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INTRAVENOUS rtPA; A TENTH ANNIVERSARY REFLECTION

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Abstract

Background—Clinical trials with rt-PA for treating acute ischemic stroke began 20 years ago in 1987, and the pivotal NINDS rt-PA Stroke Study was completed and published in 1995 with FDA approval in 1996, about 10 years ago. A large number of papers emanated from that study and have established the efficacy and generalizability of this treatment.

Methods—Here we summarize the background of how the NINDS trial was developed and carried out, and its main findings.

Results—The NINDS rt-PA Stroke Study resulted from preclincal and pilot studies, and paralleled similar studies carried out around the world. Its positive results, compared to the other trials, probably was due to the early time window for treatment and well organized clincal and statistical centers. Many controversies have surrounded its use since its approval. As a result of the NINDS rt-PA stroke study, many new approaches to thrombolytic therapy are under evaluation.

Conclusion—The results of the NINDS rt-PA Stroke Study have affected the management of acute stroke patients worldwide.

Background of the NINDS rt-PA Stroke Study

Investigations of the possible use of rt-PA for the treatment of acute stroke were first discussed at NINDS in 1984 when plans were made for the Master Agreement for Cerebrovascular Clinical Research, a contract program for pilot studies of stroke treatments. Later, laboratory data from Justin Zivin[54] showing the potential benefit in a focal ischemic stroke model provided the scientific impetus required to get support within the NINDS to move forward with pilot dose and safety studies. A 1982 report from the Ojemann laboratory[33] provided scientific support for a very short 60 to 90 minute window for treatment. Further discussions with Tashi Yanigahara, Bill Barsan, Chick Olinger and Michael Walker led to the final protocol outline announced by NINDS. Michael Walker, Director of the Division of Stroke and Trauma, approved the plan to move ahead with the project immediately after the 1986 New Orleans International Stroke Meeting. The proposed protocol required treatment within 90 minutes of stroke onset, a time frame considered unfeasible by many in 1986. The dose escalation study treated the first patient in February 1987.[10] Principal investigators Tom Brott, Clarke Haley and David Levy, pioneered the rapid treatment of acute stroke treatment in this study. They developed the first stroke teams and tested different strategies for rapidly treating patients. The

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Cincinnati hospital system developed by Tom Brott and his team proved most effective at recruiting patients. The study showed that stroke could be treated early in the ED and that the safe dose for stroke was probably less than standard dose being used in myocardial infarction. After the 90-minute dose escalation study was completed, several small studies were done to test the drug in the 180 minute time frame[27] and the feasibility of rapid 90-minute randomization and blinded treatment.[26]

In 1990, the NINDS announced plans for the first trial of the two randomized trials in the NINDS rt-PA Stroke Study. This phase IIB trial began in January 1991. The primary outcome was a change in the NIHSS at 24 hours. At the time, this outcome was considered a measure of activity but not long term efficacy. The principal investigators at the coordinating center were Barbara Tilley and Michael Welch of Henry Ford Hospital. The eight PIs at the end of the study were Tom Brott, Patrick Lyden, James Grotta, Steven Horowitz, Michael Frankel, E. Clarke Haley, Steven Levine, and Michael Meyer.

As the initial phase IIB trial was being completed, the investigators began to discuss a possible phase III trial. NINDS accelerated plans to start an efficacy trial immediately after the phase IIB trial completion. Randomization into the Phase III trial began with only a short delay after completion of the Phase IIB trial. The primary outcome of the Phase III efficacy trial approved by the FDA and the DSMB was a consistent and persuasive difference in four separate measures: the NIH Stroke Scale, the Modified Rankin Scale, the Glasgow Outcome Scale, and the Barthel Index. The last patient was randomized in October 1994.

