem function, major medical diseases, or who were pregnant were excluded. Patients were stratified by ICH size (25-50 mL and >50 mL). The study design used a sequential tier approach, the first tier being 0.3 mg of rt-PA. After giving consent, patients underwent MIS. The cannula and catheter were placed at 2/3 of the clot long axis and in the middle 1/3 of clot width. The clot was then aspirated until resistance occurred. The placement of the catheter was confirmed by CT scan, and 0.3 mg rt-PA was administered every 8 hours until the clot was reduced to 15 cc or 80% of the original clot size, whichever occurred first.

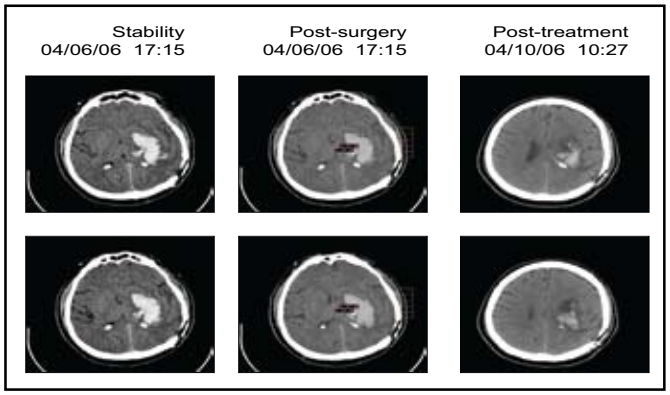
A total of 20 subjects received treatment in this tier, with 73% achieving the clot removal goal. Figure 1 contains sequential scans from a patient in the trial. The procedure had an acceptable safety profile (mortality 5%, no cerebral infections, and 10% symptomatic bleeding). Furthermore, 20% of the subjects needed only aspiration to reach the endpoint. The results indicated that catheter placement is critical, as clot resolution was not as effective if the catheter was not placed in an optimal position (Figure 2). The next steps in the MISTIE trial are to evaluate the risks and benefits of a 1.0-mg rt-PA dose, improve on the clot lysis rate and efficiency, and gather additional safety data. More information regarding this study is available at www.mistietrial.com.

Figure 1. MIS + rt-PA: Thumbnail Experience.



MISTIE Trial Investigators

Figure 2. Poor Placement (Subject B).



MISTIE Trial Investigators

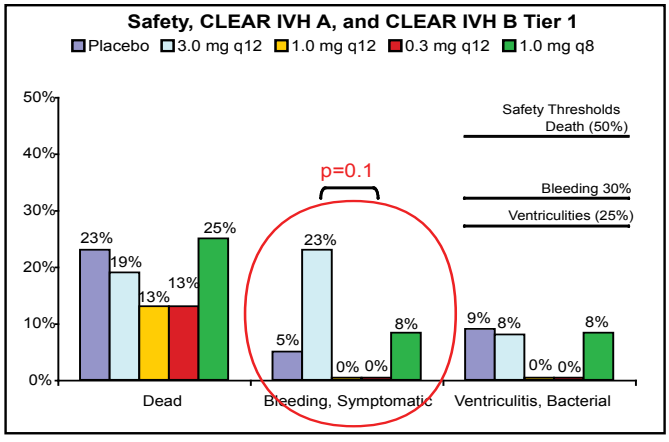
A Report From the CLEAR-IVH Trial

Data from studies such as the Surgical Trial in Intracerebral Hemorrhage (STICH) and Factor Seven for Acute Hemorrhagic Stroke Treatment (FAST) trial have suggested that intraventricular hemorrhage (IVH) volume is a predictor of mortality. Preclinical data suggest that intraventricular thrombolysis leads to faster ventricular clearance and better recovery. The CLEAR- IVH trial sought to follow up on these ideas in a phase 2 study. The study completed enrollment at the end of 2007, and Issam Awad, MD, Northwestern University, Evanston, IL, gave an overview of the results and plans for a phase 3 study.

