Combination of Citicoline and Physiotherapy in Children with Cerebral Palsy

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Original Article

ABSTRACT

Background: The most common cause of physical disability in children is cerebral palsy. This study was aimed to evaluate the effect of citicoline in combination to physiotherapy versus physiotherapy alone, to improve the functional outcome in pediatric cerebral palsy.

Methods: The clinical trial was performed on 50 pediatric patients aged 18-75 months with spastic diplegia or quadriplegic cerebral palsy. Patients were assessed in two groups: case group, under treatment, using injection of citicoline (10 mg/kg) every other day for 3 months and physiotherapy. Gross motor function classification system (GMFCS) levels were assessed in all patients before and after treatment.

Results: Patient's mean age was 38.7 ± 17.2 months, and 52% were girls. Differences in the frequency of GMFCS levels between groups were not statistically significant, before (P = 0.09) and after (P = 0.47) treatment. In case group improving in GMFCS, level was occurred in 9/11 with level 2 to level 1, 3/5 with level 3 to other levels and 3/7 with level 4 to other levels. In the control group improving in GMFCS, level was occurred in 3/9 with level 2 to level 1, 3/10 with level 3 to other levels, and 2/4 with level 4 other levels. GMFCS level in 64% of cases was improved, whereas in control group, 32% was improved (P = 0.02).

Conclusions: Results demonstrated that citicoline in combination to physiotherapy appears to be a promising agent to improve gross motor function in patients with cerebral palsy versus physiotherapy alone. Although, further studies are need to be done.

Keywords: Cerebral palsy, citicoline, gross motor function classification system

INTRODUCTION

Cerebral palsy is defined as a group of disorders of the development of movement and posture, is a clinical syndrome characterized by a persistent disorder in motor control and posture, and results from nonprogressive brain damage.[1,2] The most common cause of physical disability in children is cerebral palsy with a reported incidence of 2-2.5/1000 live births.[2]

Based on nature and type of motor disabilities, cerebral palsy is classified as: spastic, ataxic, and dyskinetic cerebral palsy.[3,4] Spastic cerebral palsy is the most common type and consists of 70% of all cerebral palsy.[4] Spastic cerebral palsy syndromes are classified based on the distribution of limb involvement into: spastic diplegia (Sd), spastic quadriplegia, and spastic hemiplegia. Delay in attaining developmental milestones and motor abnormalities is predominant clinical feature of cerebral palsy.[5]

The goal of the treatment in children with cerebral palsy is an improvement in functionality and increased independence, which will prepare these children for adult life.[6] A treatment program usually focuses on the reduction or normalization of tone to prevent the development of secondary complications. Treatment of cerebral palsy has been the subject of many investigations, but no effective treatment has been found despite extensive researches.[7,8] The fundamental importance to the optimization of the functional outcome is the cause of development in new therapeutic resources for use in combination with physical rehabilitation methods.[9] Physiotherapy, use of orthotics, serial casting, electrical stimulation, and more recently, the intramuscular injection of botulinum toxin type are the most common interventions. There is no drug that could be able to make the neurons to regenerate; stem cell therapy may be a promising method in the future.[7,8]

Citicoline as a neuroprotectant has been increasingly recognized that may act both in early and late stages of ischemic damage, resulting in a plethora of experimental.[10] Neuroprotective effects of citicoline may occur through its ability to improve phosphatidyl choline synthesis in the injured brain stabilizes, and repairs membranes.[11,12] Safety and efficacy of citicoline were assessed in clinical trials as a treatment for stroke. A clinical trial has investigated citicoline and reported that administration of citicoline was effective early in the postischemia recovery process, as demonstrated by improved level of consciousness.[13] Furthermore, in many trials, the safety of citicoline has also been established; there is no difference in side effects between the placebo and citicoline groups.[14]

Currently, in many countries citicoline is approved for use in stroke, head trauma, and other neurological disorders, and regarding to prove and probable neuroprotective effects of citicoline and its safety, the present study was designed to evaluate the effects of injection of citicoline in combination to physiotherapy versus physiotherapy alone, to improve the functional outcome in pediatric patients with Sd or quadriplegic cerebral palsy.

METHODS

Design and patients

This randomized controlled trial, between June, 2012 and March, 2013, was performed in accordance with the principles of the declaration of Helsinki, and the Ethics Committee of the school of medicine in the Isfahan University of Medical Sciences, Isfahan, Iran, approved the study protocol. Fifty pediatric patients aged 18-75 months with Sd or quadriplegic cerebral palsy, who referred to Isfahan subspecialty pediatric neurology clinic, enrolled in this study. Patients of any gender were eligible if etiology of cerebral palsy was prematurity and/or perinatal hypoxic–ischemic damage and had no neurometabolic or neurodegenerative disorders, orthopedic problem, and neuromuscular disorders. Furthermore, patients with uncontrolled seizure and cerebral palsy due to other etiology were excluded from the study. Participating patients' parents were explained about and informed of the purposes of the study.

