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The Effects of Citicoline on Cerebrovascular Hemodynamic Status in Ischemic Stroke Patients

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Abstract

Introduction: Some recent studies have shown that citicoline improves clinical symptoms in patients with stroke. Citicoline's mechanism of action in improving the clinical symptoms is not recognized yet. The aim of this study was to evaluate the cerebrovascular hemodynamic status in patients with ischemic stroke treated with citicoline compared with the control group.

Methods: In this study, 64 patients (20 male, 44 female) with supratentorial ischemic stroke were included. Patients underwent transcranial and extra cranial ultrasonography within 24 hours of admission and were divided into two equal groups (32 patients per group). One group was treated with citicoline (500 mg/day) and the second group was treated with placebo for one week. Then, patients underwent transcranial and extra cranial ultrasonography again. Data were analyzed by paired t-test and independent t-test.

Results: In this study, no significant difference between the groups in terms of age, gender, cardiovascular factors and NIHSS was observed. Peak systolic velocity (PSV) in RCCA, RICA, RVA, LVA, and mean flow velocity (MFV) in RICA and LACA were significantly different between two groups. As there was no significant difference in confounding variables between the two groups, therefore, the difference in PSV and MFV between the groups may be due to citicoline.

Conclusion: Prescription of citicoline for treatment of acute ischemic stroke is associated with hemodynamic changes in cerebral arteries. This finding can be one of the citicoline's mechanisms of action in ischemic stroke process.

Introduction

Stroke is the most common and morbid neurological disease and about ¾ of its cases are ischemic (1). Currently, the most effective drug that is used for treatment of the patients with acute stroke is fibrinolytic agents, but for various reasons, this drug cannot be used for 80 to 85 percent of the patients (1). Citicoline is a cytidine-5'-diphosphocholine synthetic form, actually an intermediate compound in phosphatidylcholine synthesis and a necessity for cell membrane synthesis (2). Some animal model studies have shown that citicoline leads to endogenous brain plasticity and restoration in ischemia cases, and reduces the volume of

ischemic edema as well (2). This drug has also shown neuroprotective properties in ischemic stroke cases (3,4). As citicoline is very safe and no severe systemic complication of this drug has been reported and it can be also tolerated well (1), therefore, therapeutic effects of this compound have been also investigated in human model studies such as dementia, head injury and stroke (1,5,6). A meta-analysis performed on 1371 patients with stroke showed that the consumption of citicoline decreases physical disability after stroke (1). In another study in Korea, which was conducted on 4191 patients with acute ischemic stroke, it was observed that citicoline is associated with improvement of the physical performance and quality of life (7). Some studies also suggest that memory impairment following stroke is reduced in the consumers of this drug (8). Radiological surveys also show a reduction in infarct volume after the consumption of citicoline (9). Despite the above mentioned findings, there is not enough evidence about the usefulness of citicoline in patients with ischemic stroke and treatment of these patients with this drug has not been confirmed (10-12). For example, in a meta-analysis conducted in 48 centers in Europe, the usefulness of citicolin was not reported (13). Doppler ultrasound is a noninvasive and reliable method for cerebral hemodynamic assessment which has been widely used in human studies (14). As the aim of the treatment of patients with stroke is to increase their blood flow and this technique can assess these changes, therefore, in this study, the effect of citicoline on cerebral hemodynamic in patients with ischemic stroke compared with the control group, was investigated. It is worth mentioning that this is the first research which assessed the effect of citicoline on stroke using Doppler ultrasound and its findings can be used in clinical practice.

Materials and Methods

This double-blind, placebo-controlled clinical trial study was conducted on 64 patients with acute supratentorial ischemic stroke in Shafa Hospital in Kerman in 2017. All patients had a stroke for the first time and were hospitalized within the first 24 hours after the onset of symptoms. Diagnosis was confirmed by CT scan and MRI (T1, T2 and DWI). Then, all patients were examined by a cardiologist and cardiac evaluation including transthoracic echocardiography (TTE), and if necessary, transesophageal echocardiography (TEE), was performed and embolic strokes were excluded. Patients with lacunar stroke, consumers of drugs except medications for cardiac ischemia, diabetes, hypertension, and hyperlipidemia and those with a history of other diseases (such as blood disorders or vasculitis) were also excluded from the study. Then patients were divided randomly into two equal groups (32 patients per group). Since the second day of admission, the first group was treated with Iv citicoline (500 mg/day) for one week. And the second group received placebo for one week. All patients received Standard treatment and those who received rtPA were excluded. For all patients, transcranial and extracranial cerebrovascular Doppler were performed using a bi-directional Doppler CW/PW connected to DWL software box (Sipplingen, Germany) before and after the intervention. The device uses two separate 4 MHZ probes for investigating common carotid arteries (CCA), internal carotid arteries (ICA) and a 2 MHZ probe to check anterior cerebral arteries (ACA), middle cerebral arteries (MCA), posterior cerebral arteries (PCA), ophthalmic arteries (OA), vertebral arteries (VA) and basilar arteries (BA). Blood flow of the arteries was checked in the standard depth and for each of the mentioned vessels, peak systolic velocity (PSV), mean flow

