

EFFECT OF 4 MONTH OF RESISTANCE TRAINING ON THE LEVELS OF GROWTH HORMONE, IGF-1 AND IGFBP3 IN PLASMA OF CHILDREN DIAGNOSED WITH SPASTIC QUADRIPLEGIA CEREBRAL PALSY

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ABSTRACT

Cerebral palsy is one of the most common causes of disability in children. This disorder causes motor disabilities in growing children. The present study aims to determine the effect of 4 months of resistance training on the levels of GH, IGF-1 and IGFBP3 in plasma of children diagnosed with spastic quadriplegia cerebral palsy. The method of this research is a quasi-experimental pretest – posttest method. The testees of this study were divided into two groups: an experimental group (10 people) and control group (8 people) with an age range of 10 to 13 years. In the pretest, blood sample of the members of two groups were taken in order to measure GH, IGF-1 and IGFBP3. Then, the experimental group gone through a 4-month of additional resistance training. The exercises began with weight training and then exercises with balls and resistance bands were added to them. The control group did not take part in any kind of athletic activities. After the intervention, in the posttest stage, the sampling was done again. In order to analyze the data and comparing the process of variation of GH, IGF-1 and IGFBP3 values in the two groups, analysis of variance with repeated measures was used. The results showed that participation in resistance trainings led to a 126-percent increase in GH, a 59-percent increase in IGF-1 and an 82-percent increase in IGFBP3 which were significant variations compared to the control group ($P < 0.05$). It seems that long-term resistance training can cause an enhancement in the growth factors in people diagnosed with cerebral palsy and prevent the reverse process and an excessive reduction of these factor due to these factors.

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Introduction

Cerebral palsy is a group of fixed evolution – motor disorders which are non-progressive and occur in an evolving fetus [1]. Motor disorders in children with cerebral palsy are often followed by sensory, perceptual, cognitive, communicative, behavioral damages as well as seizures [5]. According to previous studies, prevalence cerebral palsy is about 2 per 1000 live births [2, 9, 15, 22, 24, 30]. 10 to 20 percent of cerebral palsy cases are the outcome of abnormalities of the central nervous system, genetic disorders and neonatal infections and the other causes can be primary care of newborns in hospitals. There are

