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## Original Research

### Role of piracetam in treatment of cerebral palsy disease

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#### Abstract

The term cerebral palsy (CP) refers to neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination. Piracetam is a compound chemically related to gamma-aminobutyric acid (GABA). It crosses the blood-brain barrier but does not produce any overt central or autonomic nervous system effects. The aim of this prospective study was to evaluate and compare the effect of different doses of Piracetam on clinical status and intellectual power of cerebral palsy patient. The study was carried out on 40 cerebral palsy patients; 22 out of them were females, aged from 1 to 4.75 years old; from outpatient clinic at Beni Suef University Hospital. Patients were divided into four equal groups. Group A received dose 40mg/kg/day, group B received dose 80mg/kg/day, group C received dose 120mg/kg/day and group D was the control group, did not receive any Piracetam. Patients were treated and followed up for 6 month. They were represented by full history taking and clinical examination. The Intelligence quotient (IQ) test was done for every patient to evaluate mental development before starting piracetam treatment and every month for six months. There was an improvement in general health of children after therapy and quotient. Dose 120mg/kg/day of piracetam was found to be the most effective dose piracetam in the treatment of cerebral palsy disease as shown by improved scores of IQ test. The best improvement in mental and motor development was greatly observed in group C. Dose 40mg/kg/day of piracetam showed insignificant effect on improving the IQ of the patients.

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## INTRODUCTION

Cerebral palsy is a group of problems that affects body movement and posture. It is related to a brain injury or to problems with brain growth. It is one of the most common causes of lasting disability in children. Cerebral palsy causes reflex movements that a person cannot control and muscle tightness that may affect parts or all of the body [1].

Cerebral palsy (CP) is not a progressive disorder, meaning the brain damage neither improves nor worsens, but the symptoms can become more severe over time due to subdural damage. A person with the disorder may improve to some extent during childhood

if he receives extensive care from specialists. People who have CP tend to develop arthritis at a younger age than normal because of the pressure placed on joints by excessively toned and stiff muscles [2]. While in certain cases there is no identifiable cause [3]. Typical causes of CP include problems in intrauterine development, e.g. exposure to radiation, infection, asphyxia before birth, hypoxia of the brain, birth trauma during labor and delivery and complications in the perinatal period or during childhood. Cerebral palsy is also more common in multiple births and low birth weight is a risk factor for CP.

Children with cerebral palsy exhibit a wide variety of symptoms [3], e.g. lack of muscle coordination when

performing voluntary movements (ataxia); stiff or tight muscles and exaggerated reflexes (spasticity); walking with one foot or leg dragging; walking on the toes, a crouched gait, or a “scissored” gait; variations in muscle tone, either too stiff or too floppy; excessive drooling or difficulties in swallowing or speaking; shaking (tremor) or random involuntary movements; and difficulty with precise motions, such as writing or buttoning a shirt

Piracetam, the prototype of nootropic drugs, is claimed to have therapeutic value in some patients suffering from cognitive deficits, especially when hypoxia may be a factor in the deficits. The drug lacks sedative or stimulatory effects and apparently does not influence behavioral in normal people. The site of action and the mechanism by which piracetam exerts its beneficial effects are not well established [4].

Piracetam has very few side effects, it including anxiety, insomnia, irritability, headache, agitation, nervousness and tremor. Headache from large doses of piracetam may be alleviated by coadministration of an acetylcholine biosynthetic precursor, or a drug with cholinergic effects [5].

The mechanism of action of piracetam is not known [4]. It is hypothesized to act on ion channels or ion carriers, thus leading to non-specific increased neuron excitability. It also increases blood flow and oxygen consumption in parts of the brain [6]. It improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors which are implicated in memory processes [7]. Piracetam may have an effect on N-methyl-D-aspartic acid (NMDA) glutamate receptors which are involved in learning and memory processes [8]. Piracetam is thought to increase cell membrane permeability. Piracetam may exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Na<sup>+</sup>, K<sup>+</sup>) [9]. It increases oxygen consumption in the brain, apparently in connection to ATP metabolism and increases the activity of adenylate kinase in rat brain. [10]. Piracetam appears to increase the synthesis of cytochrome b<sub>5</sub>, which is a part of the electron transport mechanism in mitochondria [4]. It also increases the permeability of the mitochondria of some intermediaries of the Krebs cycle [11].

The aim of the present study was to evaluate and compare the effect of different doses of Piracetam on clinical status and intellectual power of cerebral palsy patient.

