Study on influence of transient ischemic attack on subsequent cerebral infarction

H.-L. HUANG, N. WANG, H. ZHOU, C.-Y. YU

Department of Neurology, The First Hospital of Xuzhou, Xuzhou, Jiangsu, China

Abstract. – OBJECTIVE: To investigate whether transient ischemic attack (TIA) had an ischemic preconditioning neuroprotective effect on subsequent cerebral infarction.

PATIENTS AND METHODS: 232 patients with cerebral infarction were selected and divided into Group A (<55 years old), Group B (55-75 years old) and Group C (>75 years old), according to age. Each group was further divided into subgroups A1, A2, B1, B2, C1, C2, according to whether there was any TIA within 48 hours after cerebral infarction or not, to compare the neurological deficit scores and the size of cerebral infarction in different groups.

RESULTS: Neurological deficit scores and the size of cerebral infarction in Group A1 and Group B1 were significantly lower than those in Group A2 and Group B2 (p<0.05); Differences between Group C1 and Group C2 were similar (p>0.05).

CONCLUSIONS: TIA before cerebral infarction may have a neuroprotective effect on subsequent cerebral infarction, which was closely related to the age of patients.

Key Words
Transient ischemic attack, Cerebral infarction, Cerebral protection.

Introduction
The significant endogenic viscera protection effects induced by ischemia and hypoxic preconditioning have already been confirmed by many studies1. However, due to the unpredictability of the diseases and the damage due to pretreatments, clinical studies of them remained limited. Cerebral infarction is the spontaneous ischemic and hypoxic preconditioning process of a pathological condition2. Traditionally, it was considered that TIA was an important factor of cerebral infarction. But recent studies have shown that repeated, transient ischemic preconditioning could significantly improve the tolerance of subsequent ischemia and reduce ischemia-reperfusion injury3. Many animal experiments have also confirmed that ischemic preconditioning had very strong neuroprotective effects4-6. However, since ischemic preconditioning is relatively limited in the human body, clinical studies are far from experimental studies. In our study, we regarded a TIA before cerebral infarction as an abiogenetic ischemic preconditioning process and made clinical comparisons between cerebral infarction patients with TIA and without TIA, thus laying a foundation for clinical researches of ischemic preconditioning. As for the time that preconditioning took effect, there were many different published reports7,8. In present comparative study, we have selected 232 cases of patients with or without cerebral infarction and compared their clinical records.

Patients and Methods

Patients
A total of 232 TIA patients with or without cerebral infarction, hospitalized in the Neurology Department of our hospital from, April 2010 to December 2013, were enrolled in our study. The cause of the disease was arterial atherosclerosis. Among the patients, there were 130 males and 102 females, aged between 52 to 88 years old, with an average age of 70 years old. The patients were divided into Group A (<55 years old), Group B (55-75 years old) and Group C (>75 years old) according to age. Each group was further divided into subgroups A1, A2, B1, B2, C1, C2, according to whether there was any TIA within 48 hours after cerebral infarction or not. Group A1, Group B1, and Group C1 were cerebral infarction groups with TIA. Group A2, Group B2, and Group C2 were cerebral infarction groups without TIA. Differences in the patients’ gender, age and weight were not significant among groups (p>0.05) (Table I). Inclusion criteria were onset within 72 hours and a neurological deficiency score of <40 points. Exclusion criteria were patients with hyperglycemia, severe hypertension and serious heart, liver, and renal insufficiency.
Methods

Cerebral MRI

The definition of TIA has been modified many times since the 1960s. In the mid-1960s, TIA was defined as a transient, focal, vasogenic neurologic impairment of fewer than 24 hours. In June 2009, the American Heart Association (AHA) and the American Stroke Association (AHA) decided to revise the definition. Its current definition is transient neurological impairment resulting from local cerebral, spinal cord, or retinal ischemia, with acute cerebral infarction excluded. But the most widely used TIA definition in clinic and studies at present is “TIA of less than 24 hours”. TIA in this paper also refers to the traditional definition of TIA. Cerebral infarction conformed to the diagnostic criteria stipulated by the WHO and was confirmed by a cerebral MRI examination.

Observation Indicator

The Modified Edinburgh Scandinavia Stroke Scale (MESSS) was applied to calculate scoring of all the patients in the different groups 1 day, 3 days, 7 days and 11 days after admission. The size of the cerebral infarction was calculated by measuring the cerebral MRI, length, width and thickness at the focal point. The size of the cerebral infarction was determined by Pullicino formula as below:

\[
\text{Size of cerebral infarction (cm}^3\) = \text{length} \times \text{width} \times \text{positive layers under CT scanning} \times \frac{1}{6}.
\]

The total size equals the accumulated sizes of the combined multiple focuses.

Treatment Method

Patients in all groups were treated with the same methods. Aspirin, clopidogrel, atorvastatin, hydroxethyl starch and symptomatic treatment measures were applied in accordance with the cause of the disease and its pathogenesis.