velocity (MFV), pulsatility index (PI) and resistance index (RI) were calculated automatically by the device. Stenosis criteria for MCA and ACA was MFV> 120 cm/sec, and for BA, VA and PCA was MFV> 100 cm/sec. If the difference was more than 30% in MCA and ACA and 50% in BA, VA and PCA, both sides of the case were considered as stenosis. Also for ICA in siphon of carotid, MFV was >100 cm/sec and in neck, PSV>125 cm/sec or ICA/CCA PSV Ratio>2 was considered as a measure of stenosis (15). Patients who could not go under ultrasound imaging were excluded. Power of study was 80% and statistical significant level was considered at P=0.05. For each patient, a questionnaire containing demographic information and other variables of the study, was completed. The risk factors were: arterial hypertension (treated or systolic blood pressure >160 mmHg or diastolic >90 mmHg, diabetes (treated or fasting blood glucose ≥126 mg/dL), dyslipidemia (treated), coronary heart disease (history of angina, myocardial infarction, or congestive heart failure confirmed by a cardiologist), smoking (>10 cigarettes per day for 6 months or during recent year by any number of cigarettes) (16). Demographic information and other findings were analyzed using descriptive statistics, paired t-test, and independent t-test. This study was approved by the Ethics Committee of Kerman University of Medical Sciences (N: IR. KMU. REC. 1394. 735, IRCT201705278430N9).

Results

In this study, 64 patients were evaluated. Table 1 shows demographic characteristics of the patients. No significant difference was seen between the two groups in terms of age, gender, cardiovascular factors and NIHSS. PSV in RCCA (P=0.008), RICA (P=0.02), RVA (P=0.008), LVA (P=0.002) and MFV in RICA (P=0.031) and LACA (P=0.033) were significantly different between the two groups (Table 2 and 3). Due to the lack of significant difference between confounding variables of the two groups, the difference between PSV and MFV in the case and control groups can be due to the use of citicoline.

Table 1. Demographic characteristics of the patients

Variable		Placebo		Intervention		P-value
		Number	Percent	Number	Percent	
Gender	Male	19	59.4	25	78.1	0.106
	Female	13	40.6	7	21.9	
Age	<40	2	6.2	5	15.5	0.676
	40-65	15	46.9	16	50	
	>65	15	46.9	11	44.5	
Diabetic	Yes	15	46.9	11	34.4	0.309
Hypertension	Yes	20	62.5	19	59.4	0.798
Hyperlipidemia	Yes	9	28.1	9	28.1	1.000
Ischemic heart disease	Yes	11	35.5	6	18.8	0.135
Opium addiction	Yes	12	37.5	15	46.9	0.448
Smoking	Yes	12	37.5	14	43.8	0.661
NIHSS	Mild	15	46.9	16	50.0	0.779
	Moderate	16	50.0	14	43.8	
	Severe	1	3.1	2	6.3	
Stenosis	Yes	15	46.9	13	40.6	0.614

Table 2. Peak systolic velocity in both groups

Peak Systolic Velocity		Placebo Group (n=32)		Intervention Group (n=32)		P-value
		Mean	SD	Mean	SD	
R CCA	Before intervention	45.65	15.38	37.65	14.65	0.021
	After intervention	45.25	14.09	37.40	13.89	0.008
R ICA	Before intervention	42.62	13.71	37.96	14.96	0.100
	After intervention	42.68	12.54	35.93	13.19	0.020
R MCA	Before intervention	84.50	27.8	85.31	41.63	0.596
	After intervention	82.00	23.90	75.46	24.63	0.240
R ACA	Before intervention	71.31	31.12	70.75	35.49	0.804
	After intervention	69.21	31.07	57.46	15.97	0.138
R PCA	Before intervention	48.59	17.97	48.00	15.32	0.973
	After intervention	48.75	17.37	43.62	13.41	0.224
R VA	Before intervention	56.25	16.18	49.50	10.66	0.053
	After intervention	57.12	14.57	47.56	11.05	0.008
L CCA	Before intervention	41.71	12.27	38.96	12.94	0.387
	After intervention	43.71	12.22	40.09	13.62	0.256
L ICA	Before intervention	43.34	16.86	44.71	24.79	0.742
	After intervention	41.12	12.93	42.03	19.70	0.697
L MCA	Before intervention	86.96	27.49	86.65	27.35	0.941
	After intervention	82.81	20.43	80.15	21.39	0.532
L ACA	Before intervention	69.37	27.91	65.37	22.83	0.762
	After intervention	69.93	25.14	62.56	22.72	0.158
L PCA	Before intervention	48.28	15.63	52.90	21.87	0.310
	After intervention	48.40	14.90	47.40	12.93	0.904
L VA	Before intervention	59.00	22.43	51.56	16.03	0.083
	After intervention	61.06	24.00	46.87	9.96	0.002
B A	Before intervention	52.21	19.23	57.96	16.72	0.057
	After intervention	53.53	19.30	55.51	15.34	0.441

