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Research Article

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The Effect of Lithium on Brain-Derived Neurotrophic Factor - Level in Patients With Ischemic Stroke: A Clinical Trial

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Abstract

Background and Objectives: Previous studies have indicated that lithium may increase the level of the brain-derived neurotrophic factor (BDNF), which in turn improves the recovery of patients with stroke. In this controlled trial we evaluated the effect of lithium on BDNF serum level in patients with ischemic stroke.

Methods: In this randomized controlled trial (IRCT2013110515290N1), 46 patients with ischemic stroke in the territory of middle cerebral artery in lithium group who received aspirin (80 mg/d), atorvastatin (20 mg/d), folic acid (1 mg/d), physiotherapy (10 sessions) and lithium carbonate (300 mg/BD/30 day) 48 hours after stroke, were compared with 47 patients in the control group who received the same treatment regimen except lithium, in terms of the level of BDNF at 5 and 30 days after treatment,

Findings: The BDNF level after 30 days of treatment was found to be significantly higher in lithium group compared with control group. No significant difference in mortality rate between the 2 groups was identified.

Conclusions: We obtained further indications for the positive effect of lithium on BDNF level. Administration of lithium carbonate, therefore, may provide an inexpensive approach to reduced rate of stroke-induced disability and improved patient outcome.

Keywords: Clinical trial, Patient outcome, Treatment efficiency

Background and Objectives

Stroke is the most important cause of disability in old patients and involves motor, sensory, perceptual, and cognitive systems in these patients.[1-2] Brain-derived neurotrophic factor (BDNF) is a neurotrophin in the central nervous system and affect synaptic plasticity and neuronal functioning[3,4] and it is necessary for normal brain activities such as learning and memory.[5,6] Lithium is one of the most influential drug on the treatment of affect disorders and it has antisuicidal properties. Furthermore, it is effective in resistant depression, in acute depressive episodes and shows neuroprotective and procognitive effects).[7,8] Moreover, it is established in animal studies that lithium improves neurologic functions and reduces the infarct volume and neurological deficits in animals, after stroke.[8] Additionally, lithium has been used for a long time and literature have indicated that lithium is an effective and safe agent, moreover, the effective serum level and a toxic dose of lithium during recent 50 years are well investigated.[9] However, studies about the role of lithium in patients with stroke are rare and based on our knowledge, previous study by Mohammadianinejad et al that showed motor recovery improvement in patients with stroke after lithium treatment, was the first study in this field).[10] Therefore, we directed this clinical trial to evaluate the effect of lithium on BDNF serum level in patients with ischemic stroke referring to Golestan hospital in Ahwaz, Iran.

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Methods

Trial

In this randomized double-blind controlled trial (IRCT2013110515290N1) 782 patients with ischemic stroke referring to Golestan hospital in Ahwaz, Iran, in 2014 were recruited. Of 782 patients 123 patients were selected, however, of 123 patients 30 patients did not

complete the treatment course and finally, 93 patients were randomized in lithium (46 patients) and control group (47 patients). The criteria for enrollment were: age between 50-90 years old, ischemic stroke in middle cerebral artery including subclasses I, IV, V based on TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, in recent 48 hours and signed written consent. On the other hand, exclusion criteria were as follow: subarachnoid or intraparenchymal hemorrhage, creatinine >1.2, ejection fraction < 40%, jugular vein pressure >9 cm or history of dyspnea, infarction in recent 3 months, pulmonary edema, respiratory distress, acute or chronic diarrhea, thiazides, ACE or nonsteroidal anti-inflammatory drug (NSAID) intake, pregnancy and breastfeeding. Then the patients were randomized according to random 1:1 allocation in (lithium) or control (placebo) group. The patients in lithium group received standard stroke treatment regimen including aspirin 80 mg/d, atorvastatin 20 mg/d, folic acid 1 mg/d, physiotherapy and lithium carbonate 300 mg twice per day for 30 days, 48 hours after stroke. The patients in the control group received the same treatment regimen except lithium and received placebo (like lithium in shape and color) instead of lithium. The placebo was made of talc. The lithium serum level was measured at 5 and 30 days after treatment. Blood samples were obtained 8-12 hours after lithium intake and measured by flame photometry. The goal of treatment with lithium was achieving the serum level of lithium 0.4-0.8 mmol/L. If the level of lithium did not reach to 0.4-0.8 mmol/L, the second dosage was increased to 300 mg/8 h and was measured 5 days later. If the level of lithium reached to 0.8-1.2 mmol/L, the dose of lithium was decreased by half and renal function was evaluated again. Finally, if the level of lithium was 1.2 mmol/L or more the lithium was discontinued and the patients were excluded from the study. The level of BDNF was measured on 5 and 30 days after treatment. The mortality rate and the side effects of treatment regimen were recorded. Moreover patients' families were educated about any adverse effect related to treatment, like diarrhea, nausea, and vomiting or drug intolerance. In the presence of these side effects, lithium was cut. Fifteen days after discharge all patients were asked by telephone about the treatment course and adverse effects if any.

The patients in case and control groups were referred to the same physiotherapy clinic and 10 session's physiotherapy were performed considering the level of disability.

Data Analysis

Data were analyzed using SPSS version 20. Categorical data are presented as numbers (%), and continuous data as mean ± standard deviation (SD). We used the chi-square or Fisher exact test to compare categorical variables and the Student's *t* test, the paired *t* test, to compare continuous variables. A $P < .05$ was considered significant.

Ethical Issues

The study was approved by the Ethics Committee of Ahwaz Jundishapour University of Medical Sciences. The study procedure was explained to the patients or their guardians and their informed written consents of were taken.

