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Position Statement on the Use of Intravenous Thrombolytic Therapy: Treatment of Stroke

AAEM Comment by Robert McNamara, MD, FAAEM

This AAEM position statement has been met with a great deal of support from our primary constituency, the practicing emergency clinician. Some in academic centers are not happy with this statement because of their opinion that the NINDs trial is definitive. AAEM expected both sides to understand each view point. We are aware of lawsuits against some emergency physicians alleging a deviation from the standard of care failure to administer thrombolytics in stroke. This statement should address such matters. It is important to note that AAEM is not the first organization to cast doubt on the widespread use of thrombolytics in stroke. The Association of Emergency Physicians in their position statement made recommendations including having an expert in neuroradiology read the scan first, having a neurologist directly involved and recommend use within an approved research protocol or formal clinical practice protocol with tight adherence to the NINDs criteria. For those in academic or other settings who are currently using this treatment, the AAEM statement should not inhibit their practice as "use" is also not considered a standard of care.

How can we further reconcile this divergence on this matter? First, the board is always open to member input on any position it takes and as always, we will be responsive to the members. I have already engaged a few of them on this statement and have left the door open for them to submit comments or modifications to the board for consideration. However, in reviewing submissions the board will be acutely aware that its primary constituency, the EP at the bedside has not been convinced by those promoting the use of this therapy. The rank and file accepted thrombolytics for MI despite its risks because there was clear evidence to them of the significant benefit. A challenge to those who are critical of this statement is to convince the community as was done for MI that this should be the standard of care. It may be difficult to do that without further research. Certainly, there

be recognition that the circumstances and resources surrounding a major research trial cannot be easily duplicated by the average center. A document will certainly not be welcomed by the makers of tPA. For the Academy has carefully developed itself in a manner that has preserved its dependence on funding from outside sources. We therefore are speaking to what we feel best serves the majority of the membership. This position statement was passed with that intent. We look forward to your input. Thanks for your support.

On its January 9, 2002, conference call, the AAEM Board of Directors adopted an official position statement on whether the use of tPA should be regarded as the standard of care for the treatment of eligible patients with acute ischemic stroke. The board adopted its position after reviewing the report submitted by the AAEM workgroup established to study this issue. The full report and position statement are included below.

Position Statement of the American Academy of Emergency Medicine on the Use of Intravenous Thrombolytic Therapy in the Treatment of Acute Ischemic Stroke

Submitted to AAEM by the Work Group on Thrombolytic Therapy in the Treatment of Acute Ischemic Stroke

Background

For many years physicians have been frustrated by the lack of an effective treatment for ischemic stroke. Thus, the introduction of tPA therapy for acute ischemic stroke was met with considerable enthusiasm. Following favorably reported results of the 1995 National Institute of Neurological Disorders and Stroke (NINDS) trial¹ the Food and Drug Administration approved tPA use for stroke. This therapy was subsequently endorsed by several medical professional societies, including the American Heart Association (AHA) and the American Academy of Neurology. In 2002 the AHA upgraded its recommendation on the use of tPA for acute ischemic stroke from a Class IIb ('optional') to a Class I ('definitely recommended') intervention.^{2,3} Despite these endorsements, debate about the efficacy, safety, and applicability of tPA has limited its widespread use. Nonetheless, an increasing number of liability suits are emerging against physicians who do not administer tPA based on the assumption that it represents a standard of care. Because of these continuing concerns, the American Academy of Emergency Medicine established a workgroup to study whether or not tPA should be regarded as the standard of care for the treatment of eligible patients with acute ischemic stroke.

Discussion

Efficacy concerns. The NINDS trial was a randomized controlled study evaluating the efficacy and safety of tPA when administered to care

selected stroke patients within 180 minutes of symptom onset.¹ It is an 11% absolute increase in the number of patients recovering with significant disability at 90 days (number needed to treat = 9).

Though these results appeared promising, the NINDS trial has been criticized for two potential methodological flaws. First, the trial selectively enrolled an equal number of patients treated within 0-90 and 91-180 minutes of onset, with greater benefit shown for those in the former group.⁴ This selective enrollment likely skewed the participants toward earlier times than would be encountered in clinical practice so that overall results were rendered poorly generalizable. Second, stroke severity in the group in the later time strata was greater in the placebo than in the tPA group, again potentially biasing the results in favor of treatment.^{4,5}

Other thrombolytic trials have demonstrated less encouraging results. In addition, seven randomized controlled studies have evaluated the efficacy of thrombolytic therapy for stroke. With the exception of the NINDS trial, none have shown benefit in any of their primary outcome measures.^{1,6,7,8}

Safety concerns. Three trials have evaluated streptokinase for acute ischemic stroke. Each was prematurely terminated due to excessive bleeding in the treatment group.^{6,7,8} Four trials have evaluated tPA for stroke and showed higher rates of intracranial hemorrhage and increases in either short-term or long-term mortality with treatment.^{1,9,10,11} In the NINDS trial, tPA-treated patients had a 10-fold increase in the incidence of symptomatic intracranial hemorrhage with an absolute increase in risk of 5.8% (number needed to harm = 17). One in 34 tPA-treated patients died as a result of intracranial hemorrhage.

Applicability concerns. The NINDS trial was conducted in expert centers with dedicated stroke teams, designated laboratory, and rapid radiology imaging resources. This infrastructure allowed rapid identification of eligible patients having strokes and of those with contraindications to thrombolytic therapy. Issues regarding the need for such resources to ensure appropriate patient selection must be addressed.

Two studies have shown that patients with stroke mimics were frequently misdiagnosed with strokes.^{12,13} Administration of tPA to such patients can carry all of the bleeding risks without any of the potential benefits. A separate study assessing clinicians' ability to interpret CT scans showed an alarming rate of misread CT's, with emergency physicians identifying 73% of hemorrhages.¹⁴ Only 52% of radiologists in this study were able to identify all cases of hemorrhage on five cranial CT scans. Post-market registries and regional databases have yielded conflicting results regarding the effectiveness of this therapy in clinical practice, making it difficult to determine the true impact of widespread implementation of thrombolytic protocols.^{15,16}

Conclusion

It is the position of the American Academy of Emergency Medicine that the current objective evidence regarding the efficacy, safety, and applicability of intravenous thrombolytic therapy for acute ischemic stroke is insufficient to warrant its classification as a standard of care. Until additional evidence clarifies such controversies, physicians are advised to use their discretion when considering its use. Given the absence of definitive evidence, AAEM believes it is inappropriate to recommend that either use or non-use of intravenous thrombolytic therapy constitute a standard of care issue in the treatment of stroke.

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