Table 3. Mean flow velocity in both groups

Mean Flow Velocity		Placebo Group (n=32)		Intervention Group (n=32)		P-value
		Mean	SD	Mean	SD	
R CCA	Before intervention	17.21	4.85	16.65	5.83	0.291
	After intervention	17.65	5.56	16.40	5.38	0.123
R ICA	Before intervention	20.25	6.83	18.81	7.63	0.294
	After intervention	20.65	6.69	17.18	6.08	0.031
R MCA	Before intervention	51.12	19.33	52.68	30.41	0.680
	After intervention	50.68	17.90	43.28	12.91	0.085
R ACA	Before intervention	28.53	17.20	42.62	29.50	0.995
	After intervention	37.65	15.97	33.96	10.81	0.427
R PCA	Before intervention	27.09	11.25	26.31	6.34	0.819
	After intervention	27.34	11.35	23.68	5.13	0.247
R VA	Before intervention	30.06	9.90	27.06	6.99	0.167
	After intervention	31.15	9.72	25.71	7.11	0.058
L CCA	Before intervention	17.43	5.76	17.68	5.45	0.859
	After intervention	19.56	6.20	18.40	6.32	0.480
L ICA	Before intervention	20.65	6.50	24.50	18.71	0.835
	After intervention	20.96	7.21	20.71	10.84	0.400
L MCA	Before intervention	52.75	15.95	51.12	15.51	0.502
	After intervention	50.56	14.18	48.40	13.94	0.489
L ACA	Before intervention	39.28	14.28	37.03	10.29	0.472
	After intervention	39.84	12.37	33.06	9.36	0.033
L PCA	Before intervention	26.87	10.61	30.21	11.64	0.216
	After intervention	27.15	9.41	26.78	7.30	0.930
L VA	Before intervention	29.93	12.02	28.84	10.04	0.667
	After intervention	30.09	11.60	27.18	7.30	0.236
BA	Before intervention	27.03	11.64	35.06	11.60	0.004
	After intervention	27.75	12.31	31.51	9.52	0.109

Conclusion

This study was conducted on patients with ischemic stroke receiving citicoline, to investigate the cerebrovascular hemodynamic status. The results of this study showed that the prescription of citicoline is associated with hemodynamic changes of intracranial and extracranial cerebral arteries. However, these changes were not observed in all cerebral vessels. So far, no similar study in this field has been done to compare our results with its findings, but several important points can be extracted from this research: first, citicoline significantly increases the cerebral blood flow in acute phase of stroke. Due to the fact that therapeutic target in acute phase of ischemic stroke is to increase the cerebral blood flow, it can be concluded that prescription of citicoline in acute phase can lead to increased cerebral perfusion pressure and eventually to clinical improvement. Second, this effect is not seen in all vessels. However, the cause of increase in blood flow must be investigated through more studies. The effects of citicoline on vessels in acute phase of stroke may not be the same for all arteries, depending on the type and extent of stenosis. Third, citicoline can influence hemodynamic status of both intracranial and extracranial cerebral arteries; therefore, the effect of this drug is not related only to intracranial or extracranial cerebral arteries. It should be noted that in this study, decreased blood flow was reported in CCA in case group. However, it can be considered as an incidental finding. Many studies have investigated the possibility of citicoline positive effect on stroke. The research was mainly on the ischemic stroke cases but included hemorrhagic cases (17). Most of these studies were related to the mortality and complications in the ischemic stroke cases (18- 19) and provided various results. Some studies have reported positive effects (13,20) and some reported no clinical effect of consumption of this drug (19,21). A study showed that citicoline reduces lesion growth in brain MRI (7). The latest review implies that citicoline has a positive effect on the stroke, although this effect is limited (12). Different mechanisms that have been reported for the effects of citicoline on the stroke include neuroprotective properties (3,22), increase of circulating endothelial progenitor cells (5) and neurogenesis (23).

For the first time, the results of the present study suggest that citicoline is associated with change in cerebral blood flow, therefore, the therapeutic effects of citicoline may be due to citicoline's mechanism of action. The main limitations of this study are as following: First, it was better to compare the hemodynamic status of the stenotic vessel with other vessels to achieve a clearer view of the effects of citicoline. Second, it was better to prescribe different doses of citicoline. Third, other Doppler sonography parameters should be evaluated.

In general, the findings of this research showed that prescription of citicoline in acute phase of ischemic stroke is associated with changes in cerebral blood flow and therapeutic effect of this drug may be related to this finding.

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