numerous risk factors that enhance cerebral palsy such as birth asphyxia, neonatal meningitis and neonatal seizures [4]. Disorders associated with social interaction and communication have been reported in 58% of children diagnosed with cerebral palsy, visual impairments have been reported in 42% of these children, hearing impairments have been reported in 7% of them and seizures have been reported in 28% of these children [7]. Under such circumstances, failures in information processing, memory, thinking, speech, language and sensory – motor disabilities are likely to be seen. Cerebral palsy is also often followed by nutrition and growth disorders. Children with severe motor disabilities are the most exposed to the risk of suffering from cerebral palsy [8]. Eating disorders, neurological factors and endocrine glands all play roles in a level of growth that is under the desirable level. Weak nutrition and growth together with poor general health are associated with reduction of level of participation in different affairs [9]. A high percentage of children diagnosed with CP suffer from GH secretion deficiency. Nonetheless, it seems logical that severe cerebral damage might affect a number of neurotransmitter pathways that are involved in controlling GH, which consequently influence the natural secretion of hormone as well [3]. Other causes of reduction of growth in children suffering from CP include mental abnormalities and poor nutrition (malnutrition). These factors are also involved in the uncommon secretion of GH (18). Growth hormone (GH) deficiency might affect the growth of children suffering from CP. There is a tendency towards reduction of the levels of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) in children diagnosed with CP in comparison with ordinary children of the same age. Research shows that most children suffering from CP have had a weak linear growth in childhood which leads to short stature in adolescence [14]. The results of previous studies show that an eighteen-month GH therapy in children suffering from CP receiving sufficient nutrition improved linear growth in comparison with the control group [11]. Many of the metabolic effects of GH are mediated by GH peptide hormone [13]. The IGF-GH axis plays a crucial role in bone metabolism. Considerable improvements were seen in spine bone mineral density (BMD) in the group of children going through GH therapy. Hormonal influences have affected the progress made in puberty in such a way that children with an average-to-severe level of CP experience a longer period of puberty than children with no CP [15]. Growth hormone (GH) deficiency might influence the growth of children suffering from CP. There is a tendency towards reduction of the levels of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) in children diagnosed with CP in comparison with ordinary children of the same age [29]. According to recent studies, reduction of blood cycle of IGF-1 and GH might offer some explanation for why children suffering from CP are smaller than those with normal growth [20]. On the other hand, osteoporosis is a common finding in children with CP and it seems that it is associated with reduced IGF-1 and level of IGFBP3 in plasma and common symptoms of GH secretion deficiency. A combined treatment containing replacement of the growth hormone and physical stimulation affects the motor rehabilitation of children suffering from CP or adults diagnosed with cognitive impairments caused by traumatic brain injury (TBI) [14]. GH therapy can be of use when it comes to improving the speed of growth of children with CP who have a GH deficiency. Therefore, it can improve their final height. It is a generally safe method of treatment for children suffering from short stature caused by GHD or other factors. Exercise is a strong stimulus for the release of growth hormone, prolactin and cortisol [21]. It has been reported that exercise, especially resistance training, increases the level of GH [22]. The level of growth hormone (GH) in blood enhances while one exercises and it is mostly affected by the intensity of the exercise. This hormone enhances muscle hypertrophy and growth by facilitating transmission of amino acids into cells [23]. Weight training programs lead to a maximum level of secretion of the growth hormone [22]. After a long period of resistance training, there will be an increase in the level of both types of isoform (IGF-1 and IGFBP3). IGF-1 enhances the protein synthesis throughout resistance training and increases hypertrophy [23]. It has been reported that people who had done resistance exercises have had resting levels of IGF-1. An increase in the resting levels of IGF-1 have been seen in women especially in trainings with high volume [24]. Although it has been reported that IGFBP3 increases one hour after resistance training, but in some studies, it has been reported that IGFBP3 had been reduced in weeks 13 to 25 into the resistance training program [25]. Although numerous studies have reported a significant increase in GH after resistance training [24, 26, 27]. Given that injection of the growth hormone has led to an improvement of the growth of children suffering from cerebral palsy and on the other hand, the results of some studies have been indicative of the role exercising plays in the increase of growth factors, the present study aims to determine the effect of a period of resistance training on the variations of GH, IGF-1 and IGFBP3 in children diagnosed with cerebral palsy.

Methodology

The method of this research is a quasi-experimental with a pretest – posttest design and a control group. By taking into account the duration of the research, the present study is a cross-sectional research and it is an applied research because the results obtained from it are to be used in practice. The statistical sample of this research has been comprised of 20 children suffering from cerebral palsy who were selected because they were available. There were some criteria for these children to enter the study which included being in the age range of 10-13 years, being diagnosed with spastic quadriplegia cerebral palsy who hadn't gone through occupational therapy, physiotherapy, or hydrotherapy in the rehabilitation center. Also, in case of having the following criteria, the participants would be eliminated from the study: expressing dissatisfaction with their cooperation, suffering from asthma, cardiac and respiratory diseases or taking part in physiotherapy sessions. Samples were divided into two groups: an experimental group of 10 samples and a control group of 10 samples. The division has been done after the research method was fully explained; in such a way that those who were not interested in participating in physical activities were put in the control group and others were put in the experimental group. Two testees were eliminated from the control

