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Transient Ischemic Attack Before Nonlacunar Ischemic Stroke in the Elderly

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Abstract

Background: Several studies suggest transient ischemic attack (TIA) may be neuroprotective against ischemic stroke analogous to preinfarction angina's protection against acute myocardial infarction. However, this protective ischemic preconditioning-like effect may not be present in all ages, especially among the elderly. The purpose of this study was to determine the neuroprotective effect of TIAs (clinical equivalent of cerebral ischemic preconditioning) to neurologic damage after cerebral ischemic injury in patients over 65 years of age.

Methods: We reviewed the medical charts of patients with ischemic stroke for presence of TIAs within 72 hours before stroke onset. Stroke severity was evaluated by the National Institutes of Health Stroke Scale and disability by a modified Rankin scale.

Results: We evaluated 203 patients (≥ 65 years) with diagnosis of acute ischemic stroke and categorized them according to the presence ($n = 42$, 21%) or absence ($n = 161$, 79%) of TIAs within 72 hours of stroke onset. Patients were monitored until discharged from the hospital (length of hospital stay 14.5 ± 4.8 days). No significant differences in the National Institutes of Health Stroke Scale and modified Rankin scale scores were observed between those patients with TIAs and those without TIAs present before stroke onset at admission or discharge.

Conclusion: These results suggest that the neuroprotective mechanism of cerebral ischemic preconditioning may not be present or functional in the elderly.

Keywords

Cerebral ischemic preconditioning; transient ischemic attack; elderly; stroke

Ischemic preconditioning (IPC) is defined as brief episodes of ischemia followed by a long period of ischemia, representing the most powerful endogenous mechanism against the injurious effects of ischemia.¹ Transient ischemic attack (TIA) before ischemic stroke in the

same vascular territories could represent a clinical equivalent of cerebral IPC.^{2,3} Several reports suggest TIA prestroke may be protective against cerebral damage after cerebral ischemic injury in middle-aged patients (average 56-62 years of age).^{2,4,5} Despite no significant differences in baseline characteristics, self-sufficiency and favorable outcome were significantly associated with prior TIA in those patients.²

Currently, TIA is considered a factor associated with the increased risk of stroke.⁶ It is clinically well accepted that age is the most important independent risk factor for cerebrovascular disease.⁷ The incidence of TIA in the elderly can vary by as much as 8% among industrialized populations.⁸ Recently, in a systematic review, meta-analysis from 11 previous epidemiologic studies reported early risk of stroke after TIA among the elderly.⁹ Based on these results, the early risk of stroke after TIA in the elderly is between 15% and 20% within 90 days. Within the first 2 days after TIA, the risk of stroke is approximately 9.9%. In addition, different age subgroups may have different sensitivities to TIA, a clinical equivalent of IPC.¹⁰

Investigating cerebrovascular disease among the older population is an important public health goal as the incidence of cerebrovascular disease and mortality from stroke are 3 times higher in the elderly as compared with younger patients.^{7,11} In addition, stroke is the leading cause of disability in the elderly.¹² Several changes occur during aging that may explain this age-related increase of stroke-related mortality: neuronal loss in the aging brain, enhanced free radical production, altered mitochondrial metabolism, and calcium neurotoxicity.^{13,14} However, comorbidity, typical of elderly patients, does not fully account for the age-related increased in-hospital mortality.¹⁵ This suggests that the higher stroke mortality observed in elderly patients may be caused, at least in part, by the age-related reduction of endogenous protective mechanisms against brain ischemia. Therefore, we hypothesized that IPC in the brain may diminish in elderly patients with stroke. The goal of this study was to determine whether TIA, occurring within 72 hours of onset of ischemic stroke, had a protective effect (less severe strokes and better outcome) in elderly patients with stroke.

Methods

We retrospectively reviewed the charts of 938 patients ages 65 years or older, admitted to our study institution between January 2000 and March 2005, with a diagnosis of acute stroke by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).¹⁶ Stroke was defined by codes 433.x1, 434.x1, and 436.xx.¹⁷ All procedures were approved by our ethics council. All patients gave their informed consent to participate in this study. Exclusion criteria were intracerebral hemorrhage (n = 105, 11%), subarachnoid hemorrhage (n = 77, 8%), thrombosis of cerebral sinus (n = 99, 10%), pre-existing dementia (n = 57, 6%), and previous strokes or TIAs with infarction on cerebral computed tomography (CT) within the same vascular territory (n = 219, 24%). We excluded elderly patients with previous strokes or TIAs with infarction on cerebral CT within the same vascular territory because it would be difficult to compare TIA-induced neuroprotection against stroke between patients with incidence stroke and those with recurrent stroke as the possible effect of TIA-induced neuroprotection would have been diminished in an already damaged brain.