Results

In this clinical trial, we evaluated 93 patients including 49 male and 44 female mean age 64.14 years. The difference between 2 groups regarding baseline characteristics was not significant (Table 1). We detected 64 patients (69.8%) with diabetes mellitus (DM) and 54 patients (59.7%) with Hypertension (HTN), the difference between case and control groups regarding HTN and DM was not significant (Table 1). The serum level of BDNF 30 days after treatment significantly increased in the case group ($P = .001$), and in the control group ($P = .03$). The difference between 2 groups regarding the level of BDNF before treatment was not significant ($P = .90$). However, after 30 days of treatment, the level of BDNF in lithium group was significantly more than the control group ($P = .001$) (Table 2). Mortality rate in control group was lower than lithium group, but the difference between 2 groups was not significant (Table 3).

Discussion

Previous reports have revealed stroke is a disease of the old population and related to serious disability in these

Table 1. The Patients' Characteristics in 2 Groups

	Control n = 47	Case n = 46	*P*
Age	63.97 ± 6.32	64.32 ± 6.57	.79
Sex			.87
Male	25 (53.2%)	24 (52.1%)	
Female	22 (46.8%)	22 (47.9%)	
HTN	33 (70.2%)	31 (67.3%)	.61
DM	27 (57.4%)	27 (58.7%)	.90

Abbreviations: HTN, hypertension; DM, diabetes mellitus.

Table 2. The Serum Level of BDNF Before and After 30 Days of Treatment in 2 Groups

BDNF	Before 30 Days of Treatment	After 30 Days of Treatment	*P*
Lithium group	700.00 ± 238.51	874.00 ± 278.72	.001
Control group	671.00 ± 269.40	733.00 ± 252.60	.03
P	.90	.001	

Abbreviation: Brain-derived neurotrophic factor.

Table 3. The Patients' Mortality Rate in 2 Groups

	Control Group n = 47	Lithium Group n = 46	*P*
Mortality rate	5 (5.4%)	6 (6.5%)	.72

patients.[11,12] Moreover, the treatment of stroke is one of the most challenging issues and the effective treatment is rare due to the nature of the disease that it is strongly associated with old age.[13] Several mechanisms such as anti-excitotoxicity effect due to glutamate–releasing and antiapoptotic effect due to the mitochondrial release of cytochrome C and expression of Bcl-2, may mediate the efficacy of lithium on cerebral ischemia. Moreover the neurotrophic effect of lithium by inhibition of GSK-3β and activation of cyclic adenosine monophosphate leading to up-regulation and expression of Bcl-2 and BDNF, and affect the outcome of cerebral ischemia.[14-19] Additionally, the role of BDNF in stroke recovery is well established in animal experiments.[8] Previous studies revealed the role of lithium in the improvement of function of nerves due to increasing the serum level of BDNF.[11,12] A study by Xu et al in 2003 indicated the low dose lithium has an important role in neuroprotection in rats with transient focal cerebral ischemia.[20] Moreover, another study on 66 patients by Mohammadianinejad et al revealed that early treatment of patients with cortical stroke using the low dosage of lithium significantly improved motor recovery. They showed 25% of patients who were treated with lithium achieved full function versus 14% in the placebo group).[11] In this clinical trial we evaluated 93 patients with stroke, the serum level of BDNF after 30 days of treatment with lithium significantly increased (*P*=.001), although in control group also it significantly raised (*P*=.03) but the increasing level in case group was significantly more than control group (*P*=.001), in other words, lithium increased the level of BDNF more than placebo. Several studies are in keeping with our results and detected similar findings. Ricken et al signified lithium and antidepressant agents significantly increased the level of BDNF.[21] Moreover, Yoshimura et al in a small study designated increasing in serum level of BNDF after treatment of patients with paroxetine and lithium.[22] Additionally, our results supported by de Sousa et al that indicated 28 days monotherapy with lithium increased the level of BDNF in manic patients.[23] Harmoniously another study in agreement with current practice showed lithium therapy raised the level of BDNF in patients with Alzheimer.[24] Consistently, 2 meta-analyses reinforced these findings and revealed that the most of the antidepressant raised the level of serum BDNF.[25,26] In conformity with these findings, another study on 63 patients by Rybakowski et al indicated that the level of BDNF related to the level of response to the lithium and in patients with excellent response to treatment the serum level of BDNF is higher than other patients.[27] Despite raising the level of BDNF after lithium treatment in current practice, however, we revealed BDNF did not impact on mortality rate in case group (with a higher level of BDNF) and the difference between two groups was not significant. A study by de Sousa et al supported our results and showed no improvements in outcome in spite of raising BDNF after lithium therapy (23).[23] In contrast to this study, some experiences on animal reported BDNF decreases the level of post-ischemic injuries and mortality rate and increases the patient's function after stroke.[28,29]

Relative small sample size, short duration of follow-up and lack of evaluation of other neurotrophic factors were the most important limitations of current trial, further investigations with large sample size and longer follow-up duration that evaluate other neurotrophic factors related to stroke are recommended to validate the findings reported here and to answer the question regarding whether lithium is true disease modifier.

Conclusions

Our study indicated the effect of lithium carbonate on the increased serum level of BDNF. Given the positive effect of neurotrophines (such as BDNF) on the recovery of patients with ischemic stroke,[14-19] administration of lithium carbonate thus, might result in reduced disability and more satisfactory recovery in these patients at affordable medication.

Abbreviations

Brain-derived neurotrophic factor (BDNF); hypertension (HTN); diabetes mellitus (DM).

Competing Interests

The authors declare no competing interests.

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