Procedure

Patients meeting the inclusion criteria were randomly divided into two 25-member groups of case and control. Age, gender, gestational age at delivery, type of delivery, type of cerebral palsy, magnetic resonance imaging (MRI) status, asphyxia, electroencephalography (EEG) change, and gross motor function classification system (GMFCS) levels were variables to be observed in this study. Case group, included 25 patients treated with, injection of citicoline (10 mg/kg) every other day for 3 months and physiotherapy. Control group, included 25 patients, treated with physiotherapy.

Gross motor function classification system as a five-level classification system was assessed before and after treatment. This system describes the gross motor function of children and youth with cerebral palsy on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Data are reported as mean ± standard deviation and number (%) as appropriate. Age was compared between groups using independent sample *t*-test. Gender, gestational age at delivery, type of delivery, type of cerebral palsy, MRI status, asphyxia EEG change, and GMFCS levels in study groups were assessed by applying McNemar test. The level of significance is considered to be < 0.05.

RESULTS

All patients in both groups completed follow-up period and analyzed [Figure 1]. Patient's mean age in all studied subjects was 38.7 ± 17.2 months, 24 patients (48%) were boy, and 26 (52%) were girl. Comparison of age, gender, gestational age at delivery, type of delivery, type of cerebral palsy, MRI status, asphyxia, and EEG are reported in Table 1. As shown, there were no significant differences between groups in regard to these variables.

Table 2 shows the results of GMFCS distribution between study groups. Before treatment, GMFCS level 1 was not observed in all patients, but after treatment 13 patients showed GMFCS level 1. Differences in the frequency of GMFCS levels between groups were not statistically significant, before (P = 0.09) and after (P = 0.47) treatment (P = 0.47).

Nine of 11 patients with GMFCS level 2 in case group, improved to GMFCS level 1, three of five patients with GMFCS level 3 improved to higher function (two patients GMFCS level 2 and one patient GMFCS level 1). Three of seven patients with GMFCS level 4 improved to other levels (one improved to GMFCS level 2 and one improved to GMFCS level 3). In the control group, three of nine patients with pretreatment gross motor function level 2 improved to level 1. Three of 10 patients with GMFCS level 3 improved to levels, and two of four patients with GMFCS level 4 improved to higher levels. In totally, GMFCS level in 64% (16 patients) of cases was improved whereas in the control group 32% (8 patients) were

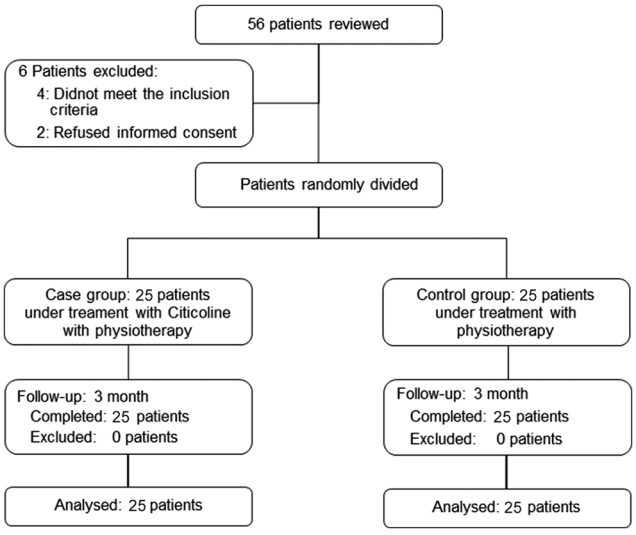

Figure 1: Study flowchart

Table 1: Baseline characteristics in studied group

	Cases (n=25)	Controls (n=25)	P value
Age (month)	36±17.02	41±17.3	*
Asphyxia	18 (72)	22 (88)	0.15†
Sex			
Boy	11 (44)	13 (52)	0.57†
Girl	14 (56)	12 (48)	
Delivery			
Cesarean	15 (60)	20 (80)	0.12†
NVD	10 (40)	5 (20)	
Type of cerebral palsy			
Sd	16 (64)	14 (56)	0.56†
Sq	9 (36)	11 (44)	
MRI			
PVL	10 (40)	7 (28)	0.17†
HIE	11 (44)	13 (52)	
Normal	1 (4)	0	
Atrophy	2 (8)	0	
PVL and HIE	1 (4)	5 (12)	
Gestational age			
Term	15 (60)	12 (48)	0.53†
Preterm	10 (40)	13 (52)	
EEG			
Normal	6 (24)	2 (8)	0.25†
Abnormal	19 (76)	23 (92)	

Data are mean±SD and number (%). Cases included patients who under treatment, using citicoline (10 mg/kg) every other day for 3 months and physiotherapy, controls included patients who under treatment, using physiotherapy. P values calculated by *Independent sample *t*-test and †Chi-square test. NVD=Normal vaginal delivery, Sd=Spastic diplegia, Sq=Spastic quadriplegia, PVL=Periventricular leukimalacia, HIE=Hypoxic ischemic encephalopathy, MRI=Magnetic resonance imaging, EEG=Electroencephalography, SD=Standard deviation