## **MATERIALS AND METHODS**

A local hospital research ethics committee approval was obtained for the patients study. 40 patients were

included in the study; 22 out of them were females; they were collected from outpatient clinic at Beni Suef University Hospital with cerebral palsy disease. An informed consent was obtained from parents or legal guardians.

Inclusion criteria:

Patients diagnosed as cerebral palsy disease.

Exclusion criteria:

Individuals with convulsion, hemostasis, major surgery, severe hemorrhage and any allergies to piracetam

All patients were evaluated by:

1. Detailed history and thorough clinical examination which include;

Demographic data (name, age, sex);

Perinatal history including antenatal history (e.g. positive mother disease or x-ray exposure during pregnancy), natal history (e.g. positive normal vaginal delivery) and post natal history (e.g. positive jaundice, convulsion and incubation admission after birth);

Present history, with concentration on motor development of the child including time of standing, sitting and walking; mental development of the child including speaking, recognition of the mother and mental retardation if present;

Family history (e.g. positive consanguinity and similar condition in the family)

2. Intelligence quotient (IQ) test (Binet Intelligence Test) was assessed for every patient at the start and every month.

Patients were divided into four equal groups A, B, C and D. Each group consisted of (10) patients.

Group (A): Represented patients who received 40 mg/kg/day Piracetam.

Group (B): Represented patients who received 80 mg/kg/day Piracetam.

Group (C): Represented patients who received 120 mg/kg/day Piracetam.

Group (D): Represented patients who did not received Piracetam. (Control group)

The four groups were subjected to:

1. Clinical examination every month for six months, which includes:

General examination: before starting the therapy and after 6 months to detect if there was any improvement in quotient and spasticity.

Local examination: for detection of motor and mental

development before starting the therapy and after 6 months.

2. Intelligence quotient (IQ) test before starting the therapy and every month for six months. Tests were done early in the morning in the same day of every month for six months.

**Statistical analysis**

A one-way analysis of variance (ANOVA) test with Bonferroni correction was used to compare the effect of different doses of Piracetam on clinical data and Intelligence quotient test using SPSS V15.0 (SPSS Inc., Chicago, IL).

**RESULTS**

Forty cerebral palsy patients completed the study; 22 out of them were females. The patients' ages ranged from 1 to 4.75 years old. Group A mean ± (SD) age

was 3.13±1.28 years. Group B mean ± (SD) age was 2.83±1.18 years. Group C mean ± (SD) age was 2.21±1.27 years. Group D mean ± (SD) age was 2.68±1.12 years.

In terms of age and sex, all groups were statistically homogenous. Data analysis of all four groups before the beginning of study showed no significant differences concerning Intelligence quotient test, motor development (e.g. sitting, standing and walking) and mental development (e.g. speaking and recognition to mother).

The baseline data of all patients before inclusion in the study are shown in Table 1. Means ± SD of the Intelligence quotient data after therapy of the four groups are shown in Table 2. Comparison between motor and mental development after therapy in groups A, B and C are shown in table 3. There was no motor and mental development Group D after therapy.

**Table 1.** General collecting data

Parameters		Group A	Group B	Group C	Group D	
Age (Years)		1-4	1-4	1-4	1-4	
Sex	Male	3	7	5	3	
	Female	7	3	5	7	
Pregnancy data	Maternal illness	0	3	1	1	
	Drug intake	0	2	1	1	
	Irradiation	0	0	0	0	
Birth data	Convulsion	0	2	2	7	
	Mode of delivery	Normal	10	9	9	7
		C.S	0	1	1	3
	Site of delivery	Home	6	5	6	5
		Hospital	4	5	4	5
	Prolonged labor	8	7	5	9	
	Jaundice	2	2	2	1	
	Cyanosis	4	5	2	6	
	Oxygen inhalation	3	5	1	4	
	Incubation admission	2	4	3	6	
Mental retardation		8	10	9	7	
Baseline Motor development	Sitting	0	0	0	0	
	Standing	0	0	0	0	
	Walking	0	0	0	0	
Baseline Mental development	Recognition to mother	2	0	0	2	
	Speaking	1	0	0	1	

**Table 2.** Mean±SD IQ values resulted from groups A, B, C and D

Group	Before	After the therapy (months)					
		1	2	3	4	5	6
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
A	58.7±16.2	58.7±16.2	58.7±16.2	58.8±16.2	58.7±16.1	58.7±16	58.6±15.9
B	57.4±8.6	57.4±8.6	57.5±8.6	57.7±8.3	58±7.9	58.4±7.4	75±16.6
C	58.1±12.9	58.2±12.8	58.7±12.3	58.9±12	59.7±11.2	59.9±10.9	82.9±22.1
D	70.5±23.9	70.5±23.9	70.5±23.9	70.5±23.9	70.5±23.9	70.5±23.9	70.5±23.9
p-value	0.245	0.246	0.254	0.26	0.27	0.277	0.067