All previous diseases were defined according to ICD-9-CM. We also excluded lacunar stroke (n = 178, 19%) defined by ICD-9-CM, code 434.91,¹⁸ and defined clinically and by brain imaging as a presence of small infarct up to 15 mm in maximum diameter located in the territory of small-vessel disease or when the two CT scans were un-revealing. We excluded lacunar stroke because prior TIA was not associated with a favorable outcome in patients with this type of ischemic stroke.^{19,20} The etiopathology of stroke and the hyalinosclerosis process typically present in the small-vessel disease before ischemia could be one of the main reasons of the lack of TIA/IPC mechanism of neuroprotection in patients with lacunar stroke.

We categorized the study population ($n = 203$, 22%) according to the presence ($n = 42$, 21%) or absence ($n = 161$, 79%) of TIA within 72 hours of ischemic stroke. We chose this time interval to test the protective effect of early cerebral IPC similar to previous IPC studies in the heart²¹ and brain.²² TIA was defined according to ICD-9-CM^{23,24} as a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 24 hours (average time 37 ± 12 minutes), and without brain imaging evidence of acute infarction.²⁵ Hemispheric TIAs were defined as acute attacks of unilateral motor or sensory symptoms or dysphasia, whereas posterior circulating TIAs were defined as attacks that included at least two of the following signs: vertigo, dysarthria, diplopia, hemianopsia, or unilateral/bilateral motor or sensory symptoms. TIA was defined by codes 362.34, 435, 435.0, 435.1, 435.3, 435.8, and 435.9.¹⁷

Age; sex; cholesterol; alcohol consumption; current smoking status; several chronic conditions such as chronic heart failure, chronic obstructive pulmonary disease, coronary heart disease, atrial fibrillation, diabetes, hypertension, and peripheral artery disease; and various drug therapies (i.e., salicylate, anticoagulants, thrombolytics, statins, diuretics, angiotensin-converting enzyme inhibitors, β -blockers, and calcium channel blockers) were considered. Hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, the use of antihypertensive drugs, or a combination of these. Hyperglycemia was defined as serum glucose level greater than or equal to 110 mg/dL, use of hypoglycemic medication, or both. Dyslipidemia was defined as triglyceride level greater than or equal to 150 mg/dL, high-density lipoprotein less than 40 mg/dL, the use of medication for dyslipidemia, or a combination of these. All other comorbidities were defined by patient history.

The stroke severity was assessed by a certified neurologist using the National Institutes of Health Stroke Scale (NIHSS)²⁶ at admission and discharge. Disability was assessed with the modified Rankin scale.²⁷ We also stratified the patients with TIA in the 3 subgroups by different time points between TIA and stroke onset: 0 to 24 ($n = 9$, 22%); 25 to 48 ($n = 22$, 52%); and 49 to 72 ($n = 11$, 26%) hours, and evaluated possible differences in neurologic impairment and disability among these groups. A brain CT scan was performed at admission, after 24 to 48 hours, and sometimes, after 72 hours from the acute stroke onset.

Continuous variables are presented as means $\pm$ SEM, and categorized as proportions. The categorical and continuous data were analyzed by the Chi square and Student's *t* test, respectively. A one-way analysis of variance followed by a multiple comparison procedure (Bonferroni's test) was used to analyze the difference among groups. A *P* value of less than .05 was considered significant.

Results

Baseline characteristics of our population of patients with stroke are shown in Table 1. Among the 203 patients with ischemic strokes who met all inclusion criteria, we identified 42 patients with prodromal TIAs. No significant differences were observed between the two groups of patients regarding any of the variables analyzed (Table 1). At the time of admission, the median patients' NIHSS score was 6 (mean $\pm$ SEM: 5.77 ± 0.88) in patients with and 5 (5.24 ± 0.65) in those without TIA before stroke ($P = .629$) (Fig 1, A). Similarly, at discharge, no significant difference in NIHSS score was observed between the two groups (TIA, NIHSS score = 4, 4.09 ± 0.78 ; non-TIA, NIHSS score = 4, 3.53 ± 0.63 ; $P = .594$) (Fig 1, A). At the time of admission, the patients' median modified Rankin score equaled 3 in patients with (3.4 ± 0.25) as well as without (2.97 ± 0.15) TIA before stroke ($P = .120$) (Fig 1, B). Similarly, at discharge, no significant difference was observed between the two groups (TIA 2.45 ± 0.34 v non-TIA 2.41

± 0.20 ; $P = .916$) (Fig 1, B). In addition, between the two groups of patients with stroke, the length of hospital stay (mean: 14.5 ± 4.8 days) was not significantly different.

After stratification of the patients according to the 3 different time points between TIA and stroke onset, no significant differences were detected in the NIHSS score between the groups, neither at admission or discharge (Fig 2) nor in the modified Rankin score at discharge.

