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Frequency of microembolic signals in patients with acute ischemic stroke in middle cerebral artery territory treated with aspirin or clopidogrel

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Keywords
Microembolic Signals; Transcranial Doppler; Middle Cerebral Artery; Aspirin; Clopidogrel

Abstract

Background: In patients with acute stroke and middle cerebral artery (MCA) stenosis, microembolic signals (MES) can predict further cerebral ischemia. Therefore, this study was designed to evaluate the prevalence of MES by transcranial Doppler (TCD) in patients with MCA stenosis under treatment of aspirin or clopidogrel.

Methods: A randomized clinical trial was performed on 40 patients with acute ischemic stroke in MCA territory. They were randomly allocated in two groups that treated with aspirin (80 mg daily) or clopidogrel (75 mg daily). Clinical and diagnostic work up was included evaluation of cerebrovascular risk factors, echocardiography, carotid color Doppler and brain imaging. TCD was performed between day 3 and 7 after symptoms onset to detect MES. All high intensity transient signals (HITS) were saved and analyzed offline.

Results: Carotid stenosis was found in 13 (65%) patients of aspirin group and 12 (60%) of clopidogrel group. Four (30.8%) of aspirin group and 5 (41.7) of clopidogrel group had stenosis between 10%-50%. One patient in each group had more than 50% stenosis and the remainder had less than 10%. There was no significant difference between two groups. MES was detected in 6 (30%) of patients treated with aspirin and 4 (20%) of those treated with clopidogrel. It showed no statistically significant differences (P-value= 0.46).

Conclusion: Our results indicate a similar effect of aspirin and clopidogrel on frequency of MES in patients with MCA territory ischemic stroke.

Introduction

Atherosclerotic stenosis of cerebral vessels is a common cause of stroke and death worldwide [1]. Over 80% of all stroke deaths in the world occur in the developing countries [2]. The risk of early recurrent stroke in patients with minor strokes or transient ischemic attacks might be as high as 8-12% in the first 7 days [3]. Intracranial stenosis also has a high early risk of recurrent stroke which decreases over time. In patients with intracranial stenosis, that endarterectomy is not possible like cervical carotid stenosis; antiplatelet therapy has been recommended [1]. In patients with intracranial stenosis, the presence of microembolic signal (MES) is associated. with increased risk of early recurrent transient ischemic attack, stroke [5-7] and new silent cerebral infarcts [8]. In acute stroke patients with middle cerebral artery (MCA) stenosis, MES predicts further cerebral ischemia [9].

In recent years transcranial Doppler (TCD) was used to detect MES successfully. Considering the routine antiplatelet therapy in declining the risk of recurrent stroke

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in patients with middle cerebral artery stenosis, we conducted this study to evaluate the prevalence of MES by TCD in patients under treatment with aspirin or clopidogrel.

Materials and Methods

Forty patients were selected among acute ischemic admissions during the study period in Razi University Hospital, Tabriz, Iran. The subjects who were enrolled in this study had clinical features compatible with a stroke in MCA territory such as hemiparesis that affects the face and upper limb more than the lower limb, homonymous hemianopia, hemianesthesia, aphasia if the dominant hemisphere is involved and hemineglect agraphesthesia and astereognosis with non-dominant hemisphere lesions [1].

All patients underwent a full clinical and diagnostic work up, including evaluation of cerebrovascular risk factors, laboratory tests and brain computed tomography (CT) imaging. Carotid stenosis was assessed by a radiologist with color Doppler scanning (ALOKA ProSound 3500, Japan) with 7.5-MHz frequency. Cardiac disease was diagnosed by a cardiologist on the basis of clinical examination, electrocardiography and transthoracic echocardiography. Those patients with the potential source of cardioembolism such as atrial fibrillation, mechanical heart value, and pacemaker were excluded. Brain CT scan was performed in all patients to rule out previous subclinical infarcts and intracranial hemorrhage. In this study patients with clinical symptoms of lacunar ischemic stroke, watershed infarct, multiple infarcts, bihemispheric infarcts and a history of previous stroke were excluded, as well. In addition, patients in an agitated or confused state, unable to endure the duration of TCD monitoring were excluded.

Eligible participants were randomized in to two groups treated with aspirin 80 mg or clopidogrel 75mg daily. TCD monitoring was performed between day 3 and 7 after onset of stroke symptoms, to detected MES in both middle cerebral arteries. The TCD method and MES identification was performed in accordance with the criteria established by International Consensus Group on Microembolus Detection [10].

In this study a 2-MHz pulse-wave transcranial Doppler device (Looki-9Tc Atys Medical-France) was used for one hour insonation of both middle cerebral arteries in depth of 45 and 55mm multigate. The signal intensity measurement algorithm used the whole screen as background. A 64-point fast Fourier transformation and bigate technique was used. A detection threshold of 9dB was used. All sonic signals automatically saved on computer hard disk and were analyzed by an experienced observer who was blinded to the clinical and laboratory data.