Table 2: Comparison of the distribution of GMFCS levels between study groups

	Before treatment (%)	After treatment (%)
GMFCS 1		
Cases	0	10 (40)
Controls	0	3 (12)
GMFCS 2		
Cases	11 (44)	6 (24)
Controls	9 (36)	9 (36)
GMFCS 3		
Cases	3 (12)	5 (20)
Controls	9 (36)	10 (40)
GMFCS 4		
Cases	4 (16)	7 (28)
Controls	2 (8)	4 (16)
GMFCS 4		
Cases	2 (8)	2 (8)
Controls	2 (8)	2 (8)
P value	0.09	0.46

Data are number (%). Cases included patients who under treatment, using citicoline (10 mg/kg) every other day for 3 months and physiotherapy, controls included patients who under treatment, using physiotherapy. *P* values calculated by McNemar test. GMFCS=Gross motor function classification system

improved. Percent of improved patients in the case group was significantly more than the control group [$P = 0.02$, Figure 2].

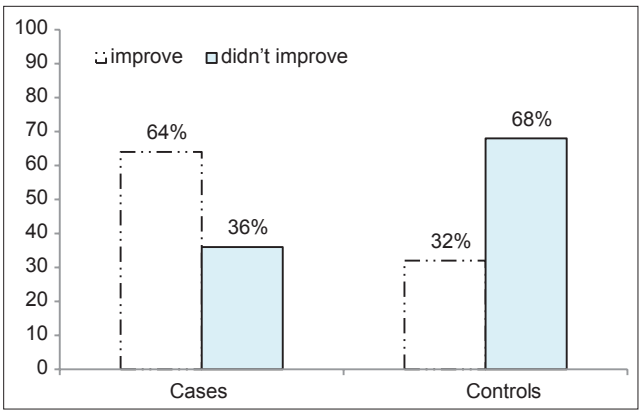

Figure 2: The frequency of patients before and after treatment in two groupsbased on gross motor function classification systemscore. Cases included patients who under treatment, using citicoline (10 mg/kg) every other day for 3 monthsand physiotherapy, Controls included patients who under treatment, using physiotherapy. McNemar test showed thatthepercent of improved patients inthecase group was significantly more thanthecontrol group ($P = 0.02$)

DISCUSSION

In numerous clinical trials, citicoline has demonstrated its neuroprotective and neuroreparative effects in a different situation of neuronal damage.[15-23] As well as worldwide, in our country, cerebral palsy is one of the most common causes of childhood disability. Although outcomes for children have generally improved by early intervention services, the specific interventions that most benefit children with cerebral palsy are uncertain, and also, therapeutic interventions change over time.[24] Regarding to established neuroprotective properties of citicoline, the present study was planned to evaluate the efficacy of citicoline in combination with physiotherapy, cerebral palsy. Results of the present study showed that the difference in the frequency of GMFCS levels between groups was not statistically significant after treatment. But citicoline in combination with physiotherapy significantly improved the gross motor performance than physiotherapy alone in cerebral palsy, and the best positive effects were observed in patients with higher levels of GMFCS level 2 and 3. No therapeutic effects were observed in patients with the most severe form of cerebral palsy (GMFCS level 5).

Clinical trials about effect of citicoline in cerebral palsy are limited, and other studies evaluated this effect in other problems. In patients with head trauma, citicoline has shown its efficacy for recovery from posttraumatic coma, improvement of memory and cognitive function, and improvement of functional outcome.[21] In patients with ischemic stroke and ischemic cerebrovascular disease, citicoline accelerated improvement of cognitive function and motor performance.[22] In several well-organized trials in patients with vascular dementia and age-related dementia, citicoline has shown its efficacy in improvement of cognitive function.[16-20] Although our study was different with reported studies in target population, but similar to these results, our findings showed improvement of cognitive function and motor performance.

Several mechanisms of action can be proposed for neuroprotective effects of citicoline in cerebral palsy. Although it may enhance neuroplasticity, the most probable mechanism

of action for its neuroprotective effects in cerebral palsy is through its effects on neuronal membrane repaired and better functioning of neurotransmitter system in central nervous system. It seems that citicoline helps to better functioning of existing neurons.

Due to deficiency of clinical research in evaluation of the effect of citicoline in combination with physiotherapy in cerebral palsy, results of the present study can be noted as basement for more researches to finding possible effects. Furthermore, the main Limitation of our study may be is its small sample size. We believed that larger randomized studies with more sample size are necessary to assess the efficacy of citicoline in combination with physiotherapy in cerebral palsy, and it is suggested that important issues such as different dosage and duration of treatment are notable in further studies.

CONCLUSIONS

Results of the present study demonstrated that the citicoline is effective and safe in the treatment of gross motor function combination with physiotherapy in patients with spastic cerebral palsy, although, these effects were particularly more pronounced in a milder form of cerebral palsy (patients with GMFCS level 2 and 3).

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