The mean NIHSS score at admission was 5.9 ± 0.7 for those who had TIA between 0 and 24 hours before stroke onset; 4.9 ± 1.4 for those with TIA between 25 and 48 hours before stroke onset; and 6.4 ± 2.1 for those with TIA between 49 and 72 hours before stroke onset ($P = .597$). The mean NIHSS score at discharge was 4.2 ± 1.3 for those who had TIA between 0 and 24 hours before stroke onset; 3.5 ± 1.0 for those with TIA between 25 and 48 hours before stroke onset; and 3.9 ± 2.0 for those with TIA between 49 and 72 hours before stroke onset ($P = .710$) (Fig 2, A). The mean modified Rankin scale score at discharge was 2.6 ± 0.6 for those who had TIA between 0 and 24 hours before stroke onset; 1.9 ± 0.7 for those with TIA between 25 and 48 hours before stroke onset; and 3.1 ± 0.7 for those with TIA between 49 and 72 hours before stroke onset ($P = .526$) (Fig 2, B). Moreover, no significant differences in neurologic impairment ($P > .507$; $P > .703$) and disability ($P > .206$) after stroke were observed among any of the 3 TIA subgroups in comparison with patients without TIA (Fig 2).

Discussion

The data suggest that elderly patients with stroke and presence of TIA within 72 hours of stroke onset present similar neurologic damage and subsequent disabilities as those patients without prior TIA. This observation confirms our hypothesis that IPC diminishes with increased age, similar to that observed in elderly patients with myocardial infarction (MI).²¹ Thus, the absence of this endogenous protective mechanism in the brain may justify, at least in part, the age-related increase in mortality for stroke.

IPC is defined as brief periods of ischemia that are able to reduce the deleterious effects of a subsequent, longer-lasting ischemic episode, first described in the heart.¹ Moreover, the neuroprotective role of cerebral IPC is demonstrated by mammalian in vivo and in vitro studies.²⁸ Focal or global cerebral ischemia is able to induce ischemic tolerance against ischemic injury in rodents.^{29,30} In vitro studies using oxygen-glucose-deprived rat hippocampal slices suggest neurons subjected to short intervals of this procedure are more resistant to successive ischemic damage.³¹ Recently, other studies have demonstrated the possible protective role of TIA as equivalent to cerebral IPC in patients with stroke.²⁻⁵ In a retrospective case-control study in 148 adult patients with stroke (mean age = 59.4 years) with and without antecedent TIA, favorable outcomes were significantly associated with prior TIA in univariate and multivariate analyses.² Moncayo et al³ screened 2490 patients younger than 65 years with diagnosis of stroke. In this study, a total of 293 patients presented ipsilateral TIA occurred few days before cerebral ischemic injury. The patients with TIA before stroke had favorable neurologic outcomes compared with patients without prior TIA. Prior TIA was associated with favorable outcomes in nonlacunar ischemic stroke in a study of 1753 consecutive patients younger than 65 years of age.²⁰ Schaller⁴ demonstrated improved NIHSS score in adult patients (mean age = 59.7 years) with TIA 1 to 7 days before ischemic stroke. In addition, an interesting study evaluated the effects of IPC in 12 adult patients with aneurysmal subarachnoid hemorrhage. IPC was induced by 2-minute proximal temporary artery occlusion followed by 30 minutes of reperfusion. A calibrated multiparameter catheter was inserted in the artery to measure oxygen tension, carbon dioxide, tension, and pH in tissue at risk of ischemia during temporary artery occlusion. The results suggest that IPC attenuates tissue hypoxia during subsequent artery occlusion in human beings.³² Recently, Wegener et al⁵ compared the brain magnetic resonance images of patients with ischemic cerebral damage with and without TIA

(mean age = 59.0 years) before stroke demonstrating that the extension of the lesion was clearly smaller in the patients with TIA before stroke. Collectively, these studies clearly demonstrate that TIA before stroke, which has similar causative effects to IPC, is neuroprotective in young to middle-aged patients. However, the data on IPC among elderly patients with stroke are limited.

In this study, the reduction of the protective effect of TIA before stroke in the elderly may be responsible for age-related increase of mortality for stroke.^{7,11} The aging human brain is characterized by a decrease in ischemic tolerance including a defect in mitochondrial metabolism, with consequent oxidative stress and increased intracellular calcium influx.^{13, 14} In addition, age-related higher comorbidity¹⁵ and lower thrombolytic therapy use³³ cannot alone justify the higher stroke-related mortality in the elderly. First demonstrated in the perfused rat heart, the reduction of IPC was attributed to the age-related decrease of norepinephrine release and alpha-adrenergic receptors.³⁴ Subsequent clinical studies showed a reduced protective effect of preinfarction angina, a clinical equivalent of IPC, against MI in the elderly.²¹ Moreover, IPC was lost in the elderly resulting in reduction of a 5-year survival after MI.³⁵ Recently, it has been demonstrated that the protective mechanism of IPC induced by 3 minutes of ischemia (4-vessel occlusion method) against global cerebral ischemia was reduced in old rats (24 months) compared with young rats (4 months).³⁶

