Ischemic Preconditioning From Transient Ischemic Attacks?
Data From the Northern California TIA Study

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Abstract—Reduced impact of ischemia after an initial ischemic insult—ischemic preconditioning—has been demonstrated in a number of animal models. Transient ischemic attack (TIA) may produce ischemic preconditioning in people who have a subsequent stroke within days of an initial ischemic insult. We performed a cohort study of all 1707 patients given a diagnosis of TIA by an emergency department physician in 1 of 16 hospitals in a managed care plan in Northern California from March 1997 to February 1998. We evaluated the impact of the timing and duration of TIA on disability in a cohort of 180 patients with TIA and subsequent ischemic stroke within 90 days of the TIA. There was no association between duration of TIA, used as a surrogate for degree of ischemia, and likelihood of disability from a subsequent stroke. Furthermore, there was no difference in rates of disability among patients with strokes occurring within 1 day, 1 to <7 days, and 7 to 90 days after the TIA. We cannot confirm results of several other studies showing an association of prior TIA with lesser stroke severity. Whether differences in underlying pathophysiology and treatment of those with prior TIA could account for differences in outcome of subsequent strokes in prior studies is unknown. Evaluating whether ischemic preconditioning occurs after TIA is extremely difficult in observational studies in humans. Given the potential hazards of inducing therapeutic transient brain ischemia in humans, a trial may not be advisable, and proof may require testing of agents that safely mimic the effects of ischemia. **(*Stroke*. 2004;35[suppl I]:2680-2682.)**

Key Words: brain ischemia ■ cerebral ischemia, transient ■ cerebrovascular accident ■ ischemic preconditioning

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There is substantial evidence supporting the existence of ischemic preconditioning in animal models. In a variety of species and models of ischemia, a prior ischemic insult in the brain is associated with protection from infarction resulting from a second insult.[1] The degree of protection from infarct is greater with longer duration and greater distribution or severity of the initial ischemia and is dependent on the duration between the initial and subsequent injuries, with some effects present within hours and others persisting for days.

Several studies have evaluated whether ischemic preconditioning occurs after transient ischemic attacks (TIAs) in humans. Published results have generally suggested that ischemic strokes are less severe in patients with prior TIA.[2–7] Because the causes and pathophysiology of strokes in patients with preceding TIAs may differ in other important ways, such as by underrepresentation of cardioembolic events, it is unclear whether these associations are due to ischemic preconditioning or confounding from other factors.

A study including only patients with TIA and subsequent stroke, both of varying severity, may avoid some of these sources of confounding by creating a more homogeneous sample. In a large cohort of patients from the Northern California TIA Study, we sought to determine whether greater duration of the original TIA was associated with decreased likelihood of disability among those with subsequent strokes. We also tested whether strokes occurring within 1 week of the TIA are less severe than those occurring later.

Methods

Details of the Northern California TIA Study have been described elsewhere.[8] Briefly, we included all patients with a diagnosis of TIA given by an emergency department physician in 1 of 16 hospitals in the Kaiser-Permanente system of Northern California between March 1997 and February 1998. We reviewed multiple record sources for evidence of subsequent stroke or other adverse events during the 90 days afterward. Strokes were adjudicated using a standard definition[9] by 2 neurologists reviewing the records independently, who also determined whether the stroke was disabling (defined as a modified Rankin Scale score ≥2); disagreements were resolved through discussion. Clinical, laboratory, and imaging characteristics were extracted from medical records and databases by trained records analysts.

For this analysis, we evaluated whether duration of the original TIA, as a surrogate for "dose" of ischemic preconditioning, was associated with the likelihood that a subsequent stroke was disabling. Among those with a stroke during follow-up, we compared duration of TIA symptoms in those with and without disability from the stroke using the Wilcoxon rank sum test. We also compared delay between TIA and subsequent stroke in those with and without disability from the subsequent stroke using the Wilcoxon rank sum test. We categorized delay as <1 day (consistent with immediate ischemic preconditioning), 1 to <7 days (delayed preconditioning), and 7 to