group because their changed their location and the number of testees in the control group was reduced to 8. The children in the control group had an age mean of 10.75 ± 1.165 and the children in the experimental group had an age mean of 10.90 ± 1.287 . During the execution of the project, all of the moral principles associated with this type of research were observed. In addition, the testees and their parents were asked to sign a written consent for taking part in the test and exercises. After the blood samples of the testees in the control and the experimental group were taken, the training program began for the experimental group; while the control group did not participate in any kind of physical activity program and did not go through occupational therapy or physiotherapy in the rehabilitation centers either. The testees in the experimental group exercised 3 times a week for four months; each exercise session contained an average of 90-minute individual resistance trainings. 48 hours after the end of the exercises, blood sampling was done again (posttest). The exercises were done individually by each testee, however the training patterns were the same for all participants (warm-ups, the primary program and cool-offs). The training protocol was as follows: in the first month (four weeks, three sessions per week), because of the severe motor weakness in the samples, the first three weeks included static and dynamic stretching exercises and PNF and in the fourth week, the testees became familiar with the weight training. In these sessions, the accurate way of doing the weight exercises, the accurate way of breathing while doing resistance exercises were done with the minimum weight possible and based on the physical condition of the child. In the second month (four weeks, three sessions per week), in addition to weight exercises, skill and resistance exercises were thought and done using balls. In the third month (four weeks, three sessions per week), bands were used so that children's body would be prepared to a large extent and it would have the ability to hold and move the weights. Resistance trainings with fitness bands were quite ideal for home exercise programs and they were quite easy to do. In the fourth month (four weeks, three sessions per week), exercises were done using dumbbells and weight cuffs that were connected to one's legs. Mediagnost laboratory kits and Elisa method were used for measuring the concentration of plasma of GH, IGF-1 and IGFBP3. The measurement unit for GH, IGF-1 and IGFBP3 was nanogram per millimeter.

In order to obtain the research results, the collected information was encoded and analyzed by SPSS version 18 software. For this purpose, the descriptive statistical methods, mean, standard deviation and inferential statistics and analysis of variance with repeated measures were used to compare the means of groups. The significance level was 0.05.

Results

Table 1 – mean and standard deviation the cycling level of GH, IGF-1 and IGFBP3 in Plasma in pretest and posttest for the control and the experimental group

| Name | | Control | Experimental |
|--------|----------|-------------------------------|-------------------------------|
| | | Mean \pm standard deviation | Mean \pm standard deviation |
| GH | Pretest | 0.84 \pm 0.42 | 1.33 \pm 0.79 |
| | Posttest | 0.48 \pm 0.3 | 2.21 \pm 1.79 |
| IGF-1 | Pretest | 65.66 \pm 204.63 | 66.99 \pm 207.30 |
| | Posttest | 64.48 \pm 201.13 | 50.29 \pm 330.20 |
| IGFBP3 | Pretest | 388.13 \pm 2882.63 | 490.49 \pm 2754.10 |
| | Posttest | 398.01 \pm 2847.037 | 545.03 \pm 5026.10 |

Table 2 – testing the intergroup and intragroup effects on the investigation of the impact of intervention on the cycling levels of IGF-1 and IGFBP3 in blood plasma

| Name | | Source of change | RMSE | Test statistic | Significance level | R ² |
|--------|------------|-------------------------------|--------------------|----------------|--------------------|----------------|
| | Intergroup | Time of measurement | 31680.80 | 50.36 | P=0.001< | 0.759 |
| IGF-1 | | Group and time of measurement | 3550.35 | 56.43 | P=0.001< | 0.779 |
| | Intragroup | Group of measurement | 38573.47 | 5.49 | P=0.032 | 0.256 |
| | Intergroup | Time of measurement | 117890.13 | 127.88 | P=0.001 | 0.889 |
| IGFBP3 | | Group and time of measurement | 11829783.47 | 136.07 | P=0.001 | 0.895 |
| | Intragroup | Group of measurement | 9340711.20 | 26.63 | P=0.001 | 0.625 |
| Gh | Control | Mean | Standard deviation | 3.50 | 0.001 | |
| | | -0.12 | 0.35 | | | |

| | | | | | | |
|--|--------------|------|------|--|--|--|
| | Experimental | 1.00 | 1.23 | | | |
|--|--------------|------|------|--|--|--|

Given the significance of the interaction between the group and time of test, the process of variations of the levels of IGF-1 and IGFBP3 have been different in the two groups.