**Table 3.** Number and percentage of patients that showed motor and mental development after therapy in groups A, B and C

		Group (A)		Group (B)		Group (C)		p-value
		No	%	No	%	No	%	
Motor development	Sitting	6	60	9	90	10	100	0.04
	Standing	4	40	4	40	3	30	0.87
	Walking	4	40	3	30	1	10	0.32
Mental development	Speaking	4	40	2	20	3	30	0.63
	Recognition to mother	5	50	7	70	7	70	0.63

After therapy, insignificant development was demonstrated in IQ during the first five months. In the sixth month of therapy, groups B and C showed significant improvements in the IQ test (p=0.049 and 0.039, respectively) compared to group D (control). However, there was no significant development in group A compared to group D (control).

In group A there was a significant improvement after therapy in sitting, standing and walking; and no significant improvement was observed in recognition to mother and speaking.

In group B there was significant improvement after therapy in standing, recognition to mother and sitting; and no significant improvement was observed in walking and speaking.

In group C there was significant improvement after therapy in recognition to mother and sitting; and no significant improvement was observed in standing, walking, speaking.

In group D no patients were improvement in motor or mental development.

The increase of the dose showed more significant improvements in sitting after therapy. (p= 0.04).

There was no significant difference between the effect of groups A, B and C after therapy on standing, walking, speaking and Recognition to mother (p = 0.87, 0.32, 0.63 and 0.63 respectively).

### DISCUSSION

The results showed that piracetam could be more advantageous for treatment of all CP complications, if the dose is properly adjusted. Piracetam given to CP patient resulted in significant improvement in motor and mental development. It was also found that treatment of CP using a dose of 120 mg/kg/day of piracetam showed the best efficacy. Also the dose of 40 mg/kg/day of piracetam as a treatment of CP was found to have no effect on improving motor or mental (IQ) development of the patients.

The study presented here agreed with Maritz (12) in that it is important to help the children affected with cerebral palsy as early as possible in order to give them

the opportunity for normal development.

In the study by Maritz [12], it was noted side-effects as nausea and vomiting in 1 patient who received piracetam in a dose of 50mg/kg/day. The vomiting stopped when the dosage was lowered and did not recur upon subsequent gradual increasing. That was noticed in our study in 3 patients in group C (the group with the highest concentration) in the fifth month.

During this Maritz study it was observed that frequency of administration of piracetam causes convulsion to the child. The convulsion is an exclusion criterion to piracetam so piracetam was stopped and that leading to retardation of the clinical status of the patient.

The study of Chagas [13] showed favorable results in the ten weeks treatment. The improvements were in spasticity, learning and nervous instability problems. The study of Maritz [12] showed favorable results in six weeks treatment. The improvements were in the general spasticity, hand movement, hand function and walking. But in our study we continued for six months and found that some patients showed little or insignificant improvement in IQ during the first few weeks. That might be due to younger patients groups used in our study compared to those in Maritz and Chagas studies. Hence it should not be generalized that the improvement was usually recognizable after 2 weeks treatment and we suggest that a further study for a longer period (more than 6 months) and more number of the patients is recommended to detect other useful uses of piracetam.

The study by Dimond [14] showed that piracetam was tested for its effects on man by administration to normal volunteers. The subjects were given 1200-1600 mg per day, in a double blind study. Each subject learned series of words presented as stimuli upon a memory drum. No effects were observed after 7 days but after 14 days verbal learning had significantly increased.

Finally the present work shows that prescribing piracetam has a very good effect on the CP and the 120 mg/kg/day dose of piracetam is better and more effective than the 80 mg/kg/day dose in improving motor or mental (IQ) development of the patients. No significant effect was observed from the 40 mg/kg/day dose on improving motor or mental (IQ) development of the patients.

## CONCLUSIONS

The piracetam has a good effect on IQ and motor and mental development when used as a treatment for cerebral palsy

Dose of 120mg/kg/day piracetam were found to be the

most effective dose in the treatment of cerebral palsy disease. It is strongly recommend that piracetam should be given to CP patients at a dose higher than 40 mg/kg/day to improve both motor and mental development.

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