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Intravenous Tissue Plasminogen Activator and Stroke in the Elderly

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Abstract

Objective—Since publication in 1995 of the National Institute of Neurological Disorders and Stroke (NINDS) trial of intravenous tissue plasminogen activator (IV tPA) for acute ischemic stroke, the benefit and frequency of use of IV tPA in the elderly have remained uncertain.

Methods—We obtained data from the NINDS trial to summarize outcomes for randomized subjects older than 80 years. We used data from the Cardiovascular Health Study, a cohort study of 5,888 elderly participants from four US communities followed longitudinally for stroke since 1989, to estimate the use of and hospital outcome after IV tPA in older adults following publication of the trial in 1995.

Results—In the NINDS trial, 44 subjects older than 80 years were randomized, and their three-month functional outcomes were not significantly improved with IV tPA. Four of 25 randomized to IV tPA experienced symptomatic intracranial hemorrhages within 36 hours of treatment. Compared with younger patients, older patients were 2.87 times more likely to experience a symptomatic intracranial hemorrhage within 36 hours of IV tPA (95% confidence interval (CI) 1.04, 7.93). Of 227 CHS participants hospitalized for ischemic stroke between 1995 and 2002, seven, whose mean was age 84, were treated with IV tPA (3.1%; 95% CI 1.2, 6.2). Two had symptomatic intracranial hemorrhages, three failed to improve, and two of the seven had good outcomes.

Conclusions—These data highlight the need to clarify the risk-benefit profile of IV tPA in ischemic stroke victims who are older than 80 years.

Keywords

Ischemic stroke; thrombolytic therapy; aged; aged, 80 and over

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1. Introduction

Intravenous tissue plasminogen activator (IV tPA) was reported in 1995 to improve outcomes after acute ischemic stroke in the National Institute of Neurological Disorders and Stroke (NINDS) trial [1], and soon thereafter the US Food and Drug Administration (FDA) approved it for this indication. The mean age of subjects in this trial was 67 years old. The initial age limit of 80 years old was removed during part 1 of the trial, and some patients over age 80 were randomized. These were the only such patients to be randomized into trials of tPA according to a 2003 Cochrane review [2]. Ischemic stroke commonly affects the elderly, and the effectiveness of IV tPA in this group is uncertain. Prompted by these observations, we obtained data from the 1995 NINDS trial [1] to evaluate efficacy and safety of IV tPA in those over 80. We also used data from the Cardiovascular Health Study (CHS), a well characterized population of older people followed longitudinally for occurrence of stroke, to determine frequency of IV tPA use for acute ischemic stroke and hospital outcomes after its use since 1995.

2. Methods

2.1. NINDS Trial

We obtained the de-identified dataset from the NINDS trial [1], which is available for purchase from the National Technical Information Service (<http://www.ntis.gov/search/product.aspx?ABBR=PB2006500032>). Using the integer for age, we identified 44 participants in that trial with baseline age over 80 years (19 placebo and 25 IV tPA) and examined outcomes used in the original trial. To avoid identification of individuals, five participants whose age was over 89 had been coded as 89. Thus average age for these 44 participants could not be calculated exactly but was over 85 years old. The Cochrane review that prompted these analyses indicated that 42 patients aged over 80 were included in the trial [2], but we identified 44. We are uncertain as to the source of this discrepancy.

2.2. CHS Cohort

Members of CHS were recruited from a random sample of people on Medicare eligibility lists in four U.S. communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pennsylvania. Participants had to be 65 years or older and could not be institutionalized, wheelchair-bound in home, or under active treatment for cancer [3]. In 1989 and 1990, 5201 participants were recruited and examined, and in 1992 and 1993, an additional 687 black participants were recruited and examined. The 5,888 consenting participants in CHS have been followed longitudinally since recruitment started in 1989. Institutional review boards at each participating center approved the study, and each participant gave informed consent.

Participants were screened for vascular diseases at baseline and during follow-up, including transient ischemic attack, stroke, angina, myocardial infarction, and congestive heart failure. The Cerebrovascular Adjudication Committee reviewed all events thought to be transient ischemic attacks and stroke, as detailed elsewhere [4]. As part of this review, the neurologist from the study site completed a form based on available records. One of the questions asked whether a patient received IV tPA. Information was also sought on time from onset of symptoms to hospital presentation but was often missing. We did not seek information from the medical records on additional exclusions in these patients. Thus we could often not know with the information available why a CHS participant with an ischemic stroke was or was not treated with IV tPA. Additional information on hospital outcomes was collected on CHS participants who received IV tPA for their ischemic stroke.