The CLEAR-IVH study enrolled patients aged 18-75 years with IVH within 12 hours of symptom onset who had extraventricular drainage per medical management. Patients with infratentorial intracerebral hemorrhage (ICH), surpratentorial ICH>30 cc, unclipped aneurysm, or active internal bleeding; who were on heparin >10,000 U/day or coumadin; or who had major medical conditions were excluded. Once they were considered stable (ie, after 6 hours and repeat CT that demonstrated no clot enlargement), patients gave informed consent and were assigned in a 1:1 ratio to either recombinant tissue plasminogen activator (rt-PA) or placebo. Dose escalation was subsequently performed in three other tiers: 0.3 mg Q12h, 1.0 mg Q12h, and 1.0 mg Q8h. If the investigator believed it was necessary, a second external ventricular drain (EVD) was allowed in cases of a trapped ventricle or intractable intracranial pressure.

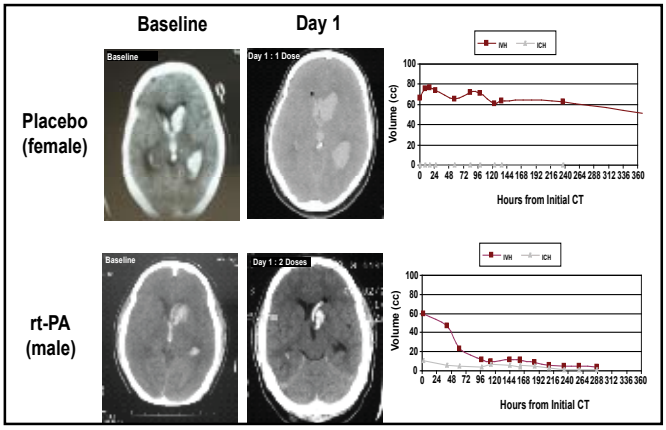
Twenty-two patients were treated with placebo and 88 with rt-PA. The bleeding threshold of 30% was never approached in any tier (Figure 1). "Cases treated with rt-PA had very dramatic clearance of the ventricles," said Dr. Awad (Figure 2). The entire cohort demonstrated a significantly faster clearance when treated with rt-PA compared with placebo ($p<0.05$). There was no relationship between dose group and overall clearance; however, there was a significant relationship between dose and clearance of the third and fourth ventricles ($p=0.01$). Modified Rankin scale data displayed a trend toward better outcomes in the treated group at 30, 90, and 180 days post-injury. Patients with rt-PA treatment had a lower number of treatment days (7.5 vs 12). For the safety phase (initial 48 subjects), only one rt-PA patient needed three EVDs, as opposed to seven patients in the placebo group.

Figure 1. 1^0 Endpoint Comparison: Safety, CLEAR A & B –IVH Trials.



CLEAR-IVH Investigators

Figure 2. Comparison Treatments: Baseline and Day 1.



CLEAR-IVH Investigators

When examining data from large clots in trapped ventricles, placement of a second catheter led to better clearance. "This clotbuster works, but you have to put the catheter in the right place," commented Dr. Awad. Based on the second catheter data, the surgeon's committee suggested that dual catheters be considered for large IVH, and that image-guided placement of the second catheters be utilized. A large phase 3 randomized, placebo-controlled trial of 500 subjects has been planned and will hopefully start later this year. For more information regarding this clinical program, visit www.clearivh.com.

Results of EPITHET

Intravenous recombinant tissue plasminogen activator (tPA) is recommended for the treatment of acute ischemic stroke within the first 3 hours of stroke onset. However, some randomized controlled trials have suggested that tPA might improve clinical outcome beyond the established 3 hour time limit. The objective of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was to evaluate the effect of the administration of tPA 3-6 hours after stroke onset as measured by echoplanar magnetic resonance imaging (MRI), diffusion-weighted MRI (DWI), and perfusion-weighted MRI (PWI). Because the probability of infarction depends on the severity and duration of hypoperfusion in the ischemic penumbra (the salvageable area around the irreversibly damaged infarct core), measurement of the mismatch between the larger PWI and smaller DWI lesion area can be used to estimate the salvageable tissue in the penumbra.