A check list was designed to collect the demographic characteristics of the participants. The data included ago, sex, relevant medical risk factors diabetes mellitus (DM), Hypertension (HTN), hyperlipidemia (HLP), ischemic heart disease (IHD) and previous aspirin consumption. All participants signed an informed consent after receiving required information regarding the study. No additional expenses were imposed by doing this study on the patients, except for the standard of the care provided for every other patient with similar conditions. This study was approved by the local ethics committee of Tabriz University of Medical Sciences.

The results were analyzed through descriptive statistical methods, 2-chi square relation, mean, independent, Mann-Whitney u-test, samples t-test using SPSS 15 statistical software. Logistic regression was used to assessing risk factors. P-values less than 0.05 were considered as significant.

Results

Forty patients were enrolled in the study and randomized into two groups from the first day of admission 20 of them underwent treatment with aspirin (80mg daily) and others clopidogrel (75mg daily). Summary of the patients' characteristics in each therapeutic group is shown in table 1. Comparing aspirin group with clopidogrel group in regard to sex, age, HTN, DM, HLP, and IHD showed no statistically significant difference.

In all patients, electrocardiogram showed sinus rhythm and transthoracic echocardiography did not demonstrate any cardioembolic source. Frequency of carotid arteries stenosis in each therapeutic group is shown in table 2.

The mean interval time between onset of symptoms and TCD were 6.10±0.99 and 5.50±13.0 in aspirin and clopidogrel groups, respectively (P-value= 0.037). In 6 (30%) patients of aspirin group, MES were detected Among them, 2 (33.3%) had carotid stenosis less than 10% and 4 (66.6%) between 10% to 50%. Four (20%) patients of clopidogrel group were identified with microembolic signals; 1 of 4 patients (25%) had less than 10%, 2 (50%) between 10% to 50% and 1 (25%) more than 50% carotid stenosis. The comparison between two groups regarding detection of MES was not statistically significant (P-value= 0.46).

Table 1. Summary of the patients' characteristics in each therapeutic group

	Gender Male	Mean Age	HTN	DM	HLP	IHD	Previously Aspirin taking
Aspirin	7(35%)	68.95±13.55	16(80%)	3(15%)	4(20%)	1(5%)	2(10%)
Clopidogrel	12(60%)	66.10±12.17	12(60%)	8(40%)	6(30%)	7(35%)	4(20%)

Table 2. Frequency of carotid arteries stenosis in each therapeutic group

	Degree of Carotid stenosis			
	<10%	10% to 50%	50%<	Total
Aspirin	8	4	1	13
Clopidogrel	6	5	1	12

Discussion

Considering the fact that the majority of carotid emboli anatomically enter into MCA, we studied patients with ischemic stroke in MCA territories. Moreover, previous studies showed the higher prevalence of MES in patients with large-vessel atherosclerosis than in those with cardioembolic strokes, TIA or small-vessel disease [11,12].

In our study, MES was detected in 30% of patients treated with aspirin and 20% of those treated with clopidogrel. However, the comparison showed no significant difference. In addition, there were no statistically meaningful differences regarding carotid stenosis prevalence between two groups. As a result, our study found no difference in efficacy of each drug in decreasing MES.

The efficacy of aspirin versus clopidogrel in reducing the MES rate was not evaluated in previous studies. However, the efficacy of dual antiplatelet therapy versus aspirin was noticed in some of them. One of major trials, CARESS [13], showed combination therapy of aspirin and clopidogrel in reducing the MES rate in patients with symptomatic carotid stenosis were more effective than aspirin alone. These results are consistent with those from CLAIR study [14]. A recent published study evaluated the efficacy of clopidogrel versus dipyridamole in addition to aspirin in reducing embolization. They included sixty patients with recent symptomatic carotid stenosis, thirty in each group. Ambulatory transcranial Doppler were performed at baseline and after 48 hours. In patients with embolic signals at baseline, there was no difference in reduction in embolic signal frequency. The presence of MES in significant percent of our patients were in accordance with other studies [11,16]. However, absence of significant carotid arteries stenosis was in contrast to the findings of Marcus [17].

Regarding the lower cost of aspirin and no significant difference between the efficacy of aspirin and clopidogrel in decreasing the MES rate, our study suggested aspirin as a possible choice versus clopidogrel. Also in keeping with previous studies, we found transcranial Doppler as a possible beneficial and noninvasive diagnostic tool in detecting MES. Further studies with larger sample size and performing TCD at baseline for detecting MES are recommended in more confirmation of this study.

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