Limitations

This study is a retrospective medical chart review. Limitation of using ICD-9-CM codes was recognized in the analyses of administrative databases selected by using ICD-9-CM codes 433 through 436.³⁷ This study has a limited number of patients; however, other clinical studies reporting on TIA among patients with stroke had similar sample sizes.^{2,4} The current study evaluated elderly patients with stroke only; therefore, the neuroprotective mechanism of TIA in younger patients could not be elucidated. The effect of TIA as clinical equivalent of IPC in young to middle-aged patients was extrapolated from recent publications.²⁻⁵ We excluded the patients with lacunar ischemic stroke, because the protective mechanism of IPC may not be present in lacunar stroke as previously reported.^{19,20} In addition, statistical analysis is limited to univariate analysis. However, no significant differences were observed regarding the risk factors or treatment between the two groups of patients.

Conclusion

Our results showed no significant differences in the NIHSS and modified Rankin scale scores between elderly patients with or without TIA before stroke, either at admission or at discharge. These data suggest that the protective mechanism of cerebral IPC is not present in elderly patients. Further studies are needed to verify the protective role of TIA before stroke and the loss of cerebral IPC in elderly patients. The possible absence of preconditioning in the brain might account in part for the higher mortality from stroke observed in elderly patients.

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Figure 1. Neurologic status evaluated according to NIHSS (A) and disability assessed with modified Rankin scale (B) in elderly patients with or without TIA before stroke (P value $\leq .05$ represents statistical significance). ns, Not significant via Student's t test.

Figure 2.

Comparison between patients with and without TIA before stroke stratified by 3 different time points between TIA and stroke onset: 0 to 24 (n = 9), 25 to 48 (n = 22), and 49 to 72 (n = 11) hours. Neurologic status evaluated according to NIHSS (A) and disability assessed with modified Rankin scale (B) in elderly patients with or without TIA before stroke. No significant differences are present among groups (P value $\leq .05$ represents statistical significance). ns, Not significant via Bonferroni's test.

Table 1

Characteristics of all patients studied and stratified for the presence and absence of TIA before stroke (p value less or equal to 0.05 represents statistical significance; ns, denotes not significant via Bonferroni's test)

Variables	All patients (n = 203)	TIA n = 42 (21%)	No TIA n = 161 (79%)	P
Age (mean $\pm$ SEM)	75.15 $\pm$ 0.7	75.43 $\pm$ 2.27	74.13 $\pm$ 0.87	0.570 (ns)
Female (n, %)	93 (46)	23 (55)	70 (44)	0.225 (ns)
Male (n, %)	110 (54)	19 (45)	91 (56)	0.129 (ns)
Alcohol consumption (n, %)	77 (38)	14 (33)	63 (39)	0.478 (ns)
Current smoking status (n, %)	71 (35)	9 (21)	62 (38)	0.065 (ns)
Hypercholesterolemia (n, %)	105 (52)	20 (47)	85 (53)	0.341 (ns)
Chronic heart failure (n, %)	38 (19)	7 (17)	31 (19)	0.444 (ns)
Chronic obstructive pulmonary disease (n, %)	53 (26)	8 (19)	45 (28)	0.178 (ns)
Coronary heart disease (n, %)	69 (32)	18 (43)	51 (32)	0.103 (ns)
Atrial fibrillation (n, %)	27 (13)	5 (12)	22 (14)	0.535 (ns)
Diabetes (n, %)	65 (32)	16 (32)	49 (30)	0.199 (ns)
Hypertension (n, %)	138 (68)	32 (76)	106 (66)	0.160 (ns)
Peripheral artery disease (n, %)	51 (25)	12 (29)	39 (24)	0.290 (ns)
Salicylate (n, %)	94 (46)	21 (50)	73 (45)	0.308 (ns)
Anticoagulants (n, %)	105 (52)	23 (55)	82 (60)	0.339 (ns)
Thrombolysis (n, %)	15 (7)	3 (7)	12 (7)	0.638 (ns)
Statins (n, %)	29 (14)	9 (21)	20 (12)	0.99 (ns)
Diuretics (n, %)	75 (37)	14 (33)	61 (38)	0.399 (ns)
ACE-inhibitors (n, %)	87 (43)	22 (52)	65 (40)	0.086 (ns)
β -blockers (n, %)	12 (6)	4 (10)	8 (5)	0.208 (ns)
Calcium channel blockers (n, %)	47 (23)	13 (40)	34 (21)	0.115 (ns)