3. Results

3.1. NINDS Trial

In the 44 patients over 80 years old in the NINDS trial [1], IV tPA compared to placebo was associated with better outcome at three months for one measure (Barthel) but with a worse outcome for another (Glasgow Outcome Scale). None of the differences in any of the four outcomes used in the trial and measured at three months was significant (Figure 1). A significant interaction by age was lacking. The 44 patients experienced seven intracranial hemorrhages within 36 hours of treatment for stroke. All but one hemorrhage, which was asymptomatic, occurred in the 25 patients given IV tPA, who experienced two asymptomatic and four symptomatic intracranial hemorrhages within 36 hours of treatment. Patients over 80 were 2.87 times more likely than younger patients to experience a symptomatic intracranial hemorrhage within 36 hours of IV tPA: 4 of 25 (16.0%) versus 16 of 287 (5.6%) with 95% confidence interval (CI) for the ratio being 1.04 to 7.93.

3.2. CHS Cohort

From the time of first enrollment in 1989 to 2002 June 30, 654 CHS participants had an adjudicated ischemic stroke, 321 before and 333 after the article was published in December 1995 [1]. The mean age at the time of stroke was 79 (SD 6) in the 321 before 1995 and 82 (SD 5) in the 333 after 1995. None of the 321 participants before 1995 and seven, whose mean age was 84, of the 333 participants after 1995 received IV tPA. Of these 333, 227 participants were known to be hospitalized for their ischemic stroke, so 3.1 percent of hospitalized patients receiving IV tPA (95% CI 1.2, 6.2). Considering strokes occurring after FDA approval in June 1996, the percentage was similar (3.3% (7/210), 95% CI 1.4, 6.7). All seven participants treated with IV tPA were said to have met eligibility criteria according to medical records, although criteria were not typically specified. Details available from the medical records are provided in Table 1 on these seven patients. Two patients improved including one who was normal within 24 hours of onset of symptoms, although his symptoms were improving before IV tPA was given. Two worsened with intraparenchymal hemorrhages, and three failed to improve. The percentage receiving IV tPA varied by study site: 5 of 66 (7.6%) for Forsyth County, North Carolina; 2 of 64 (3.1%) for Sacramento County, California; 0 of 52 (0%) for Washington County, Maryland; and 0 of 45 (0%) for Pittsburgh (Allegheny County), Pennsylvania (p-value for Fisher exact 0.066).

Information on timing was sought from medical records of all 227 hospitalized patients but was available in only 42 (18%). Of these 42 patients, 11 (26%) arrived at hospital within three hours of onset of symptoms. Three of these 11 (27%) received IV tPA and are included in Table 1.

4. Discussion

Our data from the 44 patients over 80 years old randomized into the NINDS trial [1] indicate that 3-month functional outcomes after an acute ischemic stroke were not significantly associated with IV tPA use. As in the original trial [5], we were unable to detect significant modification by age of the effect of treatment on outcomes, but both analyses suffered from low statistical power to detect clinically meaningful differences by age. Despite these small numbers and low power, symptomatic intracranial hemorrhages within 36 hours of IV tPA were nearly three times more likely in older than younger patients ($p < 0.05$). Two systematic reviews of observational studies of ischemic stroke patients receiving tPA [6,7] and other similar studies from several countries [8–11] have compared outcomes between patients 80 years or older and younger patients. As noted by Engelter and colleagues in their systematic review of 477 octogenarians [6], unfavorable outcomes were more common in older than

younger patients, as was known before the introduction of IV tPA, but the frequency of symptomatic intracranial hemorrhages were similar. They noted favorable outcomes among survivors, as reflected in a modified Rankin scale less than or equal to one, in 33–44% of older patients and 33–53% of younger patients. Meseguer and colleagues in their systematic review came to similar conclusions [7]. They noted that despite 3-month outcomes being less favorable, 27–38% of those 80 years or older recovered completely or to a level of independence. These observational data have been used to support the contention that IV tPA is safe in these older patients [12]. Eligibility criteria for the use of tPA in observational studies may be applied differently in older and younger patients [7,11]. Such an age-related selection bias may explain in part the difference between what was seen in large numbers of patients in these observational studies versus the small numbers of patients in the NINDS randomized trial.