Statistical Analysis

Data were represented by means ± standard deviation (\(\bar{x} \pm s\)), and the variance analysis and t-test were applied to compare the multiple samples means. \(p<0.05\) was considered statistically significant.

Results

Changes of Neurological Deficit Scores

From Table I, we could see that the MESSS scores in Group A\(_1\) and Group B\(_1\) were significantly lower than those in Group A\(_2\) and Group B\(_2\) (\(p<0.01\) and \(p<0.05\), respectively). MESSS scores at different time points in Group A\(_1\) and Group A\(_2\) were significantly lower than those on the first day (\(p<0.01\), and in comparisons between Group A\(_1\), Group B\(_1\) and Group A\(_2\), Group B\(_2\) had a significant difference (\(p<0.01\)). MESSS scores in Group A\(_1\) and Group B\(_1\) began to decrease on the 7th day after admission, and the difference had statistical significance compared with that on admission (\(p<0.05\)). MESSS scores in Group C\(_1\) and Group C\(_2\) began to decrease on the 7th day after admission, and the difference had statistical significance compared with that on the 1st day (\(p<0.05\), but the difference between the two groups had no statistical significance (\(p>0.05\)).

Size of Cerebral Infarction

Differences in the size of the cerebral infarctions between Group A\(_1\) (2.17±1.92 cm\(^3\)) and Group A\(_2\) (3.68±2.19 cm\(^3\)), had statistical significance (\(p<0.01\)); differences in the size of the cerebral infarctions between Group B\(_1\) (2.20±2.05 cm\(^3\)) and Group B\(_2\) (3.57±2.43 cm\(^3\)) had statistical significance (\(p<0.01\)); differences in size of the cerebral infarctions between Group C\(_1\) and Group C\(_2\) showed no statistical significance (\(p>0.05\)).
Discussion

In our study, we have enrolled cerebral infarction patients having a TIA within 48 hours after onset as our study objective. From the results of neurological deficiency scores, we found that the initial scores of patients under 75 years old in Group A, and Group B, who had TIA were significantly lower than those in Group A, and Group B, who had no TIA. The neurological deficiency scores of patients in Group A, and Group B, began to reduce significantly on the 3rd day after admission, while neurological deficiency scores on Group A, and Group B, didn’t decrease until the 7th day after admission, and their decrease was not significant as that in Group A, and Group B. (Table I). These results indicated that patients in Group A, and Group B, had more severe illness and slower recovery. As for the patients over 75 years old, neurological deficiency scores and the size of the cerebral infarctions had no statistically significant differences between Group C, and Group C.

The result of our study showed that a TIA before cerebral infarction had protection effect on cerebral infarction and which may reduce the impact area of cerebral infarction, alleviate clinical symptoms and quicken the recovery of clinical symptoms. Our results coincided with many experimental results9,10. The underlining mechanism is still unclear. A large number of hypotheses have been put forward that ischemic preconditioning could reduce the incidence of encephaledeema after recurrent ischemia, improve the survival rate of nerve cells, and protect the blood brain barrier through many channels, including increasing the antioxidant ability, enhancing the stability of mitochondrial transmembrane potential, inhibiting the nerve cell apoptosis induced by ischemia, and increasing the release of adenosine11-13.

Results from our previous study also demonstrated that after hypoxic preconditioning, the antioxidant ability of murine brain tissues was greatly enhanced, and the activity of superoxide dismutase (SOD) in the cerebral tissues was significantly improved14,15. It was known that reperfusion injury is an important pathophysiologic process of cerebral infarction and that the outbreak of oxygen free radicals in reperfusion is an important factor that could result in ischemia reperfusion injury. Therefore, it was important to enhance the body’s antioxidant ability and then promote preconditioning to alleviate reperfusion injury. We suggest that the improving the body’s antioxidant ability was one of the most important mechanisms for the endogenic protective effect of preconditioning.

We also showed that the degree of the neuro-protective effect of TIA is related to the age of the patients. The younger the patients were, the stronger the protective effects became. Protective effects of preconditioning disappeared on patients with an age of over 75 years old. While its mechanism remains unclear, possible explanations may involve that the elders suffered from serious arteriosclerosis, which further caused their tissues and organs to be in a long-term hypoxia, or, the tissues and organs of the elders suffered from degeneration, which further led to a weaker reactivity towards ischemia and hypoxia and a weaker ischemic tolerance. Since the patient number in our work is relatively limited, the results obtained are in need of further confirmation.

Conclusions

TIA before cerebral infarction may have a neuro-protective effect on subsequent cerebral infarction, which was closely related with the age of patients. Future studies will further reevaluate the clinical significance of TIA, the influence of the onset time, the frequency and the degree of severity of a TIA on cerebral infarction, as well as its protective mechanism and potential application in cerebral infarction management.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

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