In the control group, the level of GH in blood cycle after the intervention has been reduced in comparison to its level before the intervention. However, in the experimental group, the level of GH in blood cycle after the intervention has been increased in comparison to its level before the intervention. In order to compare the difference between the levels of GH before and after the intervention in the control and the experimental group, the Mann-Whitney test has been used. According to the results obtained from this test, there was a significant difference between the two groups ($P < 0.05$ and $U = 3.50$). Therefore, the increase of the level of GH after the intervention has been significantly higher in the experimental group than the control group.

Discussion and Conclusion

The results obtained from the present study showed that the level of the growth hormone of the blood of children in the experimental group after the intervention has experienced a 126-percent increase in comparison to the pretest stage. These results comply with the results obtained from the study conducted by Kramer et al. (2005) which were indicative of an increase in the level of GH after the resistance training in healthy individuals [28]. Moreover, according to studies conducted by Marandi et al. (2004), Sadeghi et al. (2009), Rashid Lamir et al. (2011), Khosravi et al. (2010) and Ganfar et al. (2003), after a period of training, despite the difference in the intensity of exercises, there was a significant increase in GH after one training session. Therefore, it can be concluded that the level of GH increases as a result of resistance training with the essential intensity [24, 26, 29]. According to the reports of Dossa et al. the peak of disorder at the level of growth hormone was seen in 26 percent of children diagnosed with CP (28 boys, 18 girls of 3 to 11 years) [11]. Further, according to the study of Michelle et al. (2009), children of 6 to 18 years who suffered from cerebral palsy grew more slowly than healthy individuals. Although patterns of variation of IGF-1 and secretion of GH in children suffering from CP was similar to those who were healthy, but the concentration of IGF-1 and GH was lower in children diagnosed with cerebral palsy than healthy children [26]. Dusa et al. (2011) conducted a study and reviewed the effect of replacement of the recombinant form of growth hormone on neurological growth of children suffering from cerebral palsy (GHD) with GH disorder for two months. According to their results, considerable progress was seen in individual and social skills, adaptive behavior, bold motor skills and mental abilities after the combined treatment. Thus, replacement of GH can have positive impacts on the neurological growth of children diagnosed with GHD and CP [14]. Moreover, the effect of GH therapy on levels of bone density in children suffering from cerebral palsy was reviewed by Omar Ali et al. (2006). In the present study, an eighteen-month course of GH therapy increased spine bone mineral density (BMD). In addition, GH therapy led to an increase in the linear growth and level of IGF-1 and IGFBP3 in patients. A group of patients who showed a more considerable increase in height (as patients receiving GH therapy) experienced a more considerable increase in BMD as well [20]. L. Shim et al. (2004) reviewed the effect of GH therapy in three individuals diagnosed with cerebral palsy who showed a more exponential increase in the GH level after the injection [28]. Kangiloo et al. (2010) investigated two children suffering from CP with weak linear growth receiving GH therapy and the results were quite successful; in such a way that the speed of linear growth, which was 3cm in the year before the treatment, was increased to 8.3cm over the first two years of treatment. None of the potential side effects of the treatment, such as the orthopedic condition becoming worse, did not occur and some psychological advantages were also reported. According to these results, GHD might play a role in the creation of linear growth failure in some of the children diagnosed CP and the GH therapy might be useful for some of these children [17]. It seems that one of the causes of the variation of the level of GH in the present study can be the preliminary levels of GH in testees. Therefore, given the fact that the level of GH was quite low before the intervention, resistance training was able to considerably influence this factor. The results obtained from the present study, levels of IGF-1 in the plasma of children in the experimental group after the intervention has experienced a 62-percent increase in comparison with the pretest stage. The GH-IGF-1 axis in children with CP has not been systematically studied yet, but the reports have shown that secretion of IGF-1 in plasma in unnaturally low in these children and GH therapy help this factor increase in patients diagnosed with cerebral palsy. In the study conducted by Rashati et al. (2011), 52 percent of patients with CP had GH deficiency and 62 percent of them showed deficiencies in the levels of IGF-1 and IGFBP3 in comparison with other children with the same age and gender [29]. Sue et al. (2010) and Everesti et al. (2000) observed a significant increase in the level of IGF-1 after 8 weeks of training and these results comply with the results obtained the results of the present study. Conversely, in the studies conducted by Marandi et al. (2004) and the one conducted by Sadeghi et al. (2009), no significant change was seen in the level of IGF-1 after a training session. Also, after eight weeks of resistance training in individuals who exercised and those who didn't and eight weeks of exercising in water, no change was seen in the level of IGF-1 in children. Thus, it can be concluded that in response to resistance training, the intensity of exercise and time of sampling are two effective factors [27]. It has been reported that in order to review the compliance between IGF-1 and training, a minimum of 48 hours had to have passed from the time of the most recent exercise. There have been reports regarding the increase of the concentration of IGF-1 up to 28 hours after the increase of GH in response to overload in the larger muscle mass. Nevertheless, in general, GH increased after doing physical exercises and with a time delay, IGF-1 increased [16]. The results of the research that there was a 54-percent increase in the level of IGFBP3 in children in the experimental group after