We are unaware of prior population-based studies in which a cohort of elderly people has been followed longitudinally for the occurrence of ischemic stroke and the use of IV tPA. In CHS, IV tPA has been used infrequently for ischemic stroke in this cohort of elderly people in the seven years following publication in 1995 of the seminal NINDS trial results [1]. The 3.1 percent (95% CI 1.2, 6.2) of all CHS patients hospitalized for acute ischemic stroke receiving IV tPA is similar to the 3 to 8.5 percent described in four pilot prototypes of the Paul Coverdell National Acute Stroke Registry [13]. The median ages varied across these four registries from 68 to 71 years old, and data were based on experiences in 2001 and 2002. Reasons for variation in IV tPA use across CHS study sites are uncertain. These percentages of use may even be greater than found in the general population because of the scrutiny applied to these special populations. Based on a large administrative discharge database in the United States from 1999 to 2004, overall use was lower than in CHS at 1.1 percent (95% CI 0.95, 1.32) and even more so in the elderly [14].

Our study has limitations. The number of reported patients over 80 years old randomized to clinical trials of IV tPA for ischemic stroke is small, and thus statistical power to find important differences is low. Subgroup analyses of randomized trials should be interpreted cautiously. In CHS, we do not have detail necessary to understand why IV tPA was not used more frequently, if it may have been used inappropriately, and what neurologic outcomes may have been beyond hospital discharge. Perhaps results from CHS are not representative of other communities, as suggested by the recent study using a large administrative discharge database [14]. Concern over age may have been more important than suggested in previous works [15]. Other contraindications may have existed, or results might differ in subsequent years. In previous studies, the most common reason for patients with ischemic stroke not to receive IV tPA is onset of symptoms more than three hours prior to presentation [15]. Study neurologists tried to collect information on timing of symptom onset and hospital arrival from medical records, but it was lacking in 83 percent of participants, reflecting documentation during this interval from 1995 to 2002 in the many hospitals within the four study communities providing routine care for these and other patients. In the prototypes of the Paul Coverdell National Acute Stroke Registry information on timing was missing in up to 42% of patients [13].

Whether benefits of IV tPA seen in a younger selected population of patients entered into the NINDS trial, where the mean age of the participants was 67 years old [1], will translate into benefits for an older population cannot be answered in observational studies such as CHS.

Confirming a benefit for IV tPA in the most elderly, who face the greatest risk of ischemic stroke, will remain a challenge. Ongoing clinical trials may provide more direct evidence about the utility of thrombolytics in elderly patients with acute ischemic stroke [6,12].

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Figure 1.

Percentages with outcomes at three months on the National Institutes of Health Stroke Scale (NIHSS), the Barthel Index, modified Rankin Scale, and the Glasgow Outcome Scale (GOS) according to treatment in younger ($n = 580$, 293 placebo and 287 IV tPA) and older patients ($n = 44$, 19 placebo and 25 IV tPA) based on data from the NINDS trial [1]. In the 44 patients over 80 years old, none of the differences in any of the four outcomes used in the trial and measured at three months was significant: chi-square p-value for all categories for NIHSS was 0.972; for Barthel, 0.836; for Rankin, 0.981; for GOS, 0.900.

Table 1

Participants in the Cardiovascular Health Study treated with intravenous tissue plasminogen activator (IV tPA) for acute ischemic stroke between 1995 and 2002.

Year	Site	Age, Sex and handedness	Status before IV tPA	Delay to IV tPA	Bleeding into brain	Hospital outcome after IV tPA.
1998	NC	83-yo woman R-handed	R hemiplegia, aphasia	< 3 h	No	No improvement. DC to SNF with PEG.
1999	NC	88-yo man R-handed	Improving R hemiparesis, mild aphasia	< 3 h	No	Complete recovery within 24 hours. DC to home.
1999	NC	80-yo woman R-handed	L hemiplegia, neglect	< 3 h	Yes	Initially improved but worsened with brain hemorrhage. DC to rehabilitation
1999	NC	91-yo woman	R hemiparesis, fluent aphasia	2 h	Yes	Died.
2000	NC	85-yo woman R-handed	R hemiplegia, mild aphasia	1h 55m	No	Improved. DC to rehabilitation.
2001	CA	80-yo woman R-handed	R hemiplegia, aphasia	2h 30m	No	No improvement. DC to SNF.
2002	CA	83-yo woman	L hemiplegia, severe dysarthria	< 3 h	No	No improvement. DC to SNF with PEG.

NC, North Carolina; CA, California; R, right; L, left; h, hours; m, minutes; DC, discharged; SNF, skilled nursing facility; PEG, percutaneous endoscopic gastrostomy.