The NINDS rt-PA stroke study – main results

The NINDS rt-PA study[41] was in fact two consecutive randomized trials (291 patients in the phase IIB trial - Part 1, and 333 patients in the phase III trial - Part 2) of 0.9 mg/kg (10% bolus) IV rt-PA using essentially the same protocol for both parts. Important aspects of the study design included stratification of patients to ensure that half were treated within 90 minutes of symptom onset, and the rest within 180 minutes, strict blood pressure guidelines, and careful neurological monitoring. While Part 1 failed to meet its pre-specified primary outcome of improvement in NIHSS by 4 points or complete resolution at 24 hours, Part 2 was positive on its primary outcome, a global statistic that computed benefit on all 4 measured outcomes (NIHSS, Modified Rankin Score, Barthel Index, and Glasgow Outcome Scale) (OR 1.7 (1.2–2.6), P = 0.008), and both Parts 1 and 2 were each strongly positive on all of the 4 individual endpoints at 3 months. Subsequent analysis showed that this benefit persisted to 1 year[36] and was highly cost effective resulting in a net savings of $4000 when published in 1998[17]. Importantly, safety of this dose of rt-PA was confirmed. Symptomatic hemorrhage within 36 hours, defined as any blood on required follow up CT associated with clinical deterioration as adjudicated by a central blinded evaluator, was 6% in Part 1 and 7% in part 2 (vs 0% and 1% in controls, p <0.001). Asymptomatic hemorrhages occurred in 3% and 5% respectively (vs 2% and 4% in controls). Despite the increased bleeding, there was no increase in mortality with rt-PA treatment in either Part 1 or Part 2.

Data from all patients in the two studies were pooled to explore several prespecified questions. The magnitude of benefit was very similar on all four outcome measures, and in both parts—roughly 13–15% absolute increase in excellent outcome in treated patients. For example, overall 42.7% of all patients treated with rt-PA achieved a modified Rankin score of 0 or 1 vs. 26.6% in controls. 17.3% of treated patient died (including those who bled) vs. 20.5% in controls. No variable was identified that predicted benefit or lack of benefit to rt-PA, including stroke subtype, age, gender, baseline stroke severity, or preceding use of antithrombotic agents[42]. Despite the failure to detect differences in benefit when patients were dichotomized into 0–90 minute vs 91–180 minute subgroups, when time was considered as a continuous

variable (rather than dichotomized) and the data were controlled for baseline differences in stroke severity (more severely affected patients arriving earlier), a significant time to treatment interaction was observed with earlier time to treatment being the only identifiable clinical indicator of better response to rt-PA.[40] No variable was identified that predicted risk of bleeding except for baseline stroke severity[43]. While patients with higher baseline NIHSS score had worse outcome and more bleeding, they still showed a net benefit from treatment since outcomes in this group were even worse without treatment. Baseline CT scans were blindly re-evaluated looking for early ischemic changes as defined by the ECASS investigators published while the NINDS trial was ongoing[45]. Such changes were identified in 31% of patients, but did not predict either decreased response or increased risk with rt-PA treatment. Several other publications from the NINDS group included confirmation of increased reperfusion in treated patients compared to controls[19], clinical deterioration following improvement suggesting possible reocclusion[22], failure to detect increased bleeding in those who required treatment of blood pressure before and during and immediately after treatment[9], confirmation that substantial improvement at 24 hours predicted long-term response to treatment[25,8], and detailed description of how EMS, ED, and neurological services could be organized to enable treatment of patients within 3 hours [44,51].

Controversies

The NINDS studies, and the subsequent FDA approval of rt-PA treatment for AIS were both met with controversy. Among stroke neurologists, there was concern that thrombolytic treatment with its attendant risks was based on clinical impression without documentation of an arterial occlusion or definite stroke, and that patients might be better selected based on their individual clinical and imaging presentation[11]. These criticisms were answered by angiographic studies (and subsequent TCD data) that demonstrated arterial occlusions in most patients with focal neurological deficits studied within the first few hours of onset[21,37,18], that only 2.6% of patients in the placebo group spontaneously returned to normal by 24 hours, and all stroke subtypes seemed to respond to treatment[6]. Others were concerned that the data were insufficient to grant FDA approval since previous and subsequent trials of thrombolytics had been negative, and many viewed the NINDS study as a single trial. However, the FDA, AAN and AHA were convinced by the two separate consecutive blinded trials with convincing very consistent results, carried out independent of industrial sponsorship or oversight. Eventually, several large post marketing studies[3,50], most recently the SITS-most registry of 6,483 patients in Europe[52], have confirmed the NINDS study results in rt-PA treated patients, and rt-PA treatment within 3 hours is now approved in Europe, Japan, and several other countries.

The most vehement concerns were from the Emergency Medicine community who viewed with alarm the abrupt need to treat patients with rt-PA without what they perceived as the necessary supporting infrastructure in place[28]. They were concerned about risk vs. benefit, particularly less benefit in patients with more severe strokes treated towards the end of the 3 hour time window, and increased risk using the drug without the presence of a “stroke expert”. The risk/benefit and time issue was particularly vexing since in the NINDS stroke study there was an imbalance in baseline stroke severity favoring rt-PA treated patients in the 90–180 minute group. This necessitated an independent review of the data which confirmed the conclusions of the NINDS study despite the presence of these imbalances[35,30]. But the lack of infrastructure and stroke expertise available at most hospitals remains a problem. Indeed, increased risk was reported when criteria for treatment were violated[34], while post marketing studies in community hospitals that adhered to criteria showed the same risk/benefit as in the NINDS trial[46,20]. The lack of uniform expertise in stroke care in most EDs, however, resulted in lack of endorsement of rt-PA therapy as “standard of care” by the emergency medicine

community, and has been the basis for encouraging the development both of specialized stroke centers and increased stroke training for ED personnel[53,4].