the intervention in comparison to the pretest stage. According to studies conducted by Rajabi et al. (2009) and Michael et al. (2006), no significant change was seen in the levels of IGF-1 and IGFBP3 after eight weeks of training. The cause of this incompatibility might be traits of testees, who were healthy people and excessive training intensity. Further, no difference was seen in the level of IGF-1 and IGFBP3 before and after volleyball exercises in healthy children. The cause of incompatibility of these results with the results of the present study was the fact that testees were different and a heavy training protocol was used. Given that the cycling levels of IGF-1 and IGFBP3 vary over the 24 hours of a day and reduce because of long hunger, the time and conditions of measurement are crucially important [7]. According to the reports made by Omar Ebn Anis, a significant increase was seen in IGFBP3 after a 2-month training program which complies with the results obtained from the present study [26]. In addition, according to the reports of Manta et al. (2003), a 12-percent increase was seen in IGF-1 and a 20-percent increase was seen in IGFBP3 in bike riders over the course of four months of training. Also, Koziriz et al. (1999) reported an increase of concentration of IGF-1 of more than 76 percent and an increase of concentration of IGFBP3 of 30 to 90 percent in university swimmers after four months of combined training program. It seems that a threshold in receiving and consuming energy is essential for observing change in the concentrations of IGF-1 and IGFBP3. Nonetheless, levels of IGF-1 and IGFBP3 adjusted by GH increases protein synthesis. Low levels of IGFBP3 in patients with low GH secretion might cause a shorter half-life in IGF-1 and a reduction in the effects of protein induction. IGFBP3 is a mediator for functions of IGF-1; in such a way that cycling levels of IGF-1 turn into IGFBP3 [28]. Doing physical exercises causes the body to secrete GH which enters the liver and other tissues through blood and makes production of IGF-1 possible. IGF-1 applies its anabolic effects directly on various tissues. The response of GH to exercise has been widely reviewed and the results obtained from most studies have shown that exercising causes an increase in the concentration of GH. Numerous studies have been conducted in the field of the effect of GH and IGF-1 on power enhancement. Most of them have reported a direct relationship between the concentration of this hormone and enhancement of the size of muscles and power. Thus, according to the results obtained from most studies, it could be argued that the level of IGF-1 changes because of doing physical activities and exercises. Some studies claim that compatibility of IGF-1 has two stages. The first stage is the catabolic phase (5 to 6 weeks) in which in response to training, the level of IGF-1 remains the same or decreases. The second phase is the anabolic phase (more than 7 weeks) in which level of IGF-1 increases. Enhancement of the level of IGF-1 in the present study after four months of resistance exercises might be because of length and continuity of the exercises [3]. It seems that resistance training might also be able to influence the levels of IGF-1 and IGFBP3 by increasing the production of GH and increase muscle protein synthesis. In addition, resistance training might decrease the level of catabolic hormones as well. Therefore, it is recommended to future researches to measure the level of these hormones.

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