European Review for Medical and Pharmacological Sciences 2016; 20: 5164-5167

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 A_1, A_2, B_1, B_2, C_1, C_2, 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 studies[1]. 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 condition[2]. 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 injury[3]. Many animal experiments have also confirmed that ischemic preconditioning had very strong neuroprotective effects[4-6]. 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 reports[7,8]. 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 Group A_1, Group A_2, Group B_1, Group B_2, Group C_1, Group C_2 according to whether there was any TIA within 48 hours after cerebral infarction or not. Group A_1, Group B_1, and Group C_1 were cerebral infarction groups with TIA. Group A_2, Group B_2, and Group C_2 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.

Corresponding Author: Wang Nuan, MD; e-mail: 2426904934@qq.com

Table I. Comparisons of neurological deficit scores in 3 groups ($\bar{x} \pm s$).

Group	1st day	3rd day	7th day	11th day
A_1 (n=33)	16.45±3.96	13.04±4.03*	10.40±3.87**	8.09±3.80**
A_2 (n=35)	20.93±4.85°°	20.25±5.46°°	16.74±5.47*°°	16.04±5.53**°°
B_1 (n=41)	17.91±4.04	14.82±4.38*	11.79±4.51**	8.65±4.91**
B_2 (n=45)	21.42±5.62°	21.15±6.27°°	17.50±6.06*°°	14.71±6.12**°°
C_1 (n=38)	21.86±6.26	21.07±6.53	17.22±6.38*	15.41±6.46**
C_2 (n=40)	21.63±6.59	21.13±6.76	17.88±6.35*	15.53±6.67**

*p<0.05 and **p<0.01 compared with the 1st day; °p<0.05 and °°p<0.01 compared with Group A_1, Group B_1.

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[1]. 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[2].

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:

Size of cerebral infarction (cm^3) = length × width × positive layers under CT scanning × $\prod/6$.

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, hydroxyethyl 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 B_1 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_2 and Group B_2 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_1 and Group B_1 who had TIA were significantly lower than those in Group A_2 and Group B_2 who had no TIA. The neurological deficiency scores of patients in Group A_1 and Group B_1 began to reduce significantly on the 3rd day after admission, while neurological deficiency scores on Group A_2 and Group B_2 didn't decrease until the 7th day after admission, and their decrease was not significant as that in Group A_1 and Group B_1 (Table I). These results indicated that patients in Group A_2 and Group B_2 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_1 and Group C_2.

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 results[9,10]. The underlining mechanism is still unclear. A large number of hypotheses have been put forward that ischemic preconditioning could reduce the incidence of encephaledema 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 adenosine[11-13].

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 improved[14,15]. 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

1) Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009; 40: 2276-2293.

2) Truelsen T, Mähönen M, Tolonen H, Asplund K, Bonita R, Vanuzzo D; WHO MONICA Project. Trends in stroke trends in the WHO MONICA Project. Stroke 2003; 34: 1346-1352.
3) Gidday JM. Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci 2006; 7: 437-448.
4) Hamner MA, Ye Z, Lee RV, Colman JR, Le T, Gong DC, Ransom BR, Weinstein JR. Ischemic preconditioning in white matter: magnitude and mechanism. J Neurosci 2015; 35: 15599-15611.
5) Mukherjee R. Forewarned is forearmed: benefits of remote ischemic preconditioning. J Thorac Cardiovasc Surg 2016; 151: 786-787.
6) Khalid U, Jenkins RH, Pino-Chavez G, Bowen T, Fraser DJ, Chavez R. A localized ischemic preconditioning regimen increases tumor necrosis factor α expression in a rat model of kidney ischemia-reperfusion injury. Exp Clin Transplant 2015; 13: 535-542.
7) Hye Kim I, Lee JC, Ha Park J, Hyeon Ahn J, Cho JH, Hui Chen B, Na Shin B, Chun Yan B, Rueol Ryu D, Hong S, Hwi Cho J, Lyul Lee Y, Kim YM, Cho BR, Won MH. Time interval after ischaemic preconditioning affects neuroprotection and gliosis in the gerbil hippocampal CA1 region induced by transient cerebral ischaemia. Neurol Res 2016; 38: 210-219.
8) Meinertz T. No benefit after ischemic preconditioning. Dtsch Med Wochenschr 2015; 140: 1724.
9) Kapinya KJ. Ischemic tolerance in the brain. Acta Physiol Hung 2005; 92: 67-92.
10) PetroviĐová A, KurĐa E, Brozman M, Hasilla J, Vahala P, Blaško P, Andrášová A, Hatala R, Urban L, Sivák Š. Detection of occult paroxysmal atrial fibrilation by implantable long-term electrocardiographic monitoring in cryptogenic stroke and transient ischemic attack population: a study protocol for prospective matched cohort study. BMC Cardiovasc Disord 2015; 15: 160.
11) Qiao S, Mao X, Wang Y, Lei S, Liu Y, Wang T, Wong GT, Cheung CW, Xia Z, Irwin MG. Remifentanil preconditioning reduces postischemic myocardial infarction and improves left ventricular performance via activation of the janus activated Kinase-2/signal transducers and activators of transcription-3 signal pathway and subsequent inhibition of glycogen synthase Kinase-3β in rats. Crit Care Med 2015; 44: e131-45.
12) Gesuete R, Stevens SL, Stenzel-Poore MP. Role of circulating immune cells in stroke and preconditioning-induced protection. Acta Neurochir Suppl 2016; 121: 39-44.
13) Ran QQ, Chen HL, Liu YL, Yu HX, Shi F, Wang MS. Electroacupuncture preconditioning attenuates ischemic brain injury by activation of the adenosine monophosphate-activated protein kinase signaling pathway. Neural Regen Res 2015; 10: 1069-1075.
14) Huang HL, Chen BJ, Wu QZ. The change of the mice's ability to resist cumene hydrogen peroxide after hypoxic preconditioning. Basic Clin Med 2001; 21: 287.