Ongoing research spurred by the NINDS study

Presently, in addition to the development of the infrastructure that will enable more use of rt-PA, research efforts are focused on two main areas—building on the ability of IV rt-PA to achieve recanalization, and extending treatment benefit beyond 3 hours. IV rt-PA benefit has been closely linked to the success of early recanalization, but complete arterial opening only occurs in roughly 20% of patients, and any recanalization in about 50% within 2 hours[6]. Methods under evaluation to augment the effects of IV-rt-PA within the 3 hour window include combining the drug with ultrasonic energy[5], or with antithrombotic drugs such as GP2b3a antagonists[15,12], or direct thrombin inhibitors[39]. Another approach has been to follow the IV treatment with intra-arterial catheter based lytic or mechanical clot extraction[37,29,48,47].

Pooled analysis of IV rt-PA data from North American and European studies strongly suggest some benefit for treatment out to 5 hours, though once again demonstrating that most benefit occurred with early treatment[24]. Imaging studies have demonstrated “penumbral” tissue in some patients even out to 24 hours[38]. Several studies are testing the benefit of IV rt-PA, other lytics, or mechanical clot extraction up to 8–9 hours post symptom onset using MRI or CT “mismatch” criteria to select patients[14,23,16], and two other studies are ongoing testing the benefit of treatment beyond 3 hours in patients without such imaging selection[13,31].

Implementation of the results and future consequences of the NINDS rt-PA studies

Following the approval of rt-PA for acute ischemic stroke by the FDA, the community of experts in cerebrovascular disease began to incorporate this new treatment paradigm into their practices. National guidelines were written and published[1]. There was extensive discussion on the manner in which the drug would be used in practice. In 1996 the NINDS had sponsored a National Symposium on the Rapid Treatment of Acute Stroke[39]. This Symposium brought together national organizations with interests in providing emergency care for acute stroke and revitalized the Brain Attack Coalition (BAC). The executive committee of the BAC consists of the leadership of major professional, governmental, and advocacy groups[7]. The Brain Attack Coalition has sponsored initiatives to unify the stroke community’s description of the symptoms of stroke, has addressed the issue of hospital and physician reimbursement, has initiated the concept of the primary stroke center[4], and has provided a venue for the exchange of information about professional and public information programs. The cerebrovascular disease subspecialty was developed during this same time period, motivated in part by the growth of interest in acute stroke care[2].

At the present time, the use of rt-PA is growing slowly. More and more residents have entered practice with experience and confidence in the use of rt-PA for acute stroke. The efforts of the members of the Brain Attack Coalition have been successful at increasing both professional and public education. While not every patient treated with rt-PA benefits, from 12 to 50% are likely to benefit in some way. The estimated 178,000 US patients that have been treated since 1996 are only a few of the millions that have had strokes in the US, but even so, significant reductions in disability and large cost savings have justified continuing to make the effort and encourage our efforts to make rt-PA and other treatments available to even more[32].

While the results of previous research are working their way into everyday stroke practice, new ideas and treatment strategies are being developed for future application. The NINDS has set up six specialized programs for translational research in acute stroke (SPOTRIAS) and is

initiating a Neurological Emergency Treatment Trial Network (NETT) to facilitate the development of better treatments for stroke. There are many trials ongoing that are evaluating a wide range of treatments. Stroke prevention, rehabilitation, and acute treatment strategies are being tested. Taken together, all of these efforts promise continuing improvements in brain health.

Abbreviations

Rt-PA
recombinant tissue plasminogen activator

NINDS
National Institutes of Neurological Disorders and Stroke

ED
emergency department

NIHSS
National Institutes of Health Stroke Scale

FDA
U.S Food and Drug Administration

DSMB
data safety and monitoring board

CT
computed tomography

MRI
magnetic resonance imaging

OR
odds ratio

AIS
acute ischemic stroke

TCD
transcranial doppler

AAN
American Academy of Neurology

AHA
American Heart Association

GP2b3a
glycoprotein 2b 3a

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