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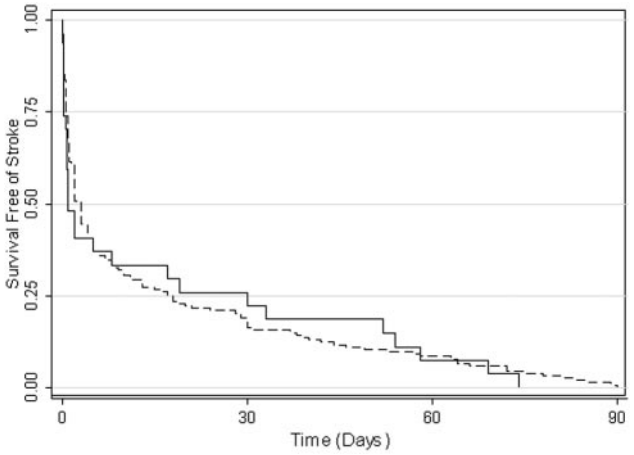

Survival free of stroke after TIA among those with stroke during 90-day follow-up, comparing those with disabling strokes (dashed line) to those with nondisabling strokes (solid line). The delay between TIA and stroke among those with disabling and nondisabling strokes was not different ($P=0.52$).

90 days (no expected preconditioning), and compared rates of disability with a Fisher exact test. In multivariable logistic regression analysis, we evaluated duration of TIA symptoms (continuous) and delay between TIA offset and stroke (categorized as described above) as predictors of whether a stroke was disabling after adjustment for age, history of diabetes, and presence of weakness and speech impairment with the TIA. Stata (version 8.0; Stata Corp) was used for all statistical analyses.

Results

Among 1707 patients diagnosed with TIA, 180 ischemic strokes occurred within the subsequent 90 days, of which 153 (85%) were disabling. Duration of TIA symptoms was similar between those with disabling (median 120 minutes, intraquartile range [IQR] 20 to 365 minutes), and nondisabling stroke (120 minutes, IQR 30 to 270 minutes; $P=0.97$).

The period between offset of TIA symptoms and onset of subsequent stroke was similar in those with disabling (median 3.0 days, IQR 0.7 to 17.0 days) and nondisabling stroke (0.9 day, IQR 0.3 to 30.0 days; $P=0.52$; Figure). Among those with stroke, the stroke was disabling in 85% when it occurred within 1 week of the TIA and in 84% of those with stroke occurring >1 week ($P=0.83$). Disability occurred in 78% of strokes occurring within 24 hours, 94% of those from 1 to <7 days, and 85% of those from 7 to 90 days ($P=0.044$).

After adjustment for age, history of diabetes, delay between TIA and stroke, and the presence of weakness and speech impairment with the original TIA, duration of TIA was not a predictor of whether a subsequent stroke was disabling ($P=0.78$). In the same model, disability was not significantly different in those with stroke occurring within 1 day of the TIA (odds ratio, 0.7; 95% CI, 0.3 to 1.9; $P=0.53$) or 1 to 7 days (odds ratio, 3.5; 95% CI, 0.9 to 14; $P=0.08$), compared with those whose stroke occurred 7 to 90 days after the TIA, when ischemic preconditioning was not expected.

Discussion

In this study of stroke after TIA, we did not find an association between disability with the stroke and duration of the TIA, a surrogate for the severity of ischemia. Similarly, we did not find a difference in rates of disability between those whose strokes occurred within 1 day, 1 to <7 days, or 7 to 90 days after the TIA. In fact, there was a trend toward *greater* disability among those whose strokes occurred 1 to <7 days after the TIA, during a period when delayed ischemic preconditioning would have been expected. Thus, we cannot confirm that ischemic preconditioning has an impact on disability after TIA.

In an attempt to find clinical evidence of ischemic preconditioning, a number of other studies have evaluated whether the *occurrence* of prior TIA is associated with the severity of stroke. These studies implicitly assume that other aspects of pathophysiology are similar in those with and without TIA. This assumption may not be valid; for example, cardioembolic strokes are less likely to be preceded by TIA and are associated with greater severity,[3,6] potentially confounding a comparison of those with and without prior TIA. Our study is distinct in limiting inclusion to those with TIA and comparing stroke severity based on timing of events and the duration of the original TIA. This approach should reduce bias.

However, our study has a number of limitations. Power is restricted because of the small number of patients with nondisabling strokes in our cohort and the absence of a continuous measurement of stroke severity. Although we adjusted for some important baseline differences that would be expected to be associated with risk of disability, the variability in distributions and causes of strokes could overwhelm an important effect of preconditioning on outcomes. We also had no real measure of the "dose" of the initial ischemia and relied on duration of symptoms. Although symptom duration is associated with severity of ischemia,[10,11] the severity of symptoms is also likely to be important and was not measurable based on clinical history. Furthermore, we would expect preconditioning to be more dramatic when the same distribution was affected by the TIA and the subsequent ischemia, but we could not determine distribution reliably from the clinical history. For all these reasons, we could have missed a clinically significant effect of preconditioning.

Other clinical studies have suggested that ischemic preconditioning may occur after TIA. Although these have been generally well designed, each has limitations inherent in observational studies.

Two studies have evaluated the impact of prior TIA on outcomes after ischemic stroke using data from the Lausanne Stroke Registry.[2,3] In the first, prior TIA was evaluated as a predictor of neurologic worsening, defined by the treating neurologist during the period of hospitalization as deterioration in neurological function that was not due to recurrent infarction.[2] Among 1968 with noncardioembolic ischemic stroke, 326 (17%) had a preceding TIA referable to the same distribution as the index stroke. Overall, neurological worsening occurred in 27% with prior TIA and in 36% without prior TIA ($P=0.01$). In multivariable analysis adjusting for other predictors of neurological worsening, the association of prior TIA with lower risk of deterioration was not present in those with large-artery atherosclerosis and was limited to those with small-artery disease. No information on timing of the preceding TIAs was provided.

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The second study from Lausanne included patients with anterior circulation ischemic strokes, of whom 293 had a preceding ipsilateral TIA lasting <60 minutes and 2086 did not.[3] Those with prior TIA were less likely to have decreased level of consciousness at hospital admission. For TIAs lasting 3 to 30 minutes, good outcomes were more frequent, but TIAs ≥60 minutes were not associated with better outcomes compared with those without prior TIA. The effect was greatest in those with TIAs occurring within the week prior to the stroke. Cardiac sources were less frequent in those with prior TIA and, after adjustment, the association remained significant only in the group with 10 to 20 minute TIAs, which is hard to reconcile with animal studies.

In a cohort of patients with ischemic stroke from Berlin Charité Hospital, 37 had preceding TIA and a sample of 111 was selected at random for comparison.[4] Those with prior TIA had more minor strokes on hospital admission and were more likely to be discharged without dependency. However, those with prior TIA died more frequently, and those dying were excluded from the overall analysis. The mean time between TIA and stroke was 21 days, at which time ischemic preconditioning is unlikely to be important, and the effect of timing or duration of TIA on outcome was not evaluated.

In a large cohort of 4797 German patients with anterior circulation infarction, 332 had a TIA at an unmeasured time in the past.[5] Prior TIA was associated with a better outcome after ischemic stroke, even after adjustment for stroke subtype and other potential, measured confounders. The authors recognized several limitations of their study including lack of information about timing and location of the prior TIA and incomplete knowledge of etiology.

The German Competence Network obtained diffusion- and perfusion-weighted magnetic resonance imaging within 12 hours of onset in patients with acute ischemic stroke, of whom 16 had prior TIA and 49 did not.[6] There was no difference in initial cerebral blood flow or blood volume in the groups. Those with prior TIA had lower burden of neurological dysfunction at hospital admission and discharge. The effect was limited to the 10 patients with TIA occurring in the preceding 4 weeks; a shorter delay was not evaluated. However, proximal internal carotid artery occlusion and vascular recanalization were more frequent in those with prior TIA.

Another recent study included 283 patients with nonlacunar stroke, of whom 38 had a TIA affecting the same territory within 72 hours before.[7] Overall, those with prior TIA were less likely to have poor outcomes and had smaller infarct volumes. The effect was present in those with both atherothrombotic and cardioembolic strokes. Contralateral TIAs were not associated with improved outcomes. However, those with prior TIA were all admitted on antithrombotic medications, whereas only 28% of others were receiving them on admission.

Each of these 6 studies has reported an association between prior TIA and reduced impact of subsequent ischemia, but each has limitations. Those with prior TIA may be different from others in a number of important ways. In particular, the occurrence of a TIA may indicate a different group of underlying causes, as demonstrated by the overrepresentation of atherothrombotic strokes and underrepresentation of cardioembolic strokes in those with prior TIA.[3,6] Identification of the true cause of a stroke is unreliable even when using standardized criteria,[12] so control will be incomplete. Furthermore, TIA often precipitates treatment with prophylactic medications and these may impact outcomes.[4,5,7] Given these difficulties, it may never be possible to completely disentangle a true clinical effect of ischemic preconditioning from confounding in an observational study. Also, given the potential dangers of inducing brain ischemia and the limited duration of its efficacy, a randomized trial is difficult to imagine. Rather, safer methods of inducing the effects of transient ischemia are required. Then, given the high risk of stroke after TIA,[13] patients with recent TIA may be excellent candidates for this medication